National Institute for Health and Care Excellence

Consultation draft

Depression in adults: treatment and management

Appendix M: Forest plots

NICE Guideline

Appendices

May 2018

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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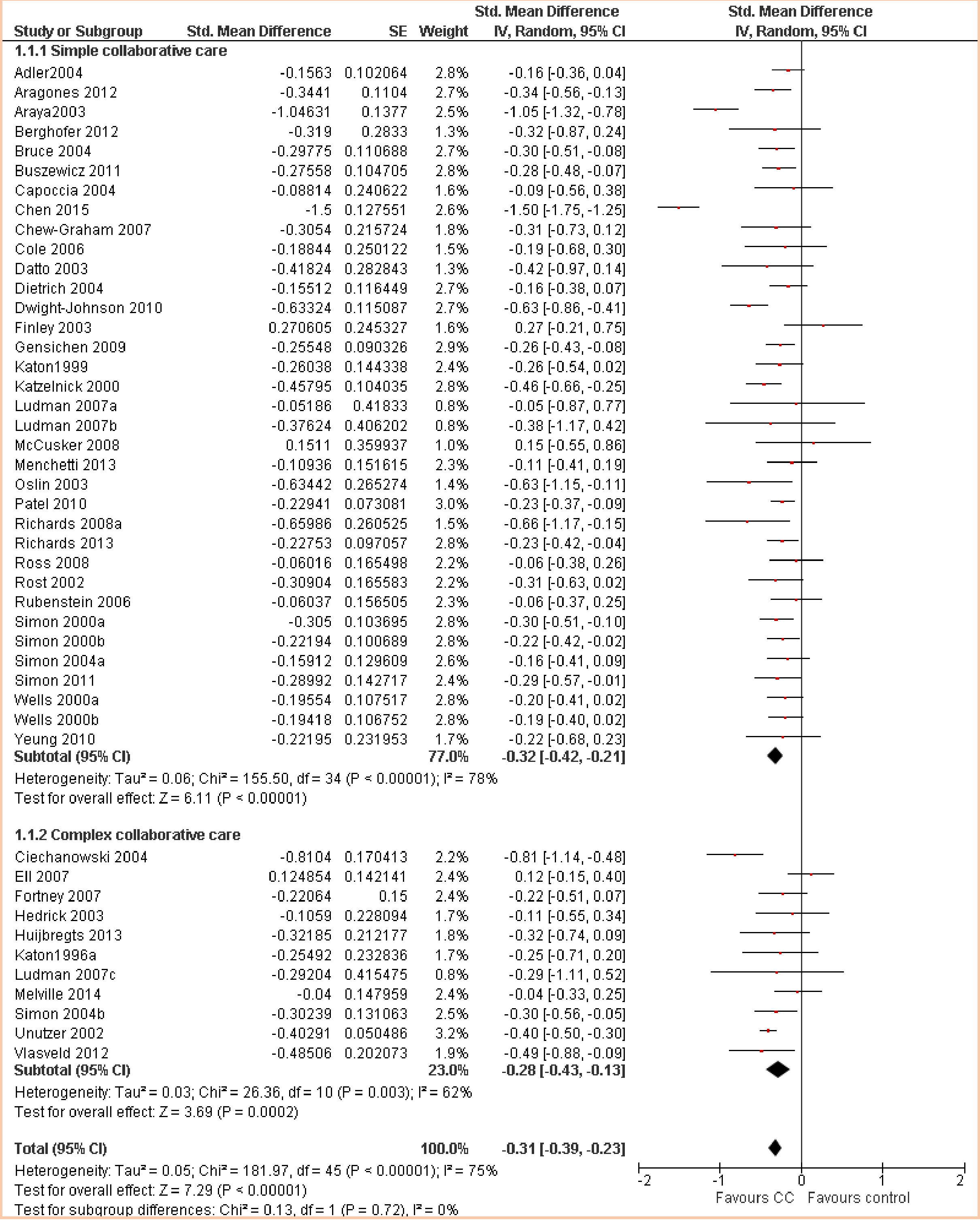
Organisation and delivery of services (chapter 5)

Service delivery models

Collaborative care versus control

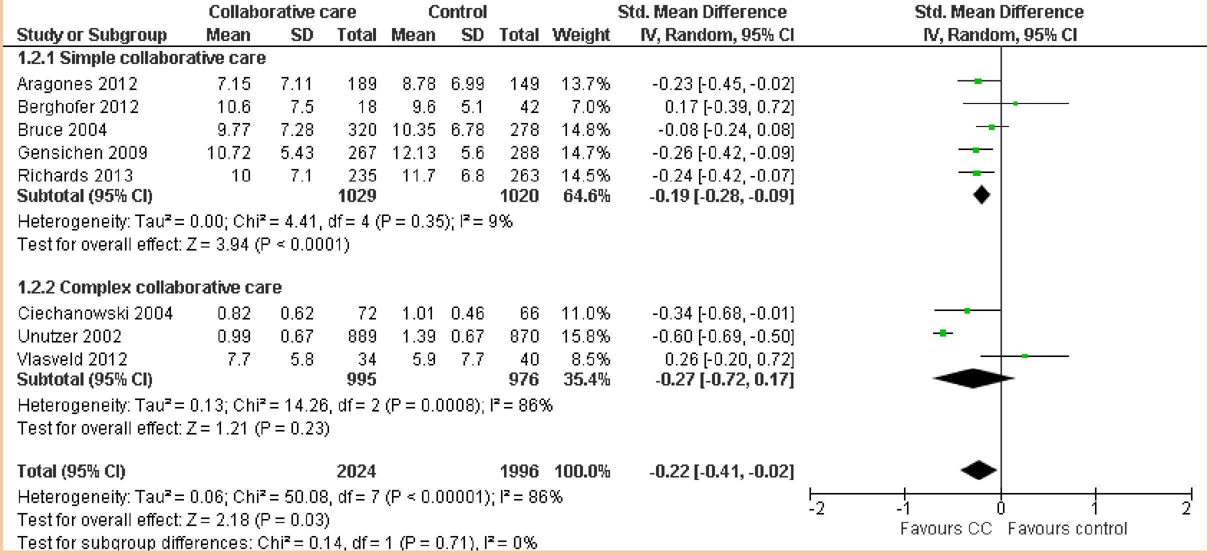
Depression symptoms at follow-up (6 months)



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Simple collaborative care				
Adler2004	-0.1563	0.102064	2.8%	-0.16 [-0.36, 0.04]
Aragones 2012	-0.3441	0.1104	2.7%	-0.34 [-0.56, -0.13]
Araya2003	-1.04631	0.1377	2.5%	-1.05 [-1.32, -0.78]
Berghofer 2012	-0.319	0.2833	1.3%	-0.32 [-0.87, 0.24]
Bruce 2004	-0.29775	0.110688	2.7%	-0.30 [-0.51, -0.08]
Buszewicz 2011	-0.27558	0.104705	2.8%	-0.28 [-0.48, -0.07]
Capoccia 2004	-0.08814	0.240622	1.6%	-0.09 [-0.56, 0.38]
Chen 2015	-1.5	0.127551	2.6%	-1.50 [-1.75, -1.25]
Chew-Graham 2007	-0.3054	0.215724	1.8%	-0.31 [-0.73, 0.12]
Cole 2006	-0.18844	0.250122	1.5%	-0.19 [-0.68, 0.30]
Datto 2003	-0.41824	0.282843	1.3%	-0.42 [-0.97, 0.14]
Dietrich 2004	-0.15512	0.116449	2.7%	-0.16 [-0.38, 0.07]
Dwight-Johnson 2010	-0.63324	0.115087	2.7%	-0.63 [-0.86, -0.41]
Finley 2003	0.270605	0.245327	1.6%	0.27 [-0.21, 0.75]
Gensichen 2009	-0.25548	0.090326	2.9%	-0.26 [-0.43, -0.08]
Katon1999	-0.26038	0.144338	2.4%	-0.26 [-0.54, 0.02]
Katzelnick 2000	-0.45795	0.104035	2.8%	-0.46 [-0.66, -0.25]
Ludman 2007a	-0.05186	0.41833	0.8%	-0.05 [-0.87, 0.77]
Ludman 2007b	-0.37624	0.406202	0.8%	-0.38 [-1.17, 0.42]
McCusker 2008	0.1511	0.359937	1.0%	0.15 [-0.55, 0.86]
Menchetti 2013	-0.10936	0.151615	2.3%	-0.11 [-0.41, 0.19]
Oslin 2003	-0.63442	0.265274	1.4%	-0.63 [-1.15, -0.11]
Patel 2010	-0.22941	0.073081	3.0%	-0.23 [-0.37, -0.09]
Richards 2008a	-0.65986	0.260525	1.5%	-0.66 [-1.17, -0.15]
Richards 2013	-0.22753	0.097057	2.8%	-0.23 [-0.42, -0.04]
Ross 2008	-0.06016	0.165498	2.2%	-0.06 [-0.38, 0.26]
Rost 2002	-0.30904	0.165583	2.2%	-0.31 [-0.63, 0.02]
Rubenstein 2006	-0.06037	0.156505	2.3%	-0.06 [-0.37, 0.25]
Simon 2000a	-0.305	0.103695	2.8%	-0.30 [-0.51, -0.10]
Simon 2000b	-0.22194	0.100689	2.8%	-0.22 [-0.42, -0.02]
Simon 2004a	-0.15912	0.129609	2.6%	-0.16 [-0.41, 0.09]
Simon 2011	-0.28992	0.142717	2.4%	-0.29 [-0.57, -0.01]
Wells 2000a	-0.19554	0.107517	2.8%	-0.20 [-0.41, 0.02]
Wells 2000b	-0.19418	0.106752	2.8%	-0.19 [-0.40, 0.02]
Yeung 2010	-0.22195	0.231953	1.7%	-0.22 [-0.68, 0.23]
Subtotal (95% CI)			**77.0%**	**-0.32 [-0.42, -0.21]**
Heterogeneity: Tau² = 0.06; Chi² = 155.50, df = 34 (P < 0.00001); I² = 78%				
Test for overall effect: Z = 6.11 (P < 0.00001)				
1.1.2 Complex collaborative care				
Ciechanowski 2004	-0.8104	0.170413	2.2%	-0.81 [-1.14, -0.48]
Ell 2007	0.124854	0.142141	2.4%	0.12 [-0.15, 0.40]
Fortney 2007	-0.22064	0.15	2.4%	-0.22 [-0.51, 0.07]
Hedrick 2003	-0.1059	0.228094	1.7%	-0.11 [-0.55, 0.34]
Huijbregts 2013	-0.32185	0.212177	1.8%	-0.32 [-0.74, 0.09]
Katon1996a	-0.25492	0.232836	1.7%	-0.25 [-0.71, 0.20]
Ludman 2007c	-0.29204	0.415475	0.8%	-0.29 [-1.11, 0.52]
Melville 2014	-0.04	0.147959	2.4%	-0.04 [-0.33, 0.25]
Simon 2004b	-0.30239	0.131063	2.5%	-0.30 [-0.56, -0.05]
Unutzer 2002	-0.40291	0.050486	3.2%	-0.40 [-0.50, -0.30]
Vlasveld 2012	-0.48506	0.202073	1.9%	-0.49 [-0.88, -0.09]
Subtotal (95% CI)			**23.0%**	**-0.28 [-0.43, -0.13]**
Heterogeneity: Tau² = 0.03; Chi² = 26.36, df = 10 (P = 0.003); I² = 62%				
Test for overall effect: Z = 3.69 (P = 0.0002)				
Total (95% CI)			**100.0%**	**-0.31 [-0.39, -0.23]**

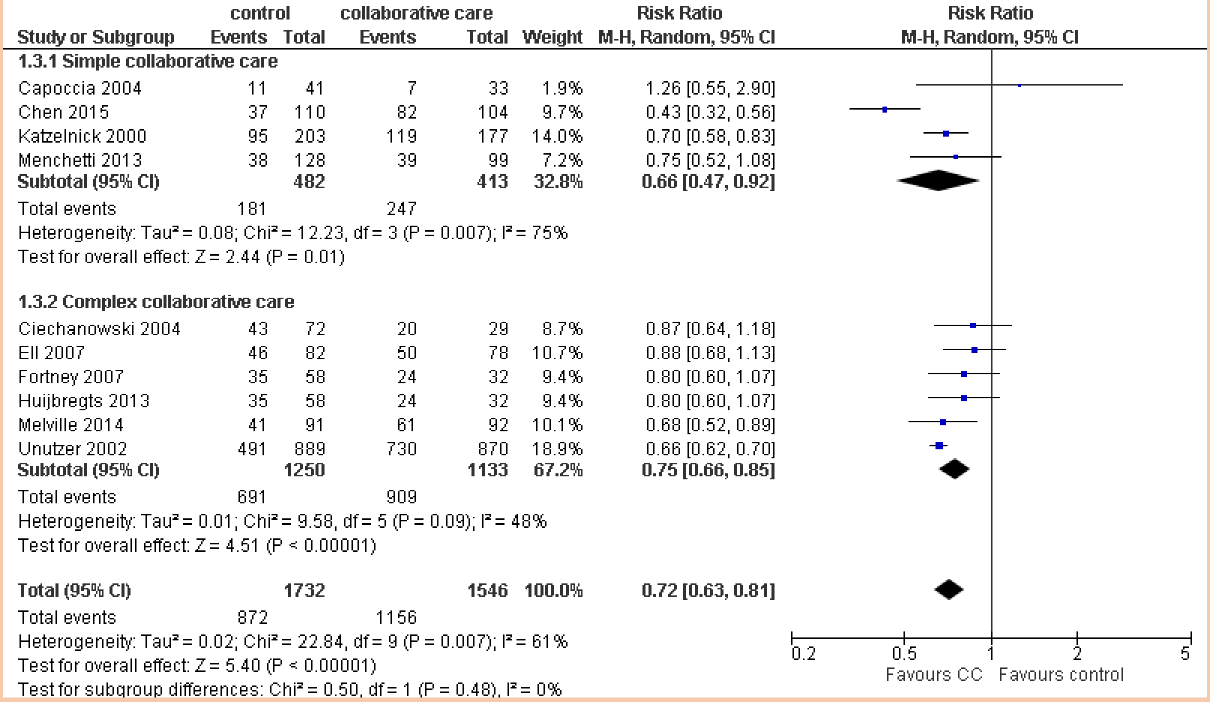
Heterogeneity: Tau² = 0.05; Chi² = 181.97, df = 45 (P < 0.00001); I² = 75%
Test for overall effect: Z = 7.29 (P < 0.00001)
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

Depression symptoms at endpoint



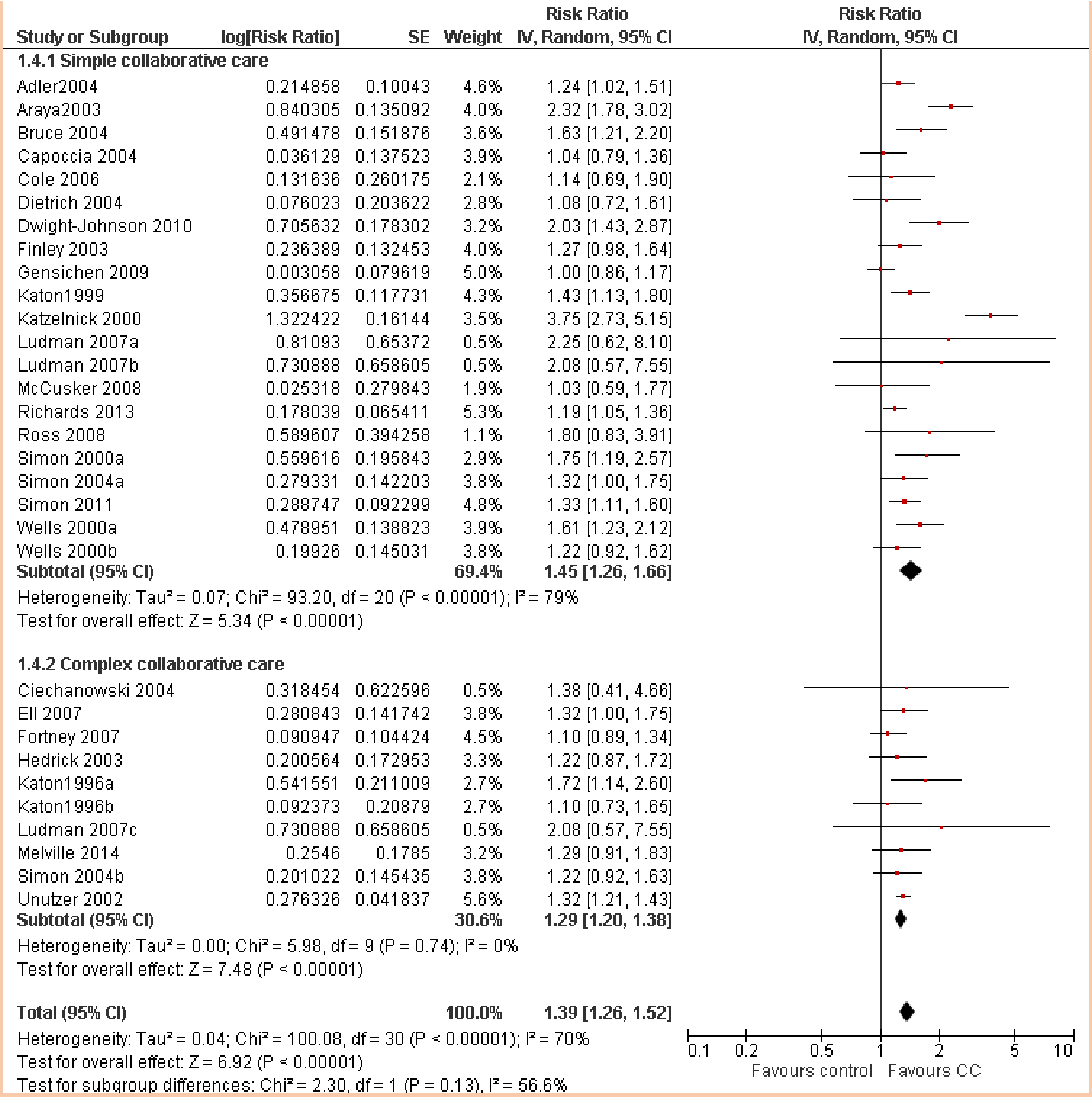
Study or Subgroup	Collaborative care Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Simple collaborative care								
Aragones 2012	7.15	7.11	189	8.78	6.99	149	13.7%	-0.23 [-0.45, -0.02]
Berghofer 2012	10.6	7.5	18	9.6	5.1	42	7.0%	0.17 [-0.39, 0.72]
Bruce 2004	9.77	7.28	320	10.35	6.78	278	14.8%	-0.08 [-0.24, 0.08]
Gensichen 2009	10.72	5.43	267	12.13	5.6	288	14.7%	-0.26 [-0.42, -0.09]
Richards 2013	10	7.1	235	11.7	6.8	263	14.5%	-0.24 [-0.42, -0.07]
Subtotal (95% CI)			**1029**			**1020**	**64.6%**	**-0.19 [-0.28, -0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%								
Test for overall effect: Z = 3.94 (P < 0.0001)								
1.2.2 Complex collaborative care								
Ciechanowski 2004	0.82	0.62	72	1.01	0.46	66	11.0%	-0.34 [-0.68, -0.01]
Unutzer 2002	0.99	0.67	889	1.39	0.67	870	15.8%	-0.60 [-0.69, -0.50]
Vlasveld 2012	7.7	5.8	34	5.9	7.7	40	8.5%	0.26 [-0.20, 0.72]
Subtotal (95% CI)			**995**			**976**	**35.4%**	**-0.27 [-0.72, 0.17]**
Heterogeneity: Tau² = 0.13; Chi² = 14.26, df = 2 (P = 0.0008); I² = 86%								
Test for overall effect: Z = 1.21 (P = 0.23)								
Total (95% CI)			**2024**			**1996**	**100.0%**	**-0.22 [-0.41, -0.02]**
Heterogeneity: Tau² = 0.06; Chi² = 50.08, df = 7 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 2.18 (P = 0.03)								
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%								

Non-response at endpoint



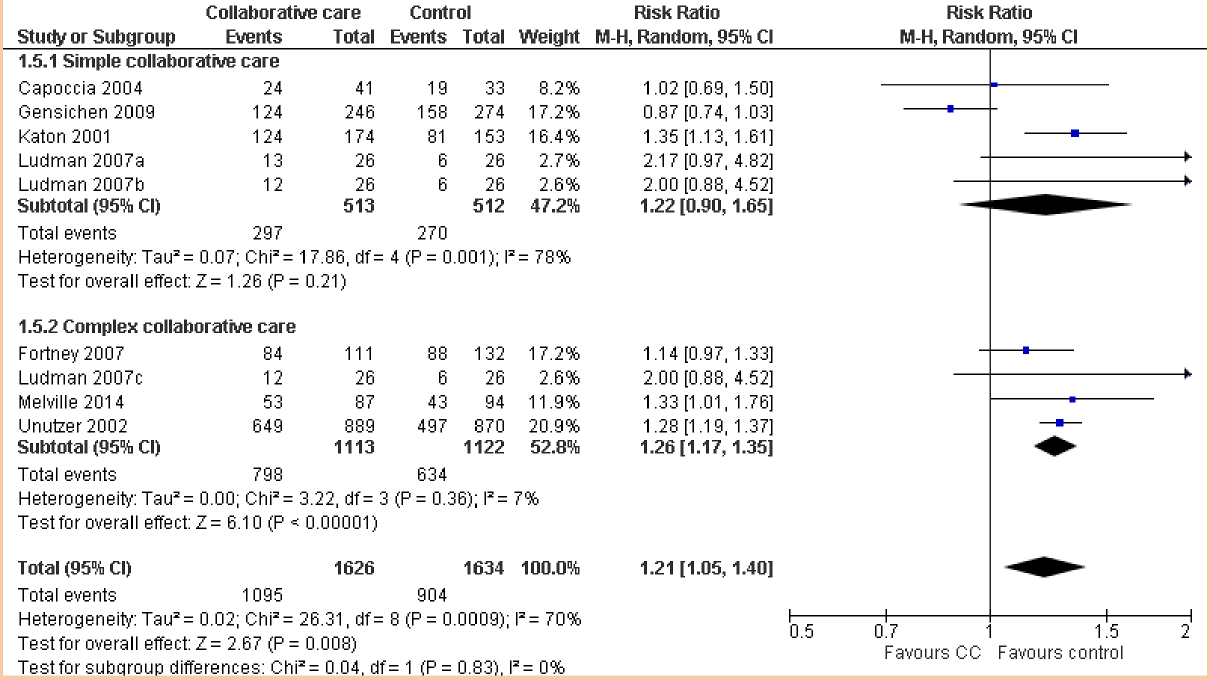
Study or Subgroup	control Events	Total	collaborative care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Simple collaborative care						
Capoccia 2004	11	41	7	33	1.9%	1.26 [0.55, 2.90]
Chen 2015	37	110	82	104	9.7%	0.43 [0.32, 0.56]
Katzelnick 2000	95	203	119	177	14.0%	0.70 [0.58, 0.83]
Menchetti 2013	38	128	39	99	7.2%	0.75 [0.52, 1.08]
Subtotal (95% CI)		**482**		**413**	**32.8%**	**0.66 [0.47, 0.92]**
Total events	181		247			
Heterogeneity: Tau² = 0.08; Chi² = 12.23, df = 3 (P = 0.007); I² = 75%						
Test for overall effect: Z = 2.44 (P = 0.01)						
1.3.2 Complex collaborative care						
Ciechanowski 2004	43	72	20	29	8.7%	0.87 [0.64, 1.18]
Ell 2007	46	82	50	78	10.7%	0.88 [0.68, 1.13]
Fortney 2007	35	58	24	32	9.4%	0.80 [0.60, 1.07]
Huijbregts 2013	35	58	24	32	9.4%	0.80 [0.60, 1.07]
Melville 2014	41	91	61	92	10.1%	0.68 [0.52, 0.89]
Unutzer 2002	491	889	730	870	18.9%	0.66 [0.62, 0.70]
Subtotal (95% CI)		**1250**		**1133**	**67.2%**	**0.75 [0.66, 0.85]**
Total events	691		909			
Heterogeneity: Tau² = 0.01; Chi² = 9.58, df = 5 (P = 0.09); I² = 48%						
Test for overall effect: Z = 4.51 (P < 0.00001)						
Total (95% CI)		**1732**		**1546**	**100.0%**	**0.72 [0.63, 0.81]**
Total events	872		1156			
Heterogeneity: Tau² = 0.02; Chi² = 22.84, df = 9 (P = 0.007); I² = 61%						
Test for overall effect: Z = 5.40 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%						

Antidepressant use at follow-up (6 months)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 Simple collaborative care				
Adler2004	0.214858	0.10043	4.6%	1.24 [1.02, 1.51]
Araya2003	0.840305	0.135092	4.0%	2.32 [1.78, 3.02]
Bruce 2004	0.491478	0.151876	3.6%	1.63 [1.21, 2.20]
Capoccia 2004	0.036129	0.137523	3.9%	1.04 [0.79, 1.36]
Cole 2006	0.131636	0.260175	2.1%	1.14 [0.69, 1.90]
Dietrich 2004	0.076023	0.203622	2.8%	1.08 [0.72, 1.61]
Dwight-Johnson 2010	0.705632	0.178302	3.2%	2.03 [1.43, 2.87]
Finley 2003	0.236389	0.132453	4.0%	1.27 [0.98, 1.64]
Gensichen 2009	0.003058	0.079619	5.0%	1.00 [0.86, 1.17]
Katon1999	0.356675	0.117731	4.3%	1.43 [1.13, 1.80]
Katzelnick 2000	1.322422	0.16144	3.5%	3.75 [2.73, 5.15]
Ludman 2007a	0.81093	0.65372	0.5%	2.25 [0.62, 8.10]
Ludman 2007b	0.730888	0.658605	0.5%	2.08 [0.57, 7.55]
McCusker 2008	0.025318	0.279843	1.9%	1.03 [0.59, 1.77]
Richards 2013	0.178039	0.065411	5.3%	1.19 [1.05, 1.36]
Ross 2008	0.589607	0.394258	1.1%	1.80 [0.83, 3.91]
Simon 2000a	0.559616	0.195843	2.9%	1.75 [1.19, 2.57]
Simon 2004a	0.279331	0.142203	3.8%	1.32 [1.00, 1.75]
Simon 2011	0.288747	0.092299	4.8%	1.33 [1.11, 1.60]
Wells 2000a	0.478951	0.138823	3.9%	1.61 [1.23, 2.12]
Wells 2000b	0.19926	0.145031	3.8%	1.22 [0.92, 1.62]
Subtotal (95% CI)			**69.4%**	**1.45 [1.26, 1.66]**
Heterogeneity: Tau² = 0.07; Chi² = 93.20, df = 20 (P < 0.00001); I² = 79%				
Test for overall effect: Z = 5.34 (P < 0.00001)				
1.4.2 Complex collaborative care				
Ciechanowski 2004	0.318454	0.622596	0.5%	1.38 [0.41, 4.66]
Ell 2007	0.280843	0.141742	3.8%	1.32 [1.00, 1.75]
Fortney 2007	0.090947	0.104424	4.5%	1.10 [0.89, 1.34]
Hedrick 2003	0.200564	0.172953	3.3%	1.22 [0.87, 1.72]
Katon1996a	0.541551	0.211009	2.7%	1.72 [1.14, 2.60]
Katon1996b	0.092373	0.20879	2.7%	1.10 [0.73, 1.65]
Ludman 2007c	0.730888	0.658605	0.5%	2.08 [0.57, 7.55]
Melville 2014	0.2546	0.1785	3.2%	1.29 [0.91, 1.83]
Simon 2004b	0.201022	0.145435	3.8%	1.22 [0.92, 1.63]
Unutzer 2002	0.276326	0.041837	5.6%	1.32 [1.21, 1.43]
Subtotal (95% CI)			**30.6%**	**1.29 [1.20, 1.38]**
Heterogeneity: Tau² = 0.00; Chi² = 5.98, df = 9 (P = 0.74); I² = 0%				
Test for overall effect: Z = 7.48 (P < 0.00001)				
Total (95% CI)			**100.0%**	**1.39 [1.26, 1.52]**
Heterogeneity: Tau² = 0.04; Chi² = 100.08, df = 30 (P < 0.00001); I² = 70%				
Test for overall effect: Z = 6.92 (P < 0.00001)				
Test for subgroup differences: Chi² = 2.30, df = 1 (P = 0.13), I² = 56.6%				

Antidepressant use at endpoint



Study or Subgroup	Collaborative care Events	Collaborative care Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Simple collaborative care						
Capoccia 2004	24	41	19	33	8.2%	1.02 [0.69, 1.50]
Gensichen 2009	124	246	158	274	17.2%	0.87 [0.74, 1.03]
Katon 2001	124	174	81	153	16.4%	1.35 [1.13, 1.61]
Ludman 2007a	13	26	6	26	2.7%	2.17 [0.97, 4.82]
Ludman 2007b	12	26	6	26	2.6%	2.00 [0.88, 4.52]
Subtotal (95% CI)		**513**		**512**	**47.2%**	**1.22 [0.90, 1.65]**
Total events	297		270			

Heterogeneity: Tau² = 0.07; Chi² = 17.86, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 1.26 (P = 0.21)

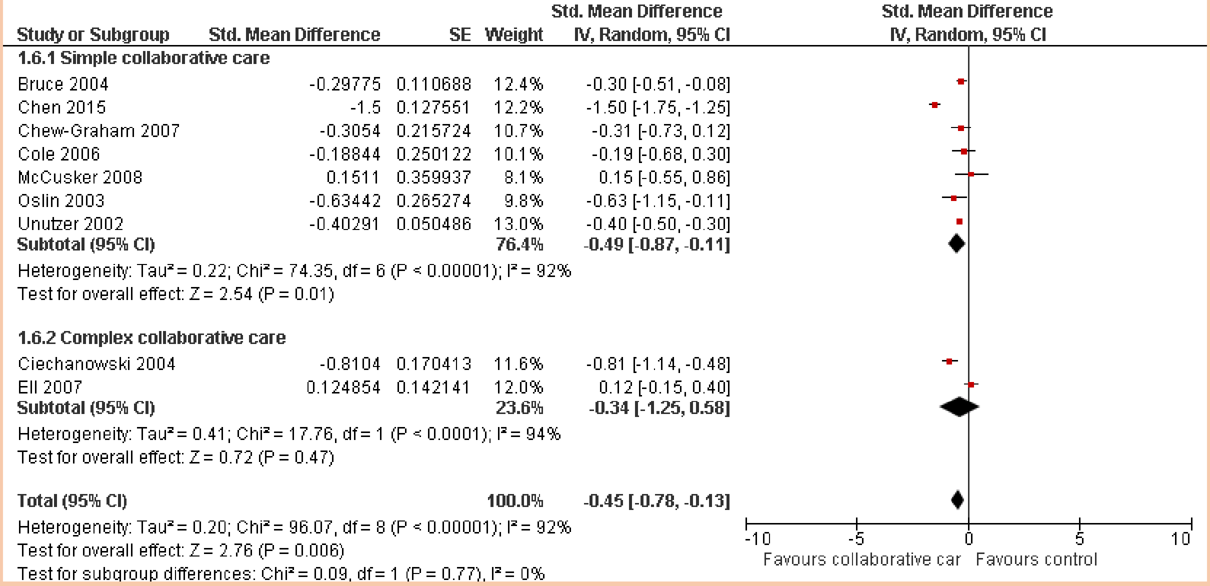
Study or Subgroup	Collaborative care Events	Collaborative care Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.2 Complex collaborative care						
Fortney 2007	84	111	88	132	17.2%	1.14 [0.97, 1.33]
Ludman 2007c	12	26	6	26	2.6%	2.00 [0.88, 4.52]
Melville 2014	53	87	43	94	11.9%	1.33 [1.01, 1.76]
Unutzer 2002	649	889	497	870	20.9%	1.28 [1.19, 1.37]
Subtotal (95% CI)		**1113**		**1122**	**52.8%**	**1.26 [1.17, 1.35]**
Total events	798		634			

Heterogeneity: Tau² = 0.00; Chi² = 3.22, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 6.10 (P < 0.00001)

Study or Subgroup	Collaborative care Events	Collaborative care Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**1626**		**1634**	**100.0%**	**1.21 [1.05, 1.40]**
Total events	1095		904			

Heterogeneity: Tau² = 0.02; Chi² = 26.31, df = 8 (P = 0.0009); I² = 70%
Test for overall effect: Z = 2.67 (P = 0.008)
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%

Sub-analysis: depression symptoms at follow-up (6months) in older people



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 Simple collaborative care				
Bruce 2004	-0.29775	0.110688	12.4%	-0.30 [-0.51, -0.08]
Chen 2015	-1.5	0.127551	12.2%	-1.50 [-1.75, -1.25]
Chew-Graham 2007	-0.3054	0.215724	10.7%	-0.31 [-0.73, 0.12]
Cole 2006	-0.18844	0.250122	10.1%	-0.19 [-0.68, 0.30]
McCusker 2008	0.1511	0.359937	8.1%	0.15 [-0.55, 0.86]
Oslin 2003	-0.63442	0.265274	9.8%	-0.63 [-1.15, -0.11]
Unutzer 2002	-0.40291	0.050486	13.0%	-0.40 [-0.50, -0.30]
Subtotal (95% CI)			**76.4%**	**-0.49 [-0.87, -0.11]**

Heterogeneity: Tau² = 0.22; Chi² = 74.35, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.54 (P = 0.01)

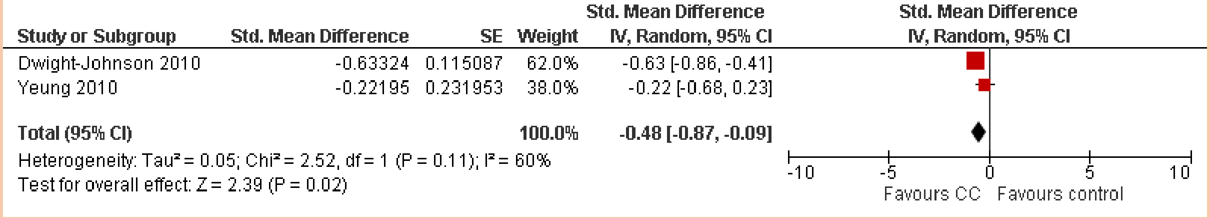
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.2 Complex collaborative care				
Ciechanowski 2004	-0.8104	0.170413	11.6%	-0.81 [-1.14, -0.48]
Ell 2007	0.124854	0.142141	12.0%	0.12 [-0.15, 0.40]
Subtotal (95% CI)			**23.6%**	**-0.34 [-1.25, 0.58]**

Heterogeneity: Tau² = 0.41; Chi² = 17.76, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 0.72 (P = 0.47)

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Total (95% CI)			**100.0%**	**-0.45 [-0.78, -0.13]**

Heterogeneity: Tau² = 0.20; Chi² = 96.07, df = 8 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.76 (P = 0.006)
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%

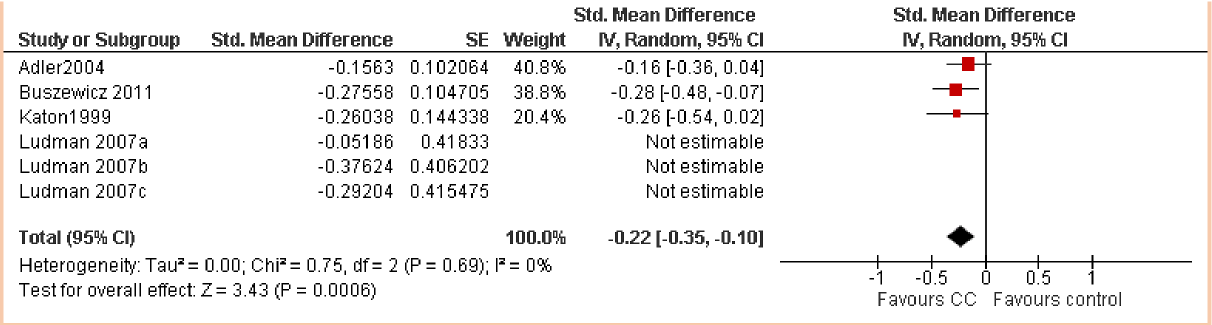
Sub-analysis: depression symptoms at follow-up (6 months) in BME individuals



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Dwight-Johnson 2010	-0.63324	0.115087	62.0%	-0.63 [-0.86, -0.41]
Yeung 2010	-0.22195	0.231953	38.0%	-0.22 [-0.68, 0.23]
Total (95% CI)			**100.0%**	**-0.48 [-0.87, -0.09]**

Heterogeneity: Tau² = 0.05; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 2.39 (P = 0.02)

Sub-analysis: depression symptoms at follow-up (6 months) in chronic depression individuals

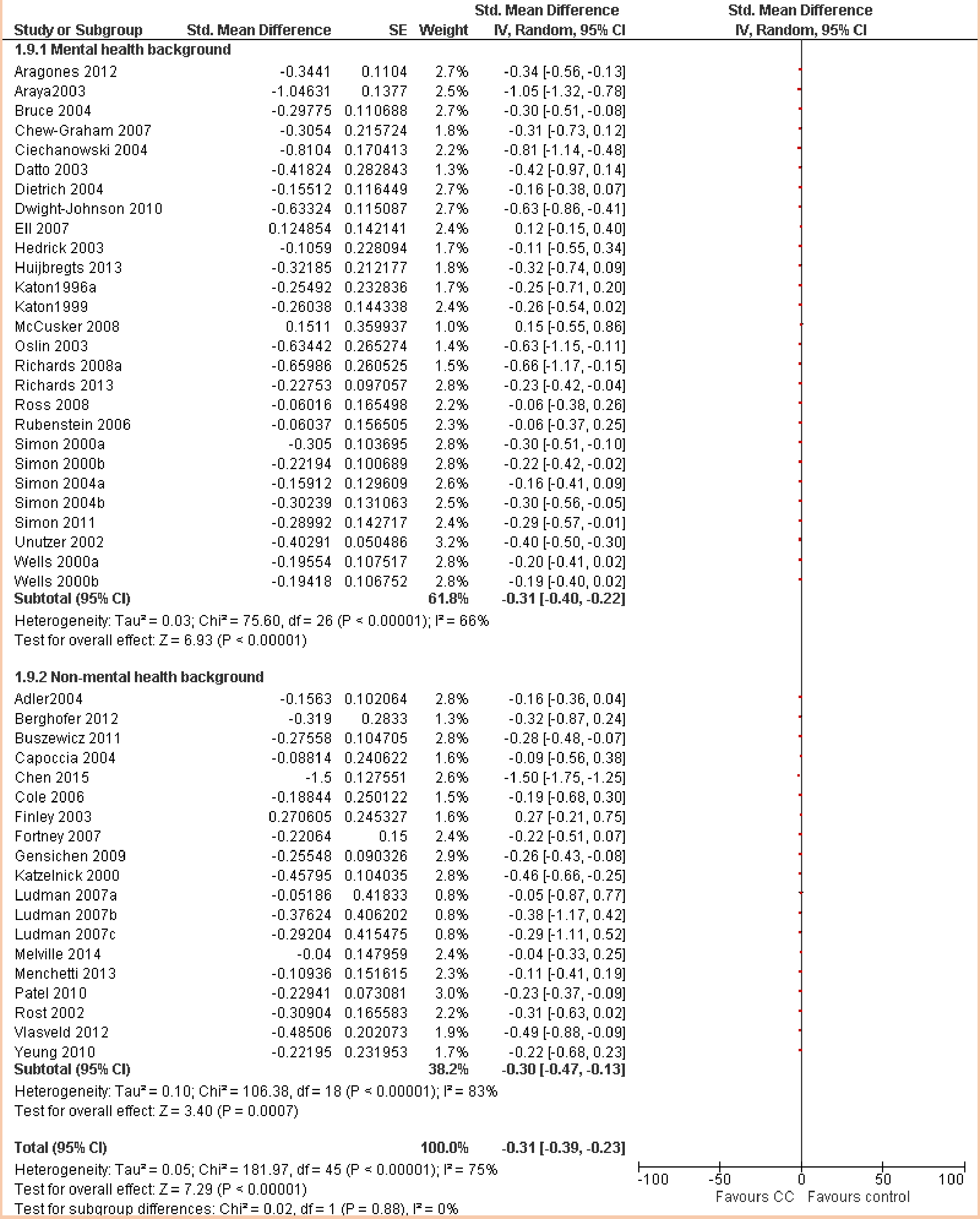


Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Adler2004	-0.1563	0.102064	40.8%	-0.16 [-0.36, 0.04]
Buszewicz 2011	-0.27558	0.104705	38.8%	-0.28 [-0.48, -0.07]
Katon1999	-0.26038	0.144338	20.4%	-0.26 [-0.54, 0.02]
Ludman 2007a	-0.05186	0.41833		Not estimable
Ludman 2007b	-0.37624	0.406202		Not estimable
Ludman 2007c	-0.29204	0.415475		Not estimable
Total (95% CI)			**100.0%**	**-0.22 [-0.35, -0.10]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.75$, df = 2 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 3.43 (P = 0.0006)

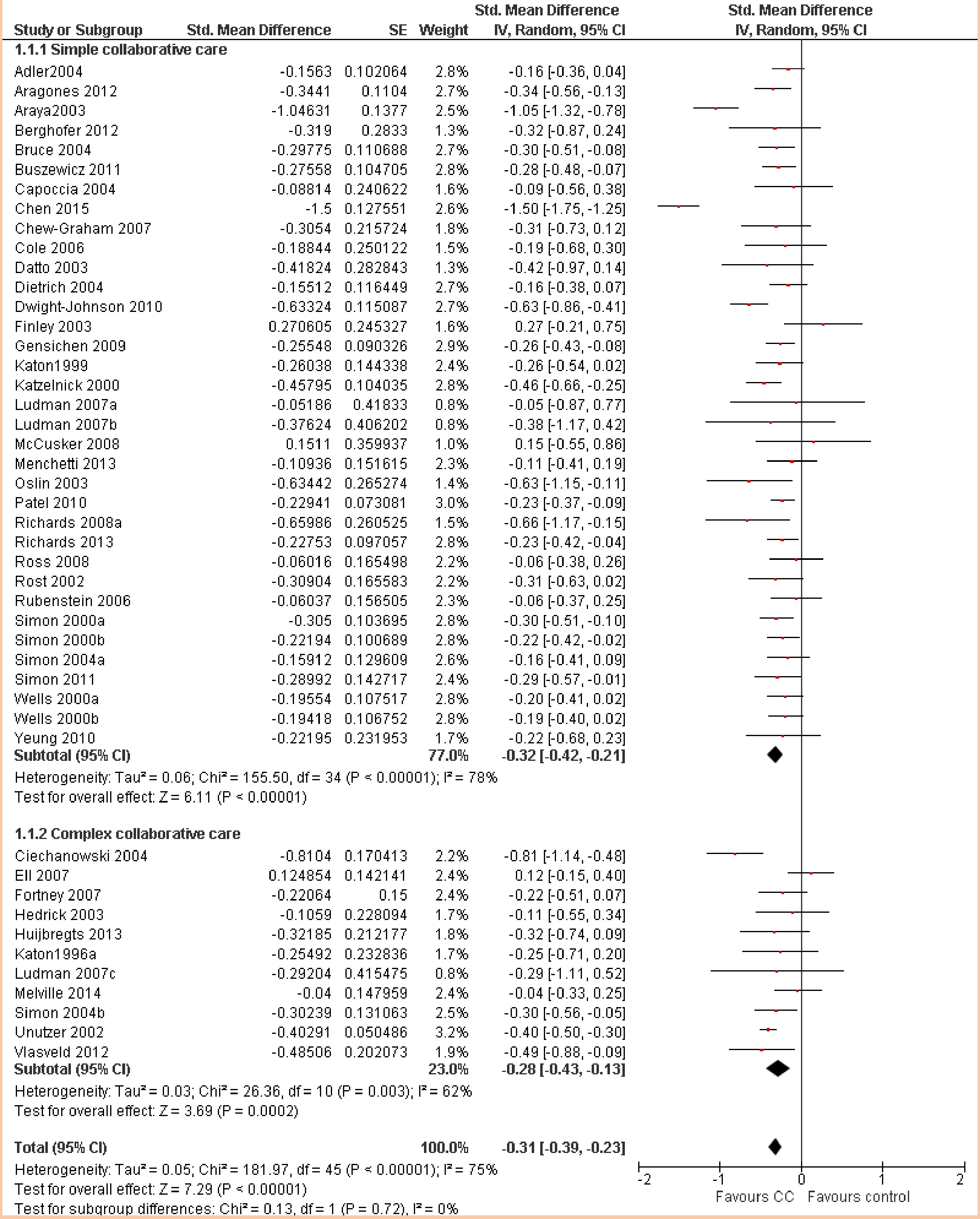
Std. Mean Difference
IV, Random, 95% CI
-1
-0.5
0
0.5
1
Favours CC
Favours control

Sub-analysis: depression symptoms at endpoint by case-manager background



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.9.1 Mental health background				
Aragones 2012	-0.3441	0.1104	2.7%	-0.34 [-0.56, -0.13]
Araya2003	-1.04631	0.1377	2.5%	-1.05 [-1.32, -0.78]
Bruce 2004	-0.29775	0.110688	2.7%	-0.30 [-0.51, -0.08]
Chew-Graham 2007	-0.3054	0.215724	1.8%	-0.31 [-0.73, 0.12]
Ciechanowski 2004	-0.8104	0.170413	2.2%	-0.81 [-1.14, -0.48]
Datto 2003	-0.41824	0.282843	1.3%	-0.42 [-0.97, 0.14]
Dietrich 2004	-0.15512	0.116449	2.7%	-0.16 [-0.38, 0.07]
Dwight-Johnson 2010	-0.63324	0.115087	2.7%	-0.63 [-0.86, -0.41]
Ell 2007	0.124854	0.142141	2.4%	0.12 [-0.15, 0.40]
Hedrick 2003	-0.1059	0.228094	1.7%	-0.11 [-0.55, 0.34]
Huijbregts 2013	-0.32185	0.212177	1.8%	-0.32 [-0.74, 0.09]
Katon1996a	-0.25492	0.232836	1.7%	-0.25 [-0.71, 0.20]
Katon1999	-0.26038	0.144338	2.4%	-0.26 [-0.54, 0.02]
McCusker 2008	0.1511	0.359937	1.0%	0.15 [-0.55, 0.86]
Oslin 2003	-0.63442	0.265274	1.4%	-0.63 [-1.15, -0.11]
Richards 2008a	-0.65986	0.260525	1.5%	-0.66 [-1.17, -0.15]
Richards 2013	-0.22753	0.097057	2.8%	-0.23 [-0.42, -0.04]
Ross 2008	-0.06016	0.165498	2.2%	-0.06 [-0.38, 0.26]
Rubenstein 2006	-0.06037	0.156505	2.3%	-0.06 [-0.37, 0.25]
Simon 2000a	-0.305	0.103695	2.8%	-0.30 [-0.51, -0.10]
Simon 2000b	-0.22194	0.100689	2.8%	-0.22 [-0.42, -0.02]
Simon 2004a	-0.15912	0.129609	2.6%	-0.16 [-0.41, 0.09]
Simon 2004b	-0.30239	0.131063	2.5%	-0.30 [-0.56, -0.05]
Simon 2011	-0.28992	0.142717	2.4%	-0.29 [-0.57, -0.01]
Unutzer 2002	-0.40291	0.050486	3.2%	-0.40 [-0.50, -0.30]
Wells 2000a	-0.19554	0.107517	2.8%	-0.20 [-0.41, 0.02]
Wells 2000b	-0.19418	0.106752	2.8%	-0.19 [-0.40, 0.02]
Subtotal (95% CI)			**61.8%**	**-0.31 [-0.40, -0.22]**
Heterogeneity: Tau² = 0.03; Chi² = 75.60, df = 26 (P < 0.00001); I² = 66%				
Test for overall effect: Z = 6.93 (P < 0.00001)				
1.9.2 Non-mental health background				
Adler2004	-0.1563	0.102064	2.8%	-0.16 [-0.36, 0.04]
Berghofer 2012	-0.319	0.2833	1.3%	-0.32 [-0.87, 0.24]
Buszewicz 2011	-0.27558	0.104705	2.8%	-0.28 [-0.48, -0.07]
Capoccia 2004	-0.08814	0.240622	1.6%	-0.09 [-0.56, 0.38]
Chen 2015	-1.5	0.127551	2.6%	-1.50 [-1.75, -1.25]
Cole 2006	-0.18844	0.250122	1.5%	-0.19 [-0.68, 0.30]
Finley 2003	0.270605	0.245327	1.6%	0.27 [-0.21, 0.75]
Fortney 2007	-0.22064	0.15	2.4%	-0.22 [-0.51, 0.07]
Gensichen 2009	-0.25548	0.090326	2.9%	-0.26 [-0.43, -0.08]
Katzelnick 2000	-0.45795	0.104035	2.8%	-0.46 [-0.66, -0.25]
Ludman 2007a	-0.05186	0.41833	0.8%	-0.05 [-0.87, 0.77]
Ludman 2007b	-0.37624	0.406202	0.8%	-0.38 [-1.17, 0.42]
Ludman 2007c	-0.29204	0.415475	0.8%	-0.29 [-1.11, 0.52]
Melville 2014	-0.04	0.147959	2.4%	-0.04 [-0.33, 0.25]
Menchetti 2013	-0.10936	0.151615	2.3%	-0.11 [-0.41, 0.19]
Patel 2010	-0.22941	0.073081	3.0%	-0.23 [-0.37, -0.09]
Rost 2002	-0.30904	0.165583	2.2%	-0.31 [-0.63, 0.02]
Vlasveld 2012	-0.48506	0.202073	1.9%	-0.49 [-0.88, -0.09]
Yeung 2010	-0.22195	0.231953	1.7%	-0.22 [-0.68, 0.23]
Subtotal (95% CI)			**38.2%**	**-0.30 [-0.47, -0.13]**
Heterogeneity: Tau² = 0.10; Chi² = 106.38, df = 18 (P < 0.00001); I² = 83%				
Test for overall effect: Z = 3.40 (P = 0.0007)				
Total (95% CI)			**100.0%**	**-0.31 [-0.39, -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 181.97, df = 45 (P < 0.00001); I² = 75%				
Test for overall effect: Z = 7.29 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%				

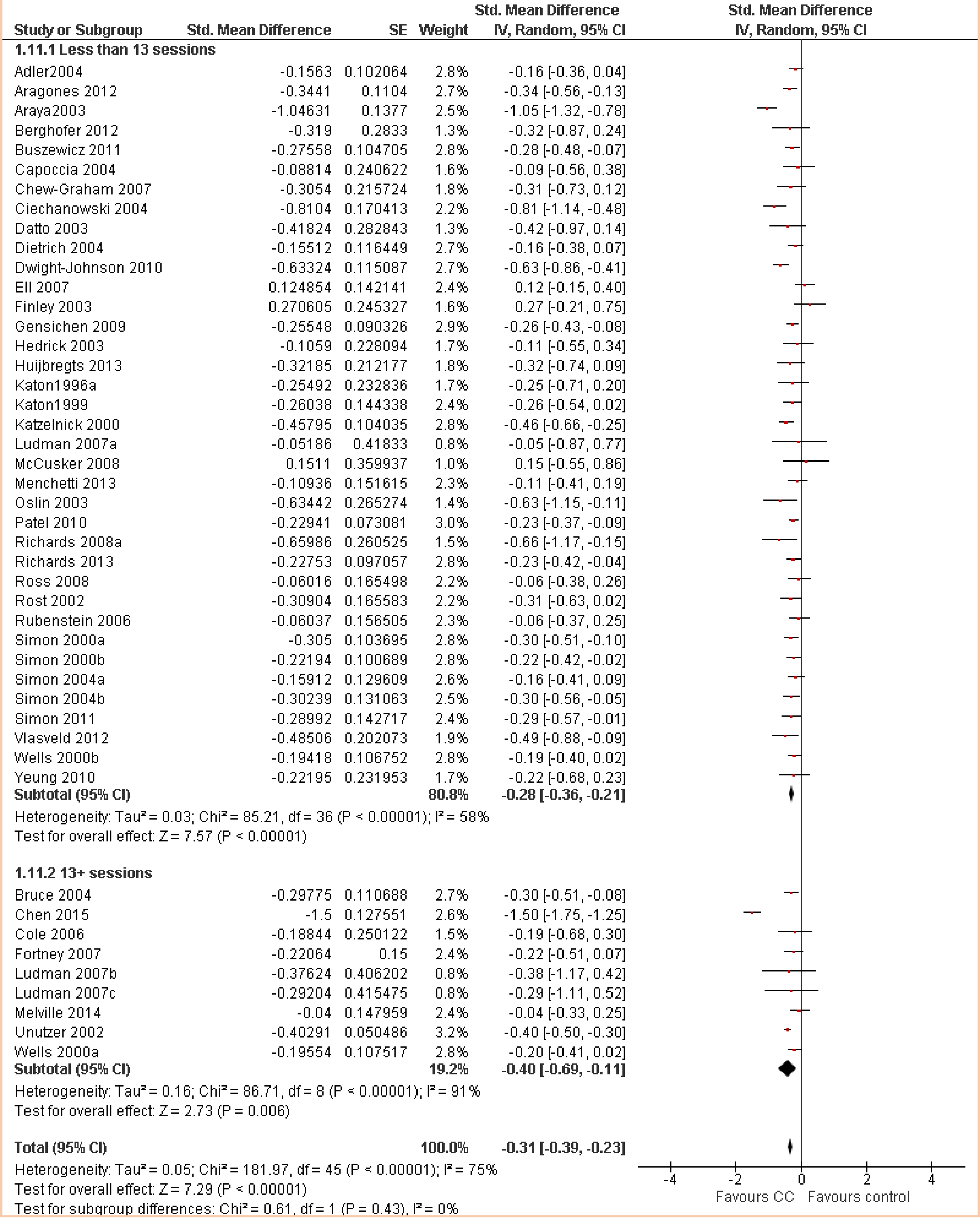
Sub-analysis: depression symptoms at endpoint by psychological intervention



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Simple collaborative care				
Adler2004	-0.1563	0.102064	2.8%	-0.16 [-0.36, 0.04]
Aragones 2012	-0.3441	0.1104	2.7%	-0.34 [-0.56, -0.13]
Araya2003	-1.04631	0.1377	2.5%	-1.05 [-1.32, -0.78]
Berghofer 2012	-0.319	0.2833	1.3%	-0.32 [-0.87, 0.24]
Bruce 2004	-0.29775	0.110688	2.7%	-0.30 [-0.51, -0.08]
Buszewicz 2011	-0.27558	0.104705	2.8%	-0.28 [-0.48, -0.07]
Capoccia 2004	-0.08814	0.240622	1.6%	-0.09 [-0.56, 0.38]
Chen 2015	-1.5	0.127551	2.6%	-1.50 [-1.75, -1.25]
Chew-Graham 2007	-0.3054	0.215724	1.8%	-0.31 [-0.73, 0.12]
Cole 2006	-0.18844	0.250122	1.5%	-0.19 [-0.68, 0.30]
Datto 2003	-0.41824	0.282843	1.3%	-0.42 [-0.97, 0.14]
Dietrich 2004	-0.15512	0.116449	2.7%	-0.16 [-0.38, 0.07]
Dwight-Johnson 2010	-0.63324	0.115087	2.7%	-0.63 [-0.86, -0.41]
Finley 2003	0.270605	0.245327	1.6%	0.27 [-0.21, 0.75]
Gensichen 2009	-0.25548	0.090326	2.9%	-0.26 [-0.43, -0.08]
Katon1999	-0.26038	0.144338	2.4%	-0.26 [-0.54, 0.02]
Katzelnick 2000	-0.45795	0.104035	2.8%	-0.46 [-0.66, -0.25]
Ludman 2007a	-0.05186	0.41833	0.8%	-0.05 [-0.87, 0.77]
Ludman 2007b	-0.37624	0.406202	0.8%	-0.38 [-1.17, 0.42]
McCusker 2008	0.1511	0.359937	1.0%	0.15 [-0.55, 0.86]
Menchetti 2013	-0.10936	0.151615	2.3%	-0.11 [-0.41, 0.19]
Oslin 2003	-0.63442	0.265274	1.4%	-0.63 [-1.15, -0.11]
Patel 2010	-0.22941	0.073081	3.0%	-0.23 [-0.37, -0.09]
Richards 2008a	-0.65986	0.260525	1.5%	-0.66 [-1.17, -0.15]
Richards 2013	-0.22753	0.097057	2.8%	-0.23 [-0.42, -0.04]
Ross 2008	-0.06016	0.165498	2.2%	-0.06 [-0.38, 0.26]
Rost 2002	-0.30904	0.165583	2.2%	-0.31 [-0.63, 0.02]
Rubenstein 2006	-0.06037	0.156505	2.3%	-0.06 [-0.37, 0.25]
Simon 2000a	-0.305	0.103695	2.8%	-0.30 [-0.51, -0.10]
Simon 2000b	-0.22194	0.100689	2.8%	-0.22 [-0.42, -0.02]
Simon 2004a	-0.15912	0.129609	2.6%	-0.16 [-0.41, 0.09]
Simon 2011	-0.28992	0.142717	2.4%	-0.29 [-0.57, -0.01]
Wells 2000a	-0.19554	0.107517	2.8%	-0.20 [-0.41, 0.02]
Wells 2000b	-0.19418	0.106752	2.8%	-0.19 [-0.40, 0.02]
Yeung 2010	-0.22195	0.231953	1.7%	-0.22 [-0.68, 0.23]
Subtotal (95% CI)			**77.0%**	**-0.32 [-0.42, -0.21]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 155.50, df = 34 ($P < 0.00001$); I^2 = 78%				
Test for overall effect: Z = 6.11 ($P < 0.00001$)				
1.1.2 Complex collaborative care				
Ciechanowski 2004	-0.8104	0.170413	2.2%	-0.81 [-1.14, -0.48]
Ell 2007	0.124854	0.142141	2.4%	0.12 [-0.15, 0.40]
Fortney 2007	-0.22064	0.15	2.4%	-0.22 [-0.51, 0.07]
Hedrick 2003	-0.1059	0.228094	1.7%	-0.11 [-0.55, 0.34]
Huijbregts 2013	-0.32185	0.212177	1.8%	-0.32 [-0.74, 0.09]
Katon1996a	-0.25492	0.232836	1.7%	-0.25 [-0.71, 0.20]
Ludman 2007c	-0.29204	0.415475	0.8%	-0.29 [-1.11, 0.52]
Melville 2014	-0.04	0.147959	2.4%	-0.04 [-0.33, 0.25]
Simon 2004b	-0.30239	0.131063	2.5%	-0.30 [-0.56, -0.05]
Unutzer 2002	-0.40291	0.050486	3.2%	-0.40 [-0.50, -0.30]
Vlasveld 2012	-0.48506	0.202073	1.9%	-0.49 [-0.88, -0.09]
Subtotal (95% CI)			**23.0%**	**-0.28 [-0.43, -0.13]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 26.36, df = 10 ($P = 0.003$); I^2 = 62%				
Test for overall effect: Z = 3.69 ($P = 0.0002$)				
Total (95% CI)			**100.0%**	**-0.31 [-0.39, -0.23]**

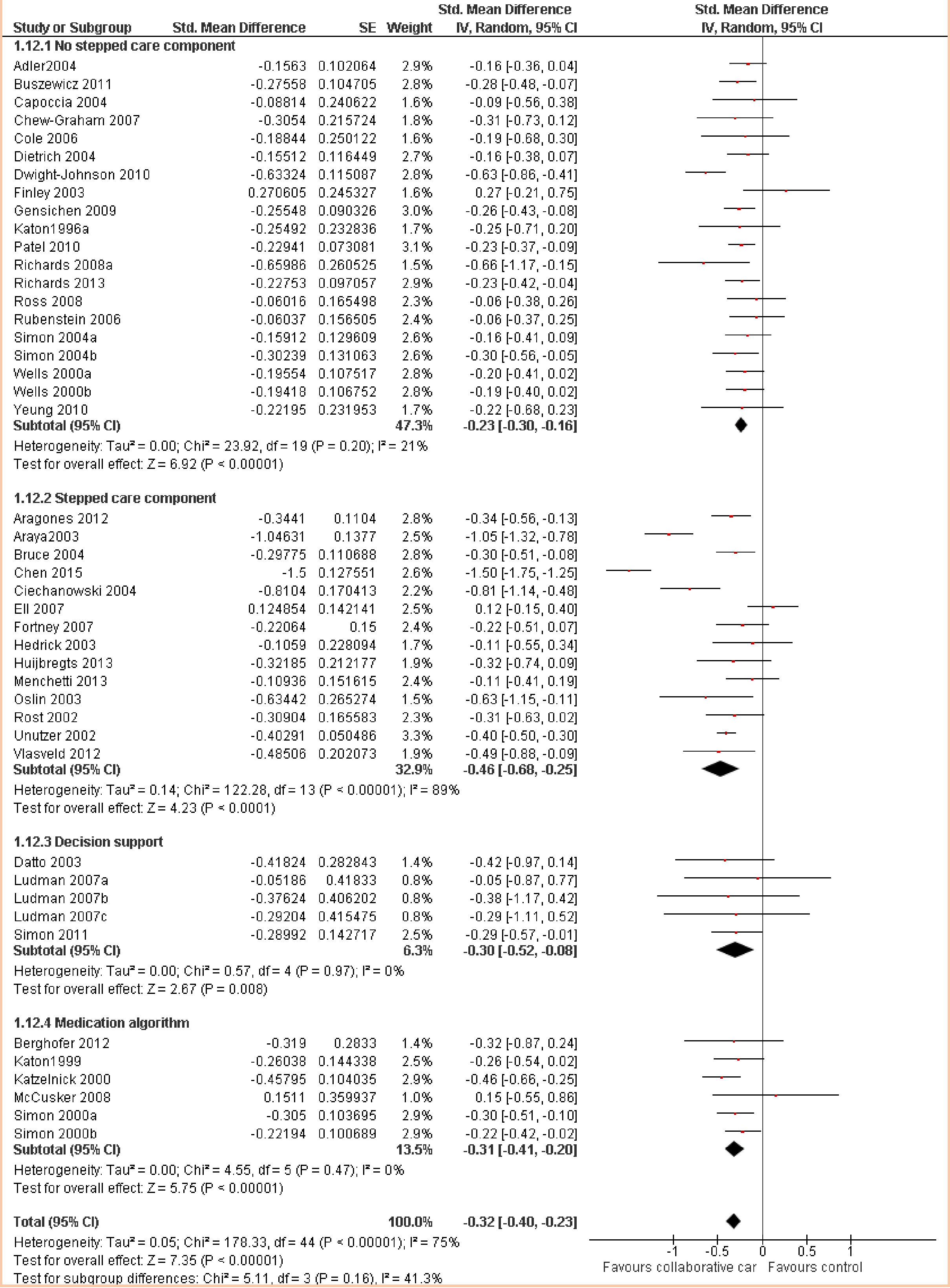
Heterogeneity: Tau^2 = 0.05; Chi^2 = 181.97, df = 45 ($P < 0.00001$); I^2 = 75%
Test for overall effect: Z = 7.29 ($P < 0.00001$)
Test for subgroup differences: Chi^2 = 0.13, df = 1 ($P = 0.72$), I^2 = 0%

Sub-analysis: depression symptoms at endpoint by number of contacts



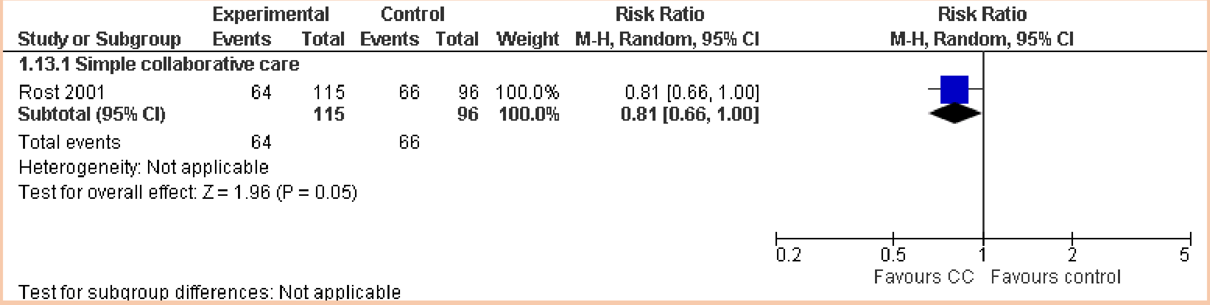
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Less than 13 sessions				
Adler2004	-0.1563	0.102064	2.8%	-0.16 [-0.36, 0.04]
Aragones 2012	-0.3441	0.1104	2.7%	-0.34 [-0.56, -0.13]
Araya2003	-1.04631	0.1377	2.5%	-1.05 [-1.32, -0.78]
Berghofer 2012	-0.319	0.2833	1.3%	-0.32 [-0.87, 0.24]
Buszewicz 2011	-0.27558	0.104705	2.8%	-0.28 [-0.48, -0.07]
Capoccia 2004	-0.08814	0.240622	1.6%	-0.09 [-0.56, 0.38]
Chew-Graham 2007	-0.3054	0.215724	1.8%	-0.31 [-0.73, 0.12]
Ciechanowski 2004	-0.8104	0.170413	2.2%	-0.81 [-1.14, -0.48]
Datto 2003	-0.41824	0.282843	1.3%	-0.42 [-0.97, 0.14]
Dietrich 2004	-0.15512	0.116449	2.7%	-0.16 [-0.38, 0.07]
Dwight-Johnson 2010	-0.63324	0.115087	2.7%	-0.63 [-0.86, -0.41]
Ell 2007	0.124854	0.142141	2.4%	0.12 [-0.15, 0.40]
Finley 2003	0.270605	0.245327	1.6%	0.27 [-0.21, 0.75]
Gensichen 2009	-0.25548	0.090326	2.9%	-0.26 [-0.43, -0.08]
Hedrick 2003	-0.1059	0.228094	1.7%	-0.11 [-0.55, 0.34]
Huijbregts 2013	-0.32185	0.212177	1.8%	-0.32 [-0.74, 0.09]
Katon1996a	-0.25492	0.232836	1.7%	-0.25 [-0.71, 0.20]
Katon1999	-0.26038	0.144338	2.4%	-0.26 [-0.54, 0.02]
Katzelnick 2000	-0.45795	0.104035	2.8%	-0.46 [-0.66, -0.25]
Ludman 2007a	-0.05186	0.41833	0.8%	-0.05 [-0.87, 0.77]
McCusker 2008	0.1511	0.359937	1.0%	0.15 [-0.55, 0.86]
Menchetti 2013	-0.10936	0.151615	2.3%	-0.11 [-0.41, 0.19]
Oslin 2003	-0.63442	0.265274	1.4%	-0.63 [-1.15, -0.11]
Patel 2010	-0.22941	0.073081	3.0%	-0.23 [-0.37, -0.09]
Richards 2008a	-0.65986	0.260525	1.5%	-0.66 [-1.17, -0.15]
Richards 2013	-0.22753	0.097057	2.8%	-0.23 [-0.42, -0.04]
Ross 2008	-0.06016	0.165498	2.2%	-0.06 [-0.38, 0.26]
Rost 2002	-0.30904	0.165583	2.2%	-0.31 [-0.63, 0.02]
Rubenstein 2006	-0.06037	0.156505	2.3%	-0.06 [-0.37, 0.25]
Simon 2000a	-0.305	0.103695	2.8%	-0.30 [-0.51, -0.10]
Simon 2000b	-0.22194	0.100689	2.8%	-0.22 [-0.42, -0.02]
Simon 2004a	-0.15912	0.129609	2.6%	-0.16 [-0.41, 0.09]
Simon 2004b	-0.30239	0.131063	2.5%	-0.30 [-0.56, -0.05]
Simon 2011	-0.28992	0.142717	2.4%	-0.29 [-0.57, -0.01]
Vlasveld 2012	-0.48506	0.202073	1.9%	-0.49 [-0.88, -0.09]
Wells 2000b	-0.19418	0.106752	2.8%	-0.19 [-0.40, 0.02]
Yeung 2010	-0.22195	0.231953	1.7%	-0.22 [-0.68, 0.23]
Subtotal (95% CI)			**80.8%**	**-0.28 [-0.36, -0.21]**
Heterogeneity: Tau² = 0.03; Chi² = 85.21, df = 36 (P < 0.00001); I² = 58%				
Test for overall effect: Z = 7.57 (P < 0.00001)				
1.11.2 13+ sessions				
Bruce 2004	-0.29775	0.110688	2.7%	-0.30 [-0.51, -0.08]
Chen 2015	-1.5	0.127551	2.6%	-1.50 [-1.75, -1.25]
Cole 2006	-0.18844	0.250122	1.5%	-0.19 [-0.68, 0.30]
Fortney 2007	-0.22064	0.15	2.4%	-0.22 [-0.51, 0.07]
Ludman 2007b	-0.37624	0.406202	0.8%	-0.38 [-1.17, 0.42]
Ludman 2007c	-0.29204	0.415475	0.8%	-0.29 [-1.11, 0.52]
Melville 2014	-0.04	0.147959	2.4%	-0.04 [-0.33, 0.25]
Unutzer 2002	-0.40291	0.050486	3.2%	-0.40 [-0.50, -0.30]
Wells 2000a	-0.19554	0.107517	2.8%	-0.20 [-0.41, 0.02]
Subtotal (95% CI)			**19.2%**	**-0.40 [-0.69, -0.11]**
Heterogeneity: Tau² = 0.16; Chi² = 86.71, df = 8 (P < 0.00001); I² = 91%				
Test for overall effect: Z = 2.73 (P = 0.006)				
Total (95% CI)			**100.0%**	**-0.31 [-0.39, -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 181.97, df = 45 (P < 0.00001); I² = 75%				
Test for overall effect: Z = 7.29 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.43), I² = 0%				

Sub-analysis: depression symptoms at endpoint by stepped care algorithm



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 No stepped care component				
Adler2004	-0.1563	0.102064	2.9%	-0.16 [-0.36, 0.04]
Buszewicz 2011	-0.27558	0.104705	2.8%	-0.28 [-0.48, -0.07]
Capoccia 2004	-0.08814	0.240622	1.6%	-0.09 [-0.56, 0.38]
Chew-Graham 2007	-0.3054	0.215724	1.8%	-0.31 [-0.73, 0.12]
Cole 2006	-0.18844	0.250122	1.6%	-0.19 [-0.68, 0.30]
Dietrich 2004	-0.15512	0.116449	2.7%	-0.16 [-0.38, 0.07]
Dwight-Johnson 2010	-0.63324	0.115087	2.8%	-0.63 [-0.86, -0.41]
Finley 2003	0.270605	0.245327	1.6%	0.27 [-0.21, 0.75]
Gensichen 2009	-0.25548	0.090326	3.0%	-0.26 [-0.43, -0.08]
Katon1996a	-0.25492	0.232836	1.7%	-0.25 [-0.71, 0.20]
Patel 2010	-0.22941	0.073081	3.1%	-0.23 [-0.37, -0.09]
Richards 2008a	-0.65986	0.260525	1.5%	-0.66 [-1.17, -0.15]
Richards 2013	-0.22753	0.097057	2.9%	-0.23 [-0.42, -0.04]
Ross 2008	-0.06016	0.165498	2.3%	-0.06 [-0.38, 0.26]
Rubenstein 2006	-0.06037	0.156505	2.4%	-0.06 [-0.37, 0.25]
Simon 2004a	-0.15912	0.129609	2.6%	-0.16 [-0.41, 0.09]
Simon 2004b	-0.30239	0.131063	2.6%	-0.30 [-0.56, -0.05]
Wells 2000a	-0.19554	0.107517	2.8%	-0.20 [-0.41, 0.02]
Wells 2000b	-0.19418	0.106752	2.8%	-0.19 [-0.40, 0.02]
Yeung 2010	-0.22195	0.231953	1.7%	-0.22 [-0.68, 0.23]
Subtotal (95% CI)			**47.3%**	**-0.23 [-0.30, -0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 23.92, df = 19 (P = 0.20); I² = 21%				
Test for overall effect: Z = 6.92 (P < 0.00001)				
1.12.2 Stepped care component				
Aragones 2012	-0.3441	0.1104	2.8%	-0.34 [-0.56, -0.13]
Araya2003	-1.04631	0.1377	2.5%	-1.05 [-1.32, -0.78]
Bruce 2004	-0.29775	0.110688	2.8%	-0.30 [-0.51, -0.08]
Chen 2015	-1.5	0.127551	2.6%	-1.50 [-1.75, -1.25]
Ciechanowski 2004	-0.8104	0.170413	2.2%	-0.81 [-1.14, -0.48]
Ell 2007	0.124854	0.142141	2.5%	0.12 [-0.15, 0.40]
Fortney 2007	-0.22064	0.15	2.4%	-0.22 [-0.51, 0.07]
Hedrick 2003	-0.1059	0.228094	1.7%	-0.11 [-0.55, 0.34]
Huijbregts 2013	-0.32185	0.212177	1.9%	-0.32 [-0.74, 0.09]
Menchetti 2013	-0.10936	0.151615	2.4%	-0.11 [-0.41, 0.19]
Oslin 2003	-0.63442	0.265274	1.5%	-0.63 [-1.15, -0.11]
Rost 2002	-0.30904	0.165583	2.3%	-0.31 [-0.63, 0.02]
Unutzer 2002	-0.40291	0.050486	3.3%	-0.40 [-0.50, -0.30]
Vlasveld 2012	-0.48506	0.202073	1.9%	-0.49 [-0.88, -0.09]
Subtotal (95% CI)			**32.9%**	**-0.46 [-0.68, -0.25]**
Heterogeneity: Tau² = 0.14; Chi² = 122.28, df = 13 (P < 0.00001); I² = 89%				
Test for overall effect: Z = 4.23 (P < 0.0001)				
1.12.3 Decision support				
Datto 2003	-0.41824	0.282843	1.4%	-0.42 [-0.97, 0.14]
Ludman 2007a	-0.05186	0.41833	0.8%	-0.05 [-0.87, 0.77]
Ludman 2007b	-0.37624	0.406202	0.8%	-0.38 [-1.17, 0.42]
Ludman 2007c	-0.29204	0.415475	0.8%	-0.29 [-1.11, 0.52]
Simon 2011	-0.28992	0.142717	2.5%	-0.29 [-0.57, -0.01]
Subtotal (95% CI)			**6.3%**	**-0.30 [-0.52, -0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 4 (P = 0.97); I² = 0%				
Test for overall effect: Z = 2.67 (P = 0.008)				
1.12.4 Medication algorithm				
Berghofer 2012	-0.319	0.2833	1.4%	-0.32 [-0.87, 0.24]
Katon1999	-0.26038	0.144338	2.5%	-0.26 [-0.54, 0.02]
Katzelnick 2000	-0.45795	0.104035	2.9%	-0.46 [-0.66, -0.25]
McCusker 2008	0.1511	0.359937	1.0%	0.15 [-0.55, 0.86]
Simon 2000a	-0.305	0.103695	2.9%	-0.30 [-0.51, -0.10]
Simon 2000b	-0.22194	0.100689	2.9%	-0.22 [-0.42, -0.02]
Subtotal (95% CI)			**13.5%**	**-0.31 [-0.41, -0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 4.55, df = 5 (P = 0.47); I² = 0%				
Test for overall effect: Z = 5.75 (P < 0.00001)				
Total (95% CI)			**100.0%**	**-0.32 [-0.40, -0.23]**
Heterogeneity: Tau² = 0.05; Chi² = 178.33, df = 44 (P < 0.00001); I² = 75%				
Test for overall effect: Z = 7.35 (P < 0.00001)				
Test for subgroup differences: Chi² = 5.11, df = 3 (P = 0.16), I² = 41.3%				

Non-remission at follow-up (6 months)

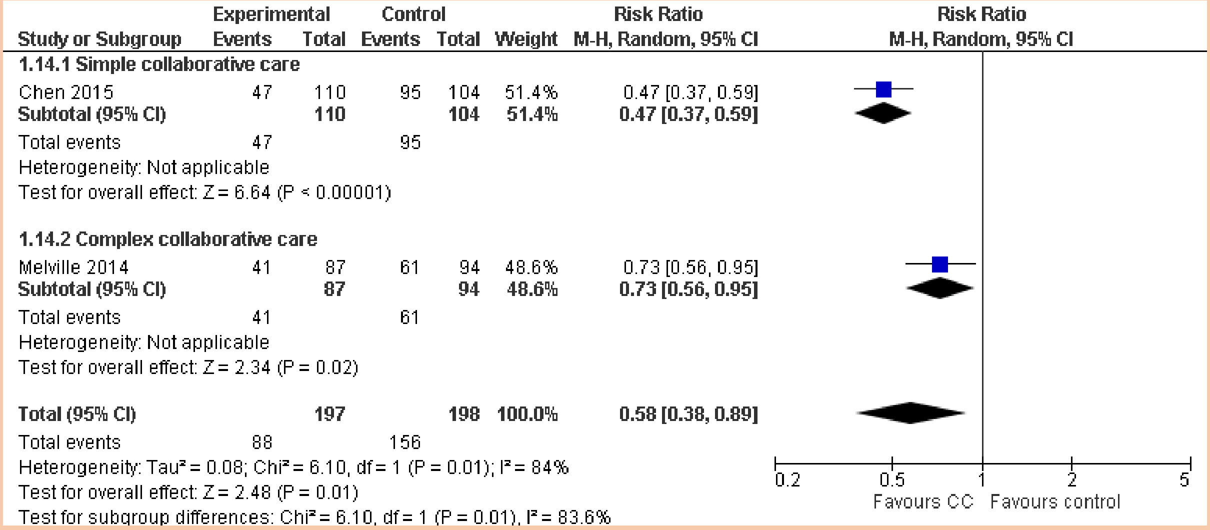


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Simple collaborative care						
Rost 2001	64	115	66	96	100.0%	0.81 [0.66, 1.00]
Subtotal (95% CI)		**115**		**96**	**100.0%**	**0.81 [0.66, 1.00]**
Total events	64		66			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)

Test for subgroup differences: Not applicable

Non-remission at endpoint

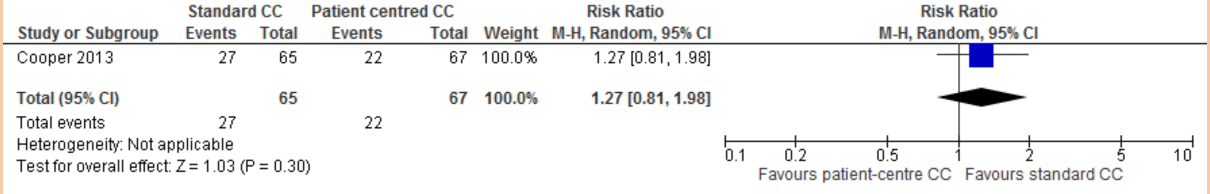


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Simple collaborative care						
Chen 2015	47	110	95	104	51.4%	0.47 [0.37, 0.59]
Subtotal (95% CI)		**110**		**104**	**51.4%**	**0.47 [0.37, 0.59]**
Total events	47		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.64 (P < 0.00001)						
1.14.2 Complex collaborative care						
Melville 2014	41	87	61	94	48.6%	0.73 [0.56, 0.95]
Subtotal (95% CI)		**87**		**94**	**48.6%**	**0.73 [0.56, 0.95]**
Total events	41		61			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.34 (P = 0.02)						
Total (95% CI)		**197**		**198**	**100.0%**	**0.58 [0.38, 0.89]**
Total events	88		156			

Heterogeneity: Tau² = 0.08; Chi² = 6.10, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Chi² = 6.10, df = 1 (P = 0.01), I² = 83.6%

Collaborative care versus other active intervention

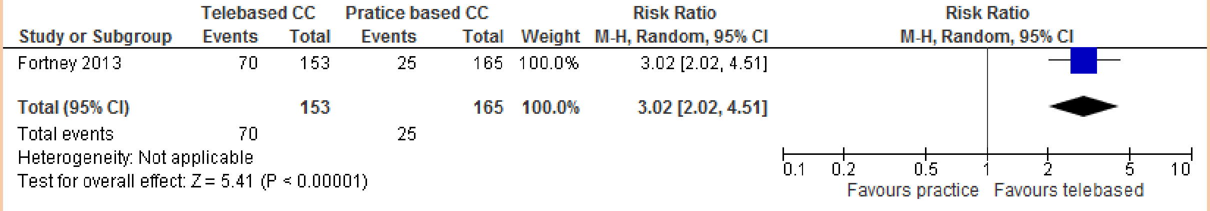
Simple collaborative care: standard versus patient-centred



Study or Subgroup	Standard CC Events	Standard CC Total	Patient centred CC Events	Patient centred CC Total	Weight	Risk Ratio M-H, Random, 95% CI
Cooper 2013	27	65	22	67	100.0%	1.27 [0.81, 1.98]
Total (95% CI)		**65**		**67**	**100.0%**	**1.27 [0.81, 1.98]**
Total events	27		22			

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

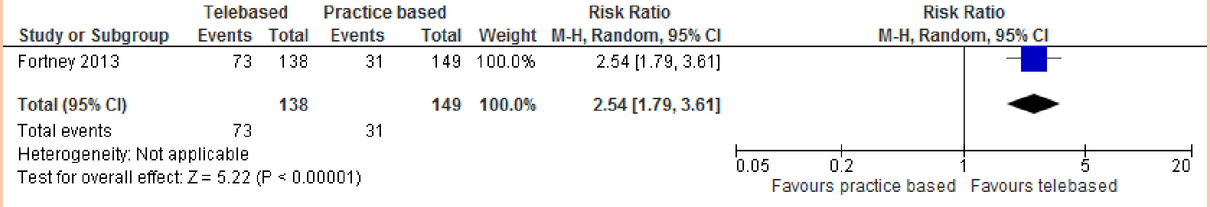
Response at endpoint: tele-based versus practice based



Study or Subgroup	Telebased CC Events	Telebased CC Total	Pratice based CC Events	Pratice based CC Total	Weight	Risk Ratio M-H, Random, 95% CI
Fortney 2013	70	153	25	165	100.0%	3.02 [2.02, 4.51]
Total (95% CI)		**153**		**165**	**100.0%**	**3.02 [2.02, 4.51]**
Total events	70		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.41 (P < 0.00001)

Response at follow-up: tele-based versus practice-based

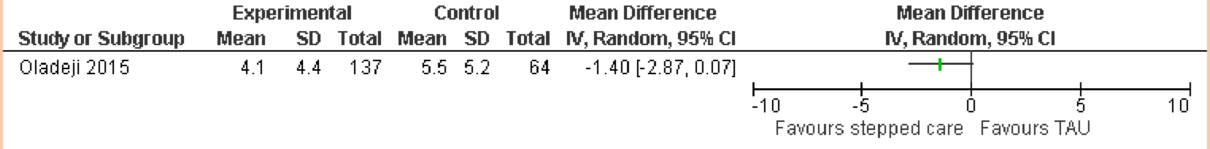


Study or Subgroup	Telebased Events	Telebased Total	Practice based Events	Practice based Total	Weight	Risk Ratio M-H, Random, 95% CI
Fortney 2013	73	138	31	149	100.0%	2.54 [1.79, 3.61]
Total (95% CI)		**138**		**149**	**100.0%**	**2.54 [1.79, 3.61]**
Total events	73		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.22 (P < 0.00001)

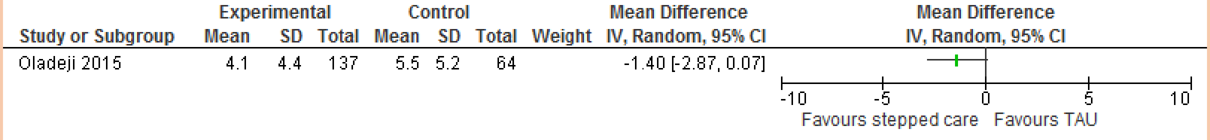
Stepped care versus control

Depression symptoms at follow-up (6 months) (PHQ-9)



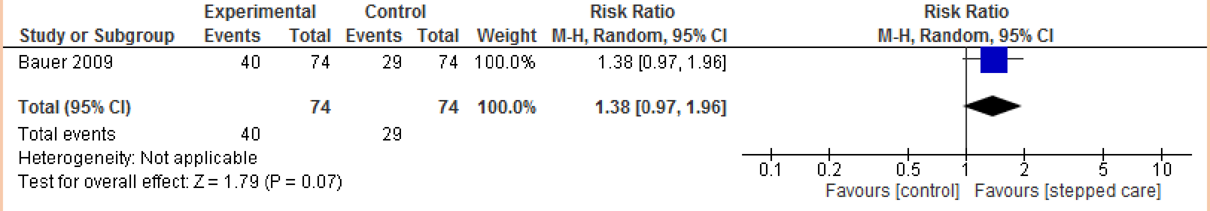
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Random, 95% CI
Oladeji 2015	4.1	4.4	137	5.5	5.2	64	-1.40 [-2.87, 0.07]

Depression symptoms at endpoint (PHQ-9)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Oladeji 2015	4.1	4.4	137	5.5	5.2	64		-1.40 [-2.87, 0.07]

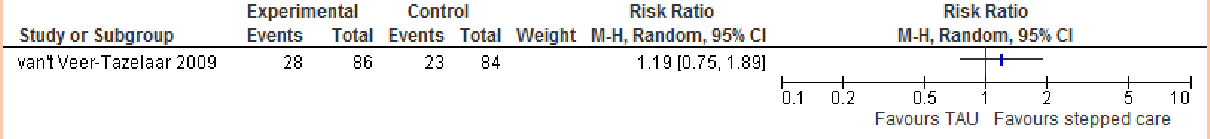
Remission at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bauer 2009	40	74	29	74	100.0%	1.38 [0.97, 1.96]
Total (95% CI)		**74**		**74**	**100.0%**	**1.38 [0.97, 1.96]**
Total events	40		29			

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

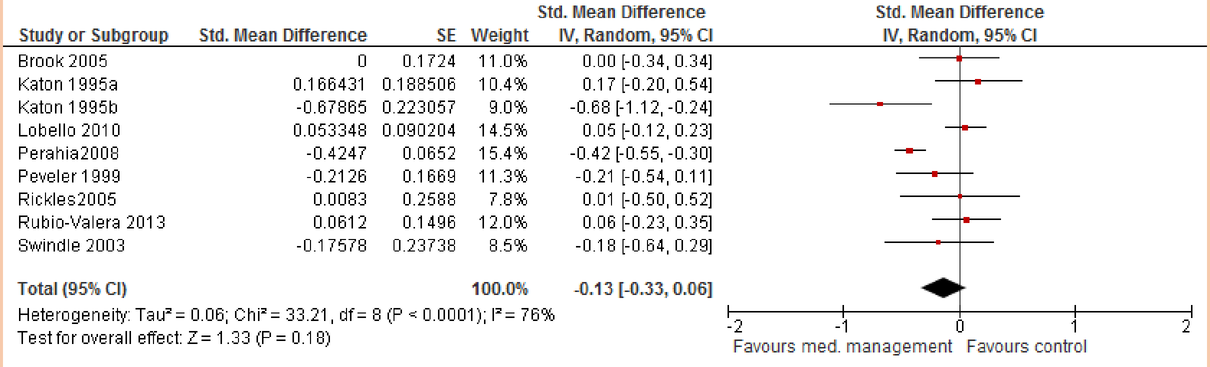
Antidepressant use



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
van't Veer-Tazelaar 2009	28	86	23	84		1.19 [0.75, 1.89]

Medication management versus control

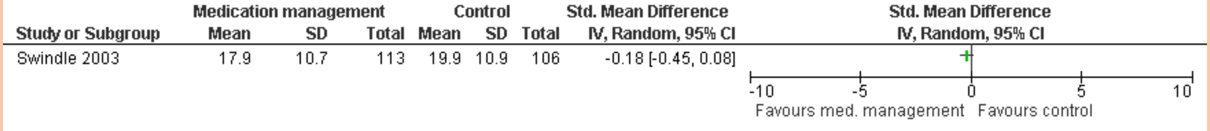
Mean change in depression scores at endpoint



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Brook 2005	0	0.1724	11.0%	0.00 [-0.34, 0.34]
Katon 1995a	0.166431	0.188506	10.4%	0.17 [-0.20, 0.54]
Katon 1995b	-0.67865	0.223057	9.0%	-0.68 [-1.12, -0.24]
Lobello 2010	0.053348	0.090204	14.5%	0.05 [-0.12, 0.23]
Perahia2008	-0.4247	0.0652	15.4%	-0.42 [-0.55, -0.30]
Peveler 1999	-0.2126	0.1669	11.3%	-0.21 [-0.54, 0.11]
Rickles2005	0.0083	0.2588	7.8%	0.01 [-0.50, 0.52]
Rubio-Valera 2013	0.0612	0.1496	12.0%	0.06 [-0.23, 0.35]
Swindle 2003	-0.17578	0.23738	8.5%	-0.18 [-0.64, 0.29]
Total (95% CI)			**100.0%**	**-0.13 [-0.33, 0.06]**

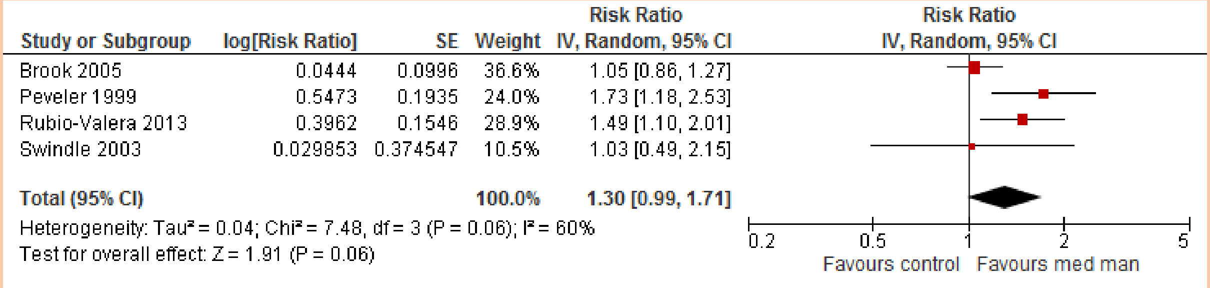
Heterogeneity: Tau² = 0.06; Chi² = 33.21, df = 8 (P < 0.0001); I² = 76%
Test for overall effect: Z = 1.33 (P = 0.18)

Mean change in depression scores at follow-up (12 months)



Study or Subgroup	Medication management Mean	SD	Total	Control Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Swindle 2003	17.9	10.7	113	19.9	10.9	106	-0.18 [-0.45, 0.08]

Antidepressant use at endpoint

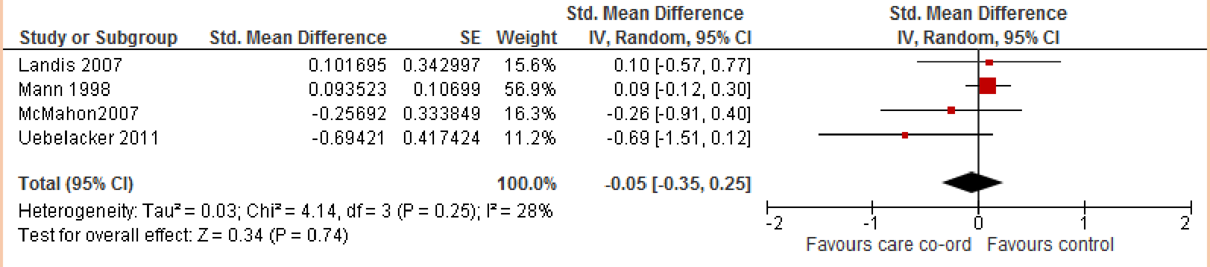


Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Brook 2005	0.0444	0.0996	36.6%	1.05 [0.86, 1.27]
Peveler 1999	0.5473	0.1935	24.0%	1.73 [1.18, 2.53]
Rubio-Valera 2013	0.3962	0.1546	28.9%	1.49 [1.10, 2.01]
Swindle 2003	0.029853	0.374547	10.5%	1.03 [0.49, 2.15]
Total (95% CI)			**100.0%**	**1.30 [0.99, 1.71]**

Heterogeneity: Tau² = 0.04; Chi² = 7.48, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 1.91 (P = 0.06)

Care co-ordination versus control

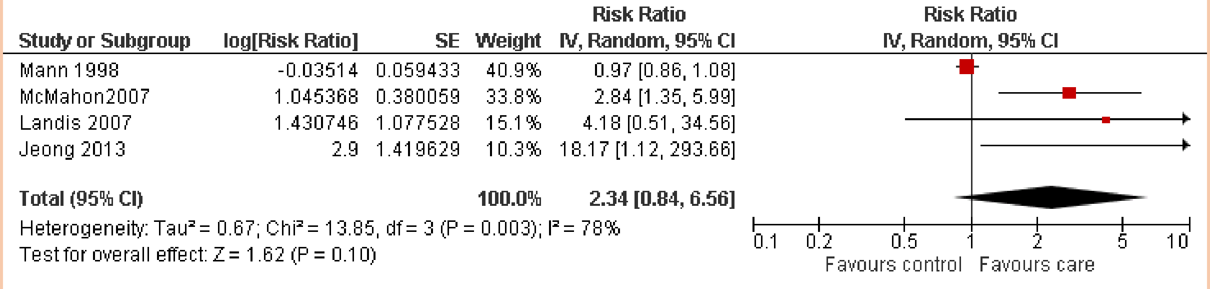
Mean change in depression scores at endpoint



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Landis 2007	0.101695	0.342997	15.6%	0.10 [-0.57, 0.77]
Mann 1998	0.093523	0.10699	56.9%	0.09 [-0.12, 0.30]
McMahon2007	-0.25692	0.333849	16.3%	-0.26 [-0.91, 0.40]
Uebelacker 2011	-0.69421	0.417424	11.2%	-0.69 [-1.51, 0.12]
Total (95% CI)			**100.0%**	**-0.05 [-0.35, 0.25]**

Heterogeneity: Tau² = 0.03; Chi² = 4.14, df = 3 (P = 0.25); I² = 28%
Test for overall effect: Z = 0.34 (P = 0.74)

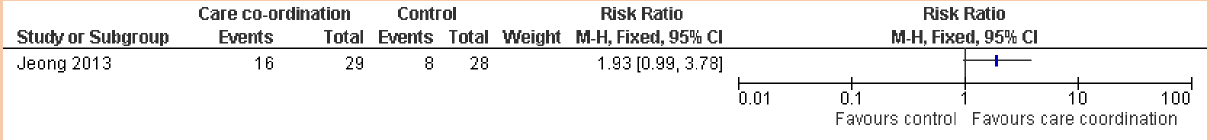
Antidepressant adherence



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Mann 1998	-0.03514	0.059433	40.9%	0.97 [0.86, 1.08]
McMahon2007	1.045368	0.380059	33.8%	2.84 [1.35, 5.99]
Landis 2007	1.430746	1.077528	15.1%	4.18 [0.51, 34.56]
Jeong 2013	2.9	1.419629	10.3%	18.17 [1.12, 293.66]
Total (95% CI)			**100.0%**	**2.34 [0.84, 6.56]**

Heterogeneity: Tau² = 0.67; Chi² = 13.85, df = 3 (P = 0.003); I² = 78%
Test for overall effect: Z = 1.62 (P = 0.10)

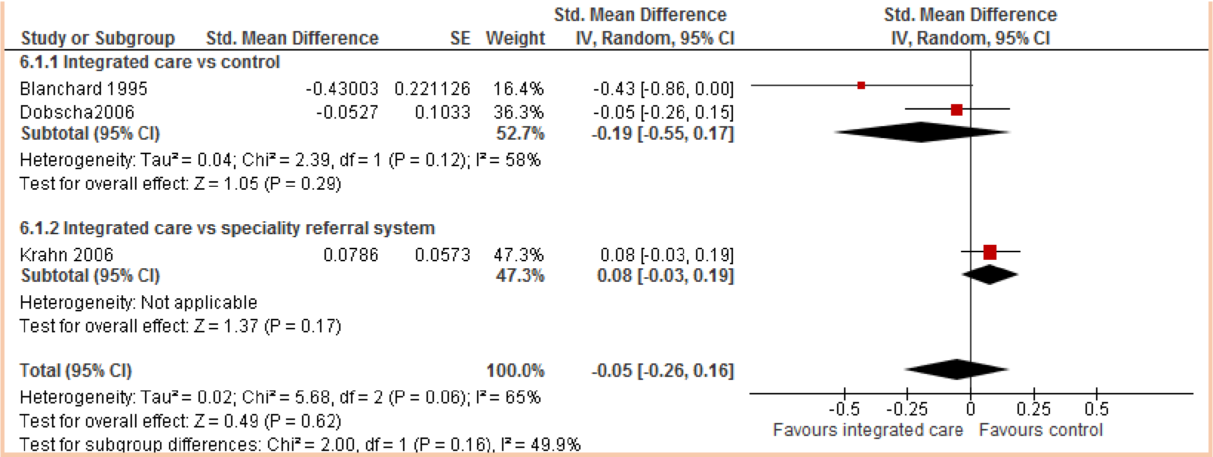
Remission (HAMD ≤ 7) at endpoint



Study or Subgroup	Care co-ordination Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jeong 2013	16	29	8	28		1.93 [0.99, 3.78]

Integrated care versus control

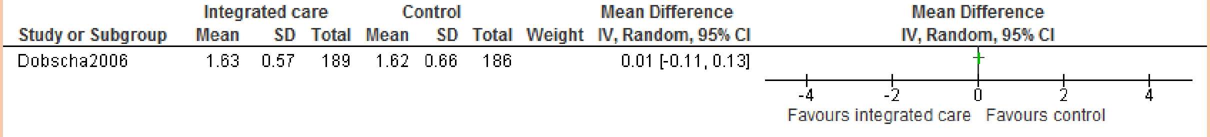
Mean change in depression scores at endpoint



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
6.1.1 Integrated care vs control				
Blanchard 1995	-0.43003	0.221126	16.4%	-0.43 [-0.86, 0.00]
Dobscha2006	-0.0527	0.1033	36.3%	-0.05 [-0.26, 0.15]
Subtotal (95% CI)			**52.7%**	**-0.19 [-0.55, 0.17]**
Heterogeneity: Tau² = 0.04; Chi² = 2.39, df = 1 (P = 0.12); I² = 58%				
Test for overall effect: Z = 1.05 (P = 0.29)				
6.1.2 Integrated care vs speciality referral system				
Krahn 2006	0.0786	0.0573	47.3%	0.08 [-0.03, 0.19]
Subtotal (95% CI)			**47.3%**	**0.08 [-0.03, 0.19]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.37 (P = 0.17)				
Total (95% CI)			**100.0%**	**-0.05 [-0.26, 0.16]**

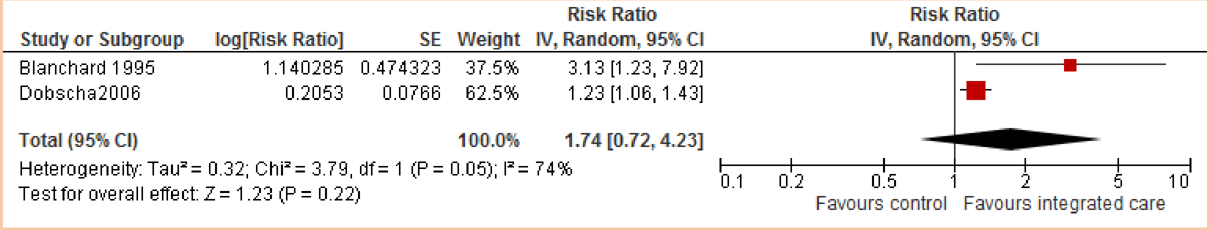
Heterogeneity: Tau² = 0.02; Chi² = 5.68, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Chi² = 2.00, df = 1 (P = 0.16), I² = 49.9%

Mean change in depression scores at follow-up (12 months)



Study or Subgroup	Integrated care Mean	Integrated care SD	Integrated care Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Dobscha2006	1.63	0.57	189	1.62	0.66	186		0.01 [-0.11, 0.13]

Antidepressant adherence

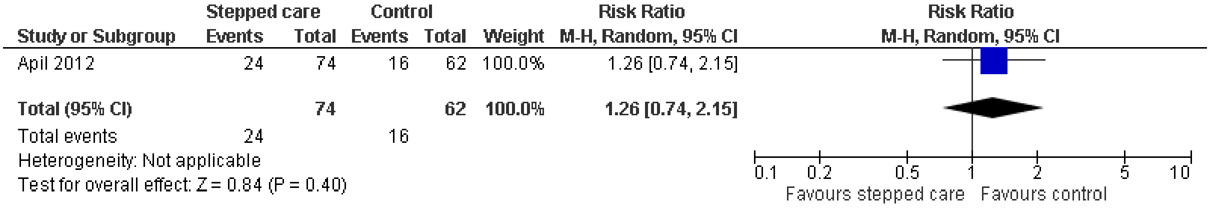


Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Blanchard 1995	1.140285	0.474323	37.5%	3.13 [1.23, 7.92]
Dobscha2006	0.2053	0.0766	62.5%	1.23 [1.06, 1.43]
Total (95% CI)			**100.0%**	**1.74 [0.72, 4.23]**

Heterogeneity: Tau² = 0.32; Chi² = 3.79, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 1.23 (P = 0.22)

Measurement-based care versus control

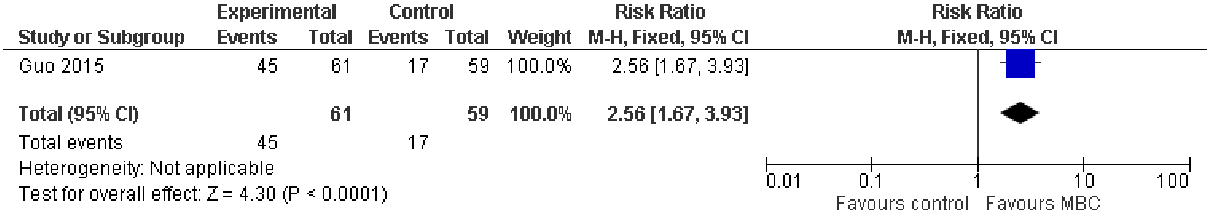
Response at endpoint (HAMD ≥50% improvement)



Study or Subgroup	Stepped care Events	Stepped care Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
April 2012	24	74	16	62	100.0%	1.26 [0.74, 2.15]
Total (95% CI)		**74**		**62**	**100.0%**	**1.26 [0.74, 2.15]**
Total events	24		16			

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

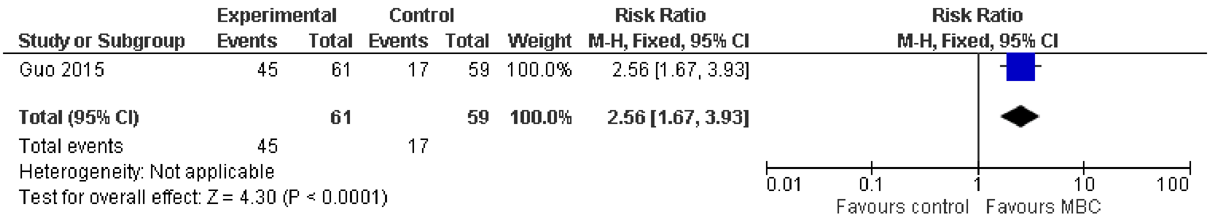
Remission at endpoint (HAMD ≤ 7)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guo 2015	45	61	17	59	100.0%	2.56 [1.67, 3.93]
Total (95% CI)		**61**		**59**	**100.0%**	**2.56 [1.67, 3.93]**
Total events	45		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.30 (P < 0.0001)

Depression symptoms at endpoint (HAMD change score)

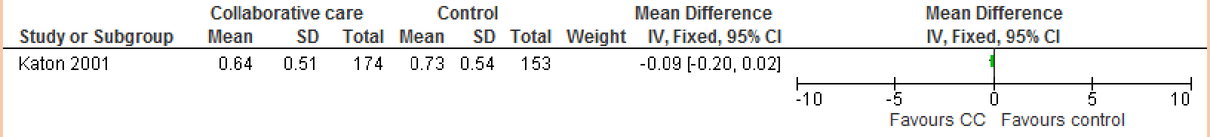


	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Guo 2015	45	61	17	59	100.0%	2.56 [1.67, 3.93]
Total (95% CI)		**61**		**59**	**100.0%**	**2.56 [1.67, 3.93]**
Total events	45		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.30 (P < 0.0001)

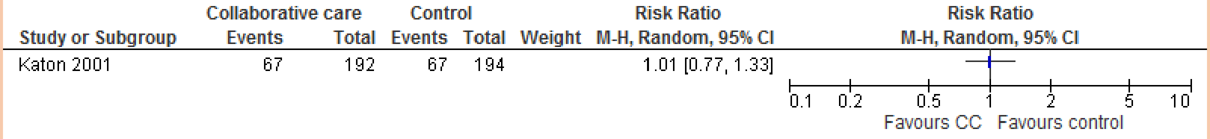
Service delivery models for relapse prevention

Depression symptoms (collaborative care)



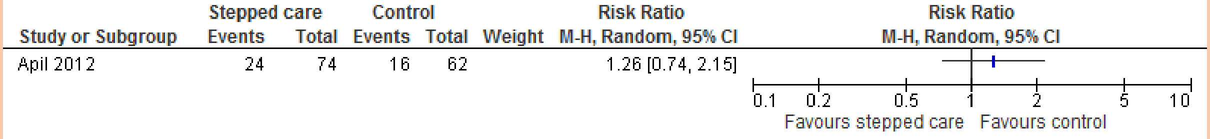
	Collaborative care			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Katon 2001	0.64	0.51	174	0.73	0.54	153		-0.09 [-0.20, 0.02]

Relapse (collaborative care)



	Collaborative care		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Katon 2001	67	192	67	194		1.01 [0.77, 1.33]

Relapse (stepped care)



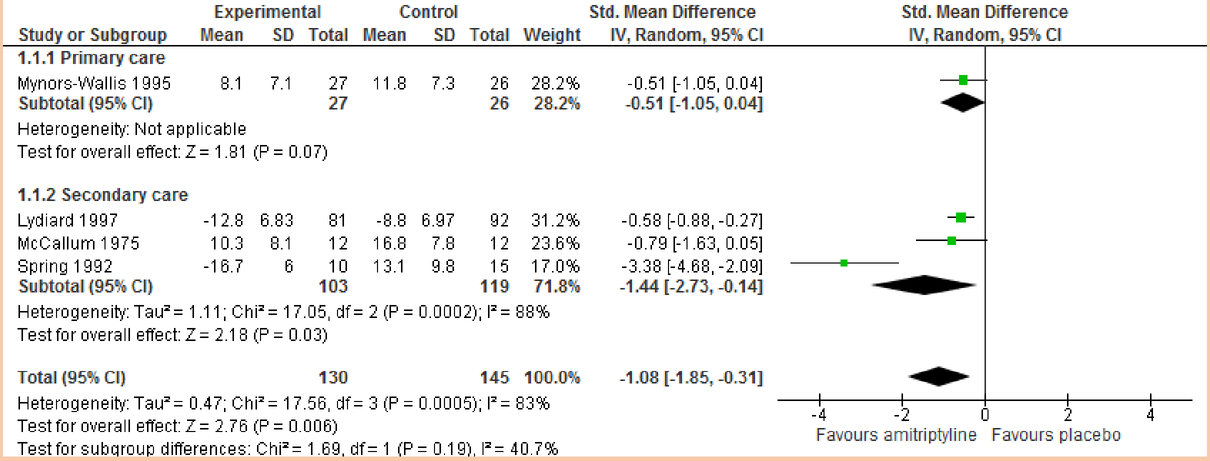
	Stepped care		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
April 2012	24	74	16	62		1.26 [0.74, 2.15]

Settings of care

Primary care versus secondary care for acute treatment (NMA sub-analysis)

Amitriptyline versus placebo

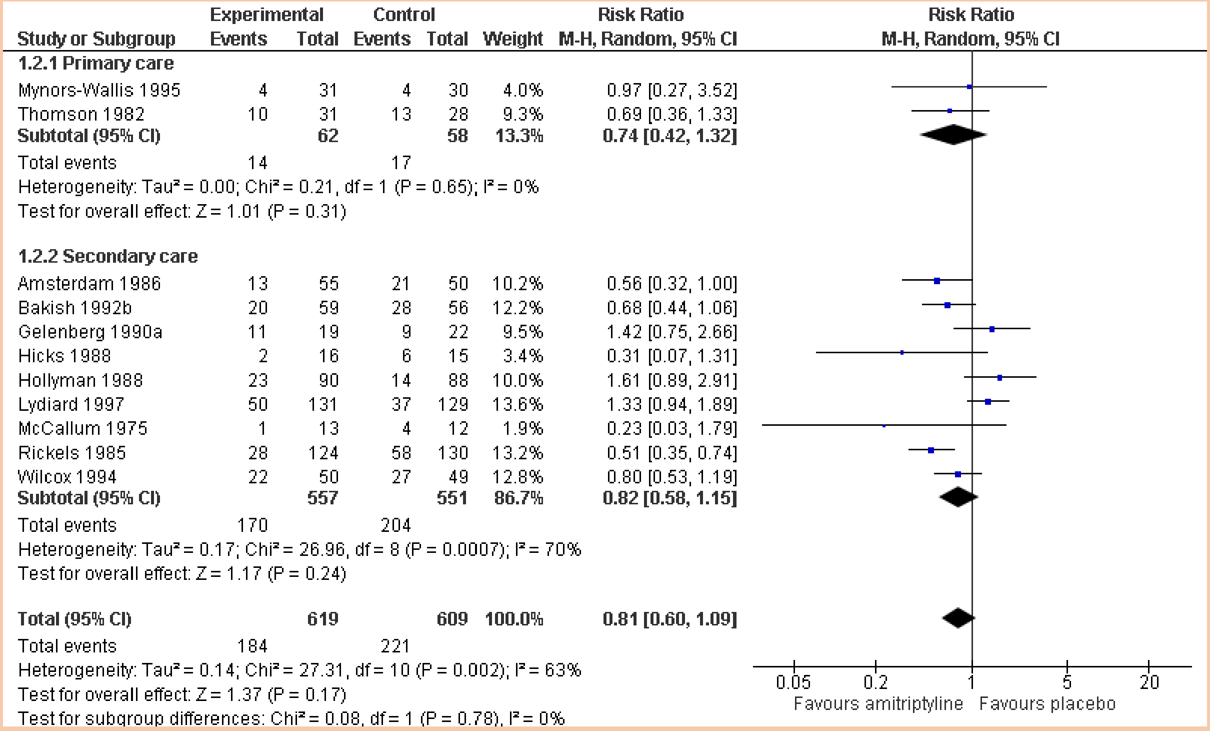
Depression symptoms at endpoint (HAMD-17/21)



	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.1.1 Primary care								
Mynors-Wallis 1995	8.1	7.1	27	11.8	7.3	26	28.2%	-0.51 [-1.05, 0.04]
Subtotal (95% CI)			**27**			**26**	**28.2%**	**-0.51 [-1.05, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.81 (P = 0.07)								
1.1.2 Secondary care								
Lydiard 1997	-12.8	6.83	81	-8.8	6.97	92	31.2%	-0.58 [-0.88, -0.27]
McCallum 1975	10.3	8.1	12	16.8	7.8	12	23.6%	-0.79 [-1.63, 0.05]
Spring 1992	-16.7	6	10	13.1	9.8	15	17.0%	-3.38 [-4.68, -2.09]
Subtotal (95% CI)			**103**			**119**	**71.8%**	**-1.44 [-2.73, -0.14]**
Heterogeneity: Tau² = 1.11; Chi² = 17.05, df = 2 (P = 0.0002); I² = 88%								
Test for overall effect: Z = 2.18 (P = 0.03)								
Total (95% CI)			**130**			**145**	**100.0%**	**-1.08 [-1.85, -0.31]**

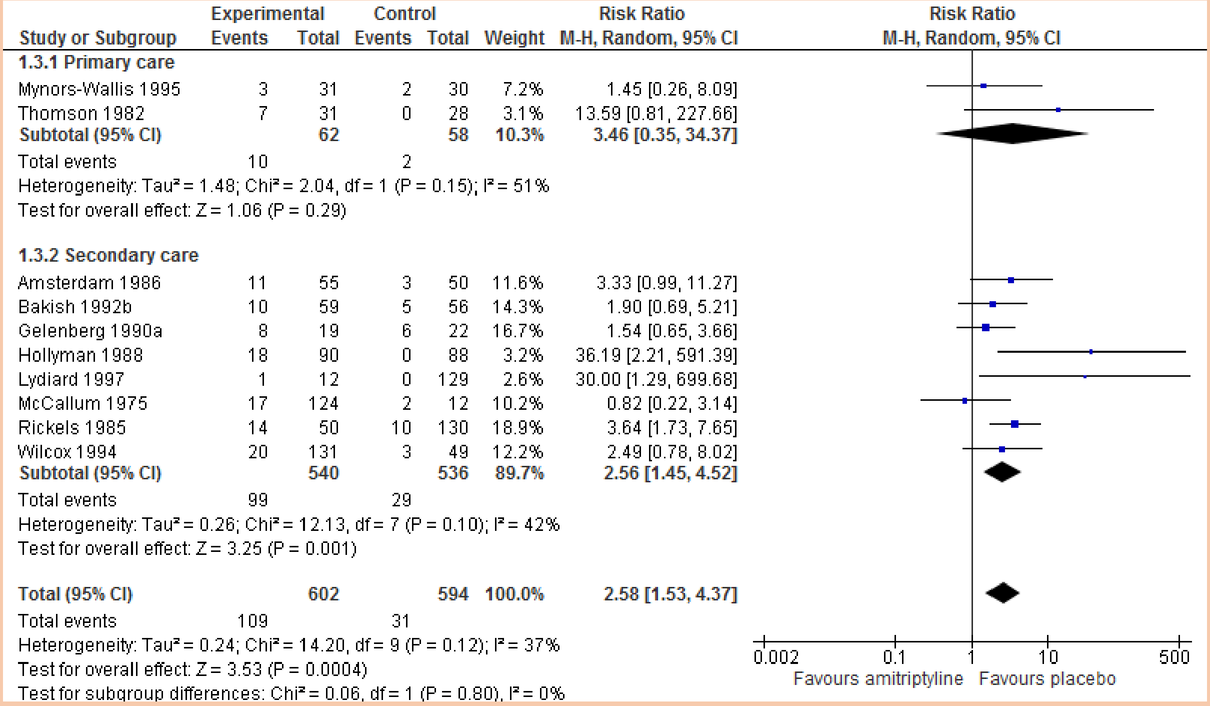
Heterogeneity: Tau² = 0.47; Chi² = 17.56, df = 3 (P = 0.0005); I² = 83%
Test for overall effect: Z = 2.76 (P = 0.006)
Test for subgroup differences: Chi² = 1.69, df = 1 (P = 0.19), I² = 40.7%

Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Primary care						
Mynors-Wallis 1995	4	31	4	30	4.0%	0.97 [0.27, 3.52]
Thomson 1982	10	31	13	28	9.3%	0.69 [0.36, 1.33]
Subtotal (95% CI)		**62**		**58**	**13.3%**	**0.74 [0.42, 1.32]**
Total events	14		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.2.2 Secondary care						
Amsterdam 1986	13	55	21	50	10.2%	0.56 [0.32, 1.00]
Bakish 1992b	20	59	28	56	12.2%	0.68 [0.44, 1.06]
Gelenberg 1990a	11	19	9	22	9.5%	1.42 [0.75, 2.66]
Hicks 1988	2	16	6	15	3.4%	0.31 [0.07, 1.31]
Hollyman 1988	23	90	14	88	10.0%	1.61 [0.89, 2.91]
Lydiard 1997	50	131	37	129	13.6%	1.33 [0.94, 1.89]
McCallum 1975	1	13	4	12	1.9%	0.23 [0.03, 1.79]
Rickels 1985	28	124	58	130	13.2%	0.51 [0.35, 0.74]
Wilcox 1994	22	50	27	49	12.8%	0.80 [0.53, 1.19]
Subtotal (95% CI)		**557**		**551**	**86.7%**	**0.82 [0.58, 1.15]**
Total events	170		204			
Heterogeneity: Tau² = 0.17; Chi² = 26.96, df = 8 (P = 0.0007); I² = 70%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**619**		**609**	**100.0%**	**0.81 [0.60, 1.09]**
Total events	184		221			
Heterogeneity: Tau² = 0.14; Chi² = 27.31, df = 10 (P = 0.002); I² = 63%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

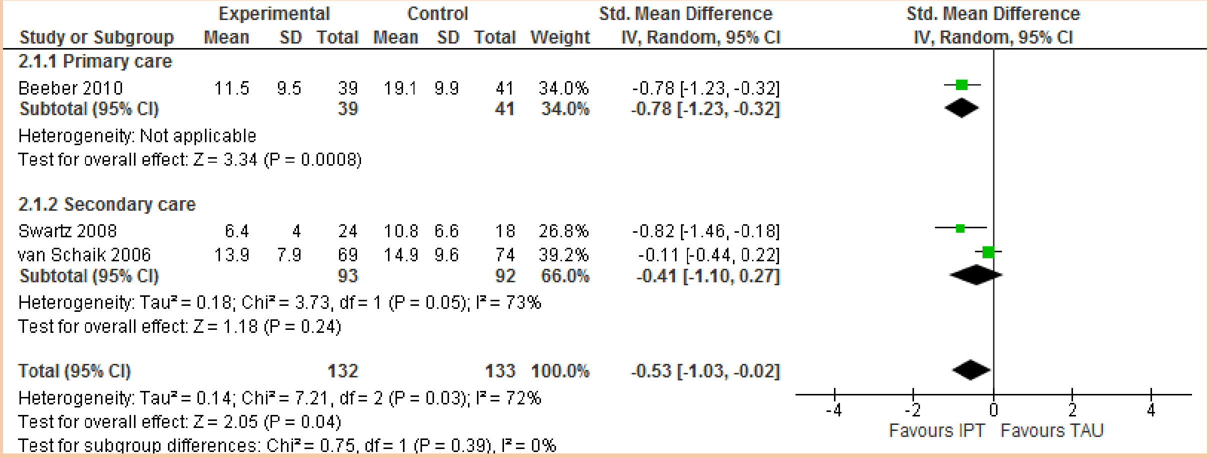
Discontinuation due to side effects



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Primary care						
Mynors-Wallis 1995	3	31	2	30	7.2%	1.45 [0.26, 8.09]
Thomson 1982	7	31	0	28	3.1%	13.59 [0.81, 227.66]
Subtotal (95% CI)		**62**		**58**	**10.3%**	**3.46 [0.35, 34.37]**
Total events	10		2			
Heterogeneity: Tau² = 1.48; Chi² = 2.04, df = 1 (P = 0.15); I² = 51%						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.3.2 Secondary care						
Amsterdam 1986	11	55	3	50	11.6%	3.33 [0.99, 11.27]
Bakish 1992b	10	59	5	56	14.3%	1.90 [0.69, 5.21]
Gelenberg 1990a	8	19	6	22	16.7%	1.54 [0.65, 3.66]
Hollyman 1988	18	90	0	88	3.2%	36.19 [2.21, 591.39]
Lydiard 1997	1	12	0	129	2.6%	30.00 [1.29, 699.68]
McCallum 1975	17	124	2	12	10.2%	0.82 [0.22, 3.14]
Rickels 1985	14	50	10	130	18.9%	3.64 [1.73, 7.65]
Wilcox 1994	20	131	3	49	12.2%	2.49 [0.78, 8.02]
Subtotal (95% CI)		**540**		**536**	**89.7%**	**2.56 [1.45, 4.52]**
Total events	99		29			
Heterogeneity: Tau² = 0.26; Chi² = 12.13, df = 7 (P = 0.10); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Total (95% CI)		**602**		**594**	**100.0%**	**2.58 [1.53, 4.37]**
Total events	109		31			
Heterogeneity: Tau² = 0.24; Chi² = 14.20, df = 9 (P = 0.12); I² = 37%						
Test for overall effect: Z = 3.53 (P = 0.0004)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%						

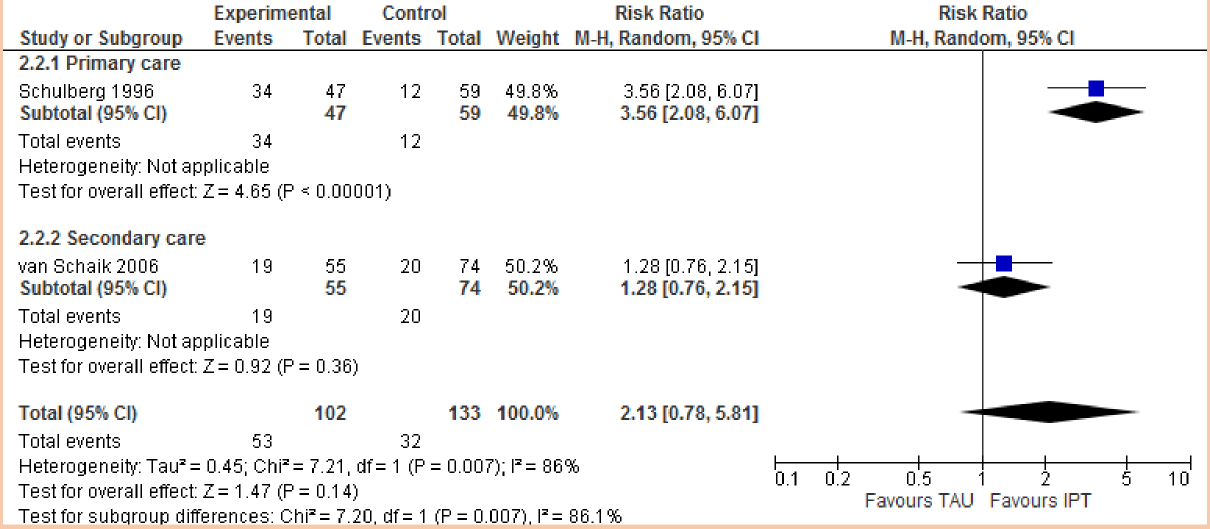
IPT versus TAU/waitlist

Depression symptoms at endpoint (CES-D/HAMD-17/MADRS)



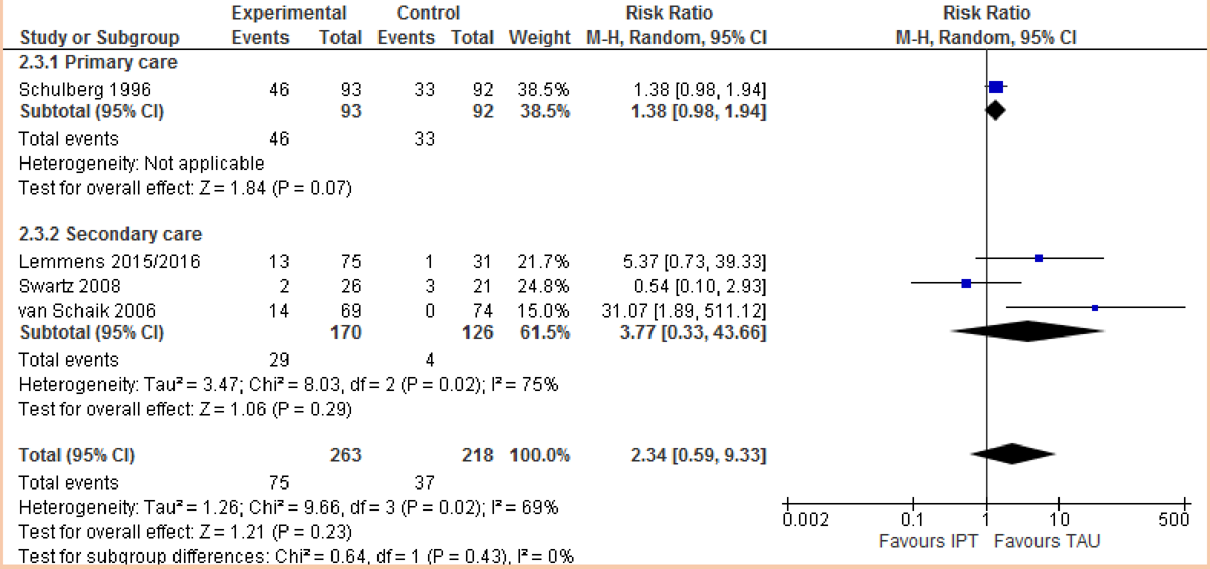
	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
2.1.1 Primary care								
Beeber 2010	11.5	9.5	39	19.1	9.9	41	34.0%	-0.78 [-1.23, -0.32]
Subtotal (95% CI)			**39**			**41**	**34.0%**	**-0.78 [-1.23, -0.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.34 (P = 0.0008)								
2.1.2 Secondary care								
Swartz 2008	6.4	4	24	10.8	6.6	18	26.8%	-0.82 [-1.46, -0.18]
van Schaik 2006	13.9	7.9	69	14.9	9.6	74	39.2%	-0.11 [-0.44, 0.22]
Subtotal (95% CI)			**93**			**92**	**66.0%**	**-0.41 [-1.10, 0.27]**
Heterogeneity: Tau² = 0.18; Chi² = 3.73, df = 1 (P = 0.05); I² = 73%								
Test for overall effect: Z = 1.18 (P = 0.24)								
Total (95% CI)			**132**			**133**	**100.0%**	**-0.53 [-1.03, -0.02]**
Heterogeneity: Tau² = 0.14; Chi² = 7.21, df = 2 (P = 0.03); I² = 72%								
Test for overall effect: Z = 2.05 (P = 0.04)								
Test for subgroup differences: Chi² = 0.75, df = 1 (P = 0.39), I² = 0%								

Remission (HAMD-17 <=7/MADRS<=10)



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
2.2.1 Primary care						
Schulberg 1996	34	47	12	59	49.8%	3.56 [2.08, 6.07]
Subtotal (95% CI)		**47**		**59**	**49.8%**	**3.56 [2.08, 6.07]**
Total events	34		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.65 (P < 0.00001)						
2.2.2 Secondary care						
van Schaik 2006	19	55	20	74	50.2%	1.28 [0.76, 2.15]
Subtotal (95% CI)		**55**		**74**	**50.2%**	**1.28 [0.76, 2.15]**
Total events	19		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**102**		**133**	**100.0%**	**2.13 [0.78, 5.81]**
Total events	53		32			
Heterogeneity: Tau² = 0.45; Chi² = 7.21, df = 1 (P = 0.007); I² = 86%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Chi² = 7.20, df = 1 (P = 0.007), I² = 86.1%						

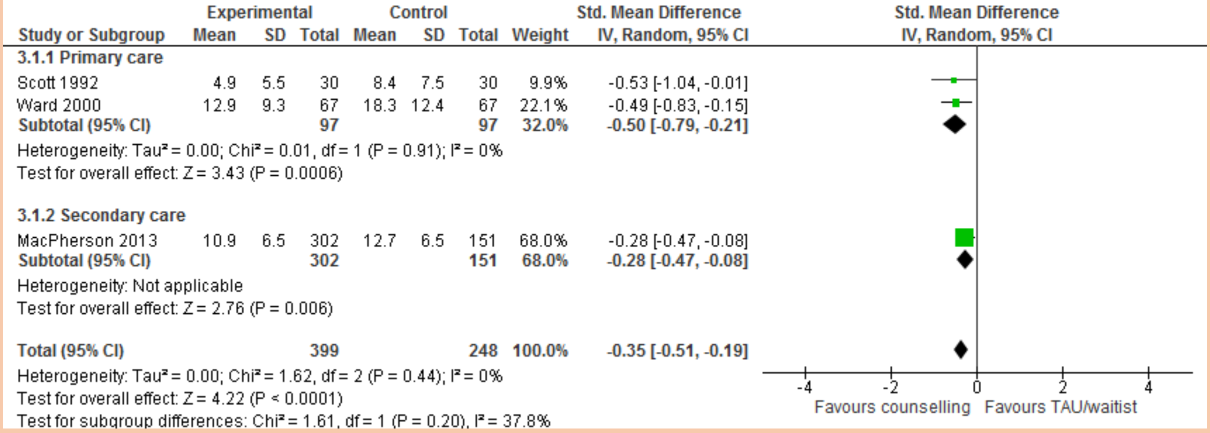
Discontinuation



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
2.3.1 Primary care						
Schulberg 1996	46	93	33	92	38.5%	1.38 [0.98, 1.94]
Subtotal (95% CI)		**93**		**92**	**38.5%**	**1.38 [0.98, 1.94]**
Total events	46		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
2.3.2 Secondary care						
Lemmens 2015/2016	13	75	1	31	21.7%	5.37 [0.73, 39.33]
Swartz 2008	2	26	3	21	24.8%	0.54 [0.10, 2.93]
van Schaik 2006	14	69	0	74	15.0%	31.07 [1.89, 511.12]
Subtotal (95% CI)		**170**		**126**	**61.5%**	**3.77 [0.33, 43.66]**
Total events	29		4			
Heterogeneity: Tau² = 3.47; Chi² = 8.03, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**263**		**218**	**100.0%**	**2.34 [0.59, 9.33]**
Total events	75		37			
Heterogeneity: Tau² = 1.26; Chi² = 9.66, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.43), I² = 0%						

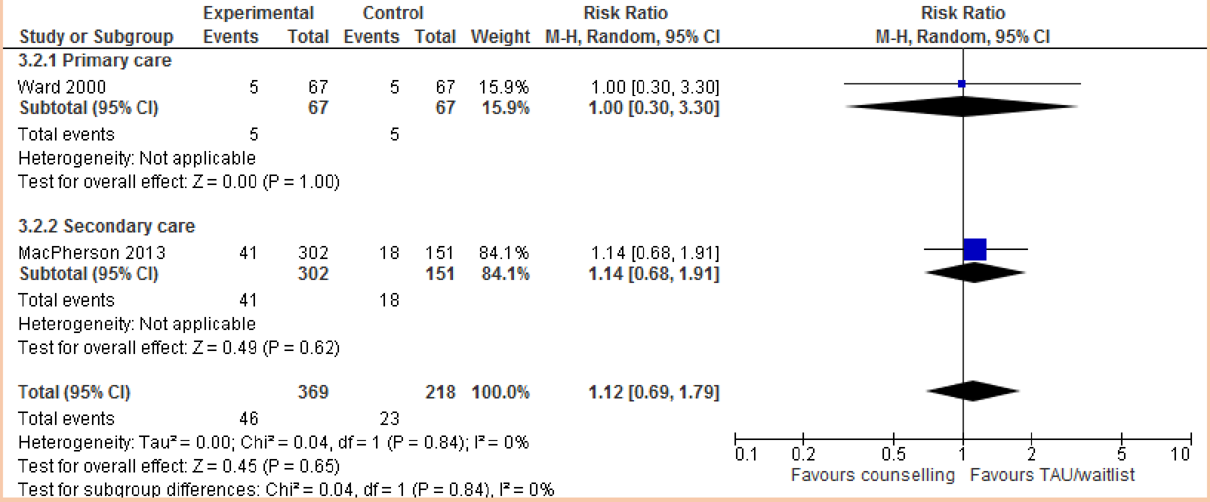
Counselling versus TAU

Depression symptoms at endpoint (HAMD-17/PHQ-9)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Primary care								
Scott 1992	4.9	5.5	30	8.4	7.5	30	9.9%	-0.53 [-1.04, -0.01]
Ward 2000	12.9	9.3	67	18.3	12.4	67	22.1%	-0.49 [-0.83, -0.15]
Subtotal (95% CI)			**97**			**97**	**32.0%**	**-0.50 [-0.79, -0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 3.43 (P = 0.0006)								
3.1.2 Secondary care								
MacPherson 2013	10.9	6.5	302	12.7	6.5	151	68.0%	-0.28 [-0.47, -0.08]
Subtotal (95% CI)			**302**			**151**	**68.0%**	**-0.28 [-0.47, -0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.76 (P = 0.006)								
Total (95% CI)			**399**			**248**	**100.0%**	**-0.35 [-0.51, -0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 2 (P = 0.44); I² = 0%								
Test for overall effect: Z = 4.22 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.61, df = 1 (P = 0.20), I² = 37.8%								

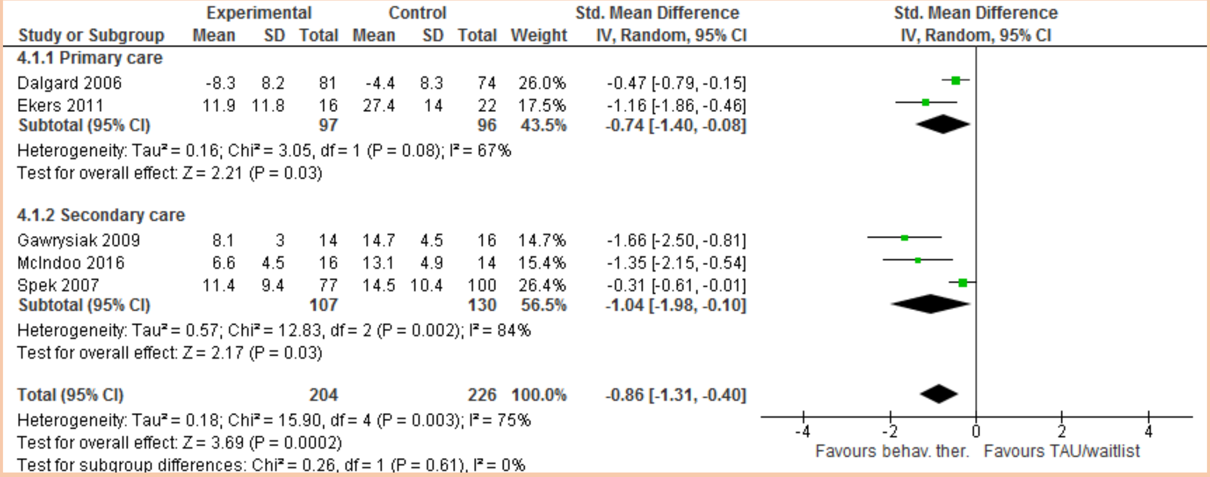
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Primary care						
Ward 2000	5	67	5	67	15.9%	1.00 [0.30, 3.30]
Subtotal (95% CI)		**67**		**67**	**15.9%**	**1.00 [0.30, 3.30]**
Total events	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
3.2.2 Secondary care						
MacPherson 2013	41	302	18	151	84.1%	1.14 [0.68, 1.91]
Subtotal (95% CI)		**302**		**151**	**84.1%**	**1.14 [0.68, 1.91]**
Total events	41		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
Total (95% CI)		**369**		**218**	**100.0%**	**1.12 [0.69, 1.79]**
Total events	46		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						

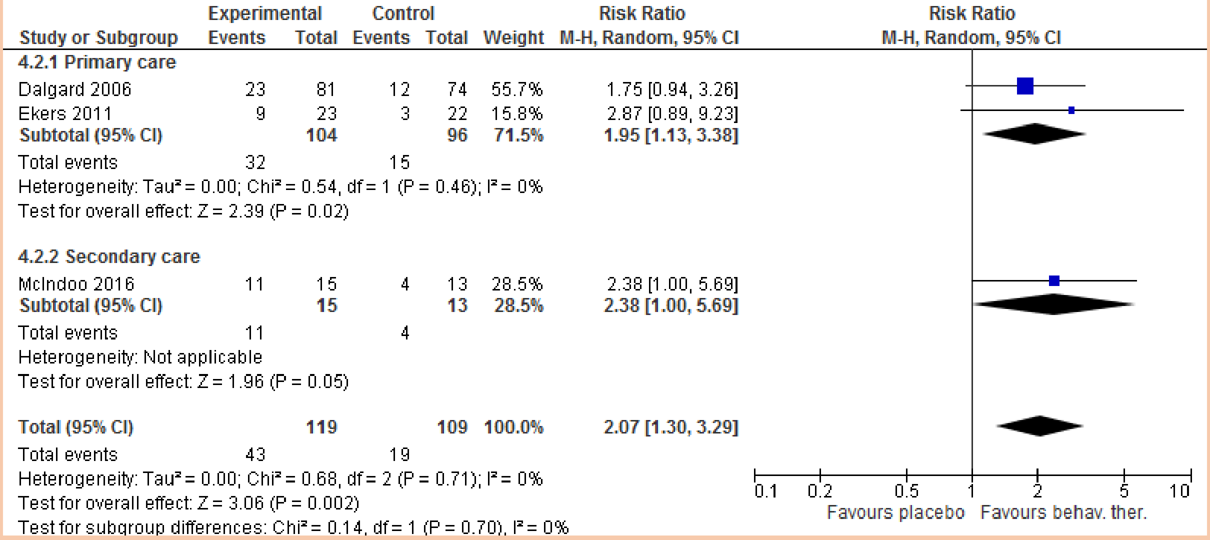
Behavioural therapies versus TAU/waitlist

Depression symptoms at endpoint (BDI[I or II]/HAM-D)



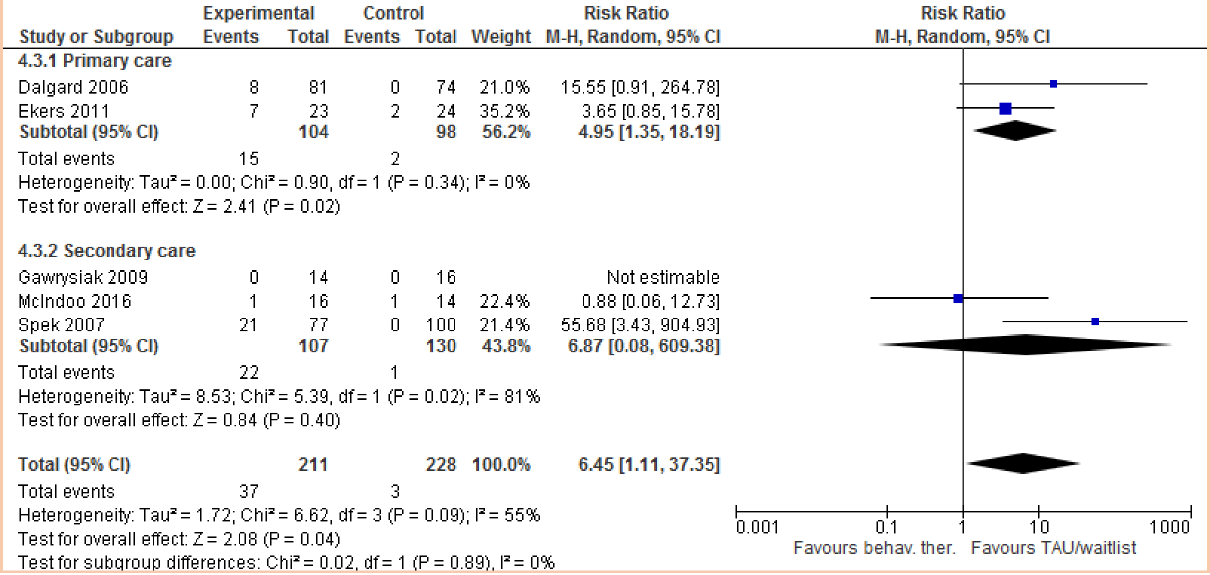
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Primary care								
Dalgard 2006	-8.3	8.2	81	-4.4	8.3	74	26.0%	-0.47 [-0.79, -0.15]
Ekers 2011	11.9	11.8	16	27.4	14	22	17.5%	-1.16 [-1.86, -0.46]
Subtotal (95% CI)			**97**			**96**	**43.5%**	**-0.74 [-1.40, -0.08]**
Heterogeneity: Tau^2 = 0.16; Chi^2 = 3.05, df = 1 (P = 0.08); I^2 = 67%								
Test for overall effect: Z = 2.21 (P = 0.03)								
4.1.2 Secondary care								
Gawrysiak 2009	8.1	3	14	14.7	4.5	16	14.7%	-1.66 [-2.50, -0.81]
McIndoo 2016	6.6	4.5	16	13.1	4.9	14	15.4%	-1.35 [-2.15, -0.54]
Spek 2007	11.4	9.4	77	14.5	10.4	100	26.4%	-0.31 [-0.61, -0.01]
Subtotal (95% CI)			**107**			**130**	**56.5%**	**-1.04 [-1.98, -0.10]**
Heterogeneity: Tau^2 = 0.57; Chi^2 = 12.83, df = 2 (P = 0.002); I^2 = 84%								
Test for overall effect: Z = 2.17 (P = 0.03)								
Total (95% CI)			**204**			**226**	**100.0%**	**-0.86 [-1.31, -0.40]**
Heterogeneity: Tau^2 = 0.18; Chi^2 = 15.90, df = 4 (P = 0.003); I^2 = 75%								
Test for overall effect: Z = 3.69 (P = 0.0002)								
Test for subgroup differences: Chi^2 = 0.26, df = 1 (P = 0.61), I^2 = 0%								

Remission (BDI <=10/HAMD-17<=7)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Primary care						
Dalgard 2006	23	81	12	74	55.7%	1.75 [0.94, 3.26]
Ekers 2011	9	23	3	22	15.8%	2.87 [0.89, 9.23]
Subtotal (95% CI)		**104**		**96**	**71.5%**	**1.95 [1.13, 3.38]**
Total events	32		15			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.54, df = 1 (P = 0.46); I^2 = 0%						
Test for overall effect: Z = 2.39 (P = 0.02)						
4.2.2 Secondary care						
McIndoo 2016	11	15	4	13	28.5%	2.38 [1.00, 5.69]
Subtotal (95% CI)		**15**		**13**	**28.5%**	**2.38 [1.00, 5.69]**
Total events	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
Total (95% CI)		**119**		**109**	**100.0%**	**2.07 [1.30, 3.29]**
Total events	43		19			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.68, df = 2 (P = 0.71); I^2 = 0%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.70), I^2 = 0%						

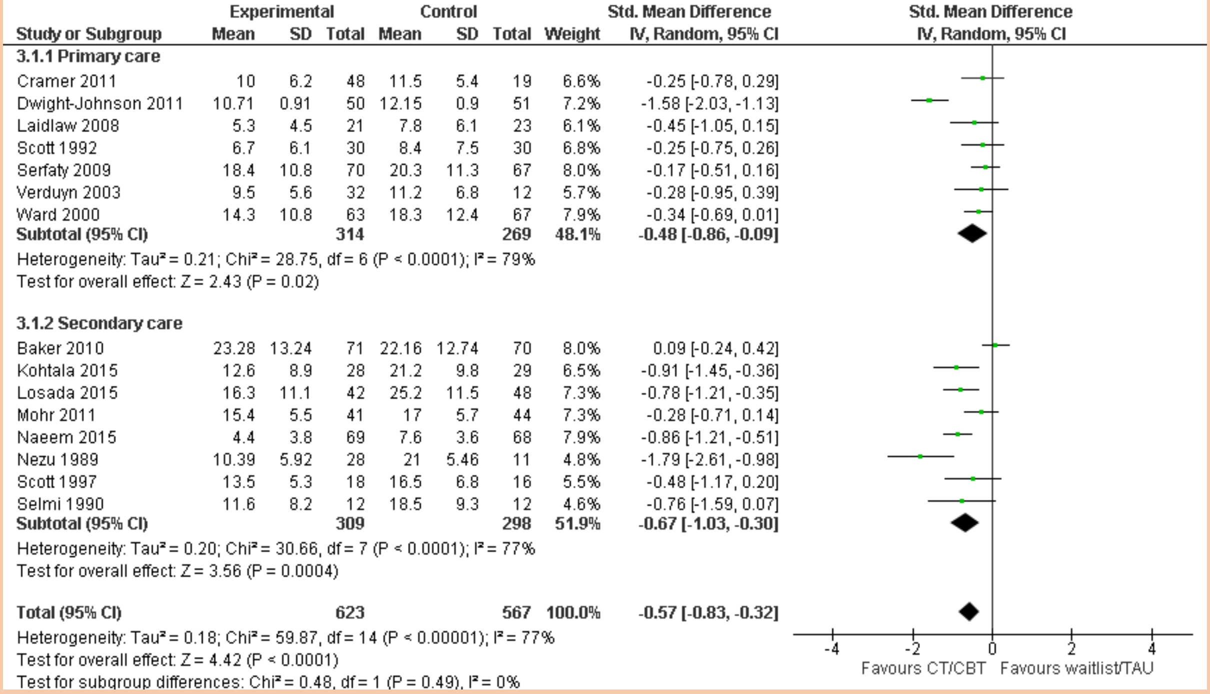
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Primary care						
Dalgard 2006	8	81	0	74	21.0%	15.55 [0.91, 264.78]
Ekers 2011	7	23	2	24	35.2%	3.65 [0.85, 15.78]
Subtotal (95% CI)		**104**		**98**	**56.2%**	**4.95 [1.35, 18.19]**
Total events	15		2			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.90, df = 1 (P = 0.34); I^2 = 0%						
Test for overall effect: Z = 2.41 (P = 0.02)						
4.3.2 Secondary care						
Gawrysiak 2009	0	14	0	16		Not estimable
McIndoo 2016	1	16	1	14	22.4%	0.88 [0.06, 12.73]
Spek 2007	21	77	0	100	21.4%	55.68 [3.43, 904.93]
Subtotal (95% CI)		**107**		**130**	**43.8%**	**6.87 [0.08, 609.38]**
Total events	22		1			
Heterogeneity: Tau^2 = 8.53; Chi^2 = 5.39, df = 1 (P = 0.02); I^2 = 81%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**211**		**228**	**100.0%**	**6.45 [1.11, 37.35]**
Total events	37		3			
Heterogeneity: Tau^2 = 1.72; Chi^2 = 6.62, df = 3 (P = 0.09); I^2 = 55%						
Test for overall effect: Z = 2.08 (P = 0.04)						
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.89), I^2 = 0%						

Cognitive and cognitive behavioural therapies versus TAU/waitlist

Depression symptoms at endpoint (HAMD-17/PHQ-9/BDI[I or II]/CES-D/HADS))



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Primary care								
Cramer 2011	10	6.2	48	11.5	5.4	19	6.6%	-0.25 [-0.78, 0.29]
Dwight-Johnson 2011	10.71	0.91	50	12.15	0.9	51	7.2%	-1.58 [-2.03, -1.13]
Laidlaw 2008	5.3	4.5	21	7.8	6.1	23	6.1%	-0.45 [-1.05, 0.15]
Scott 1992	6.7	6.1	30	8.4	7.5	30	6.8%	-0.25 [-0.75, 0.26]
Serfaty 2009	18.4	10.8	70	20.3	11.3	67	8.0%	-0.17 [-0.51, 0.16]
Verduyn 2003	9.5	5.6	32	11.2	6.8	12	5.7%	-0.28 [-0.95, 0.39]
Ward 2000	14.3	10.8	63	18.3	12.4	67	7.9%	-0.34 [-0.69, 0.01]
Subtotal (95% CI)			**314**			**269**	**48.1%**	**-0.48 [-0.86, -0.09]**

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 28.75$, df = 6 ($P < 0.0001$); $I^2 = 79\%$
Test for overall effect: Z = 2.43 (P = 0.02)

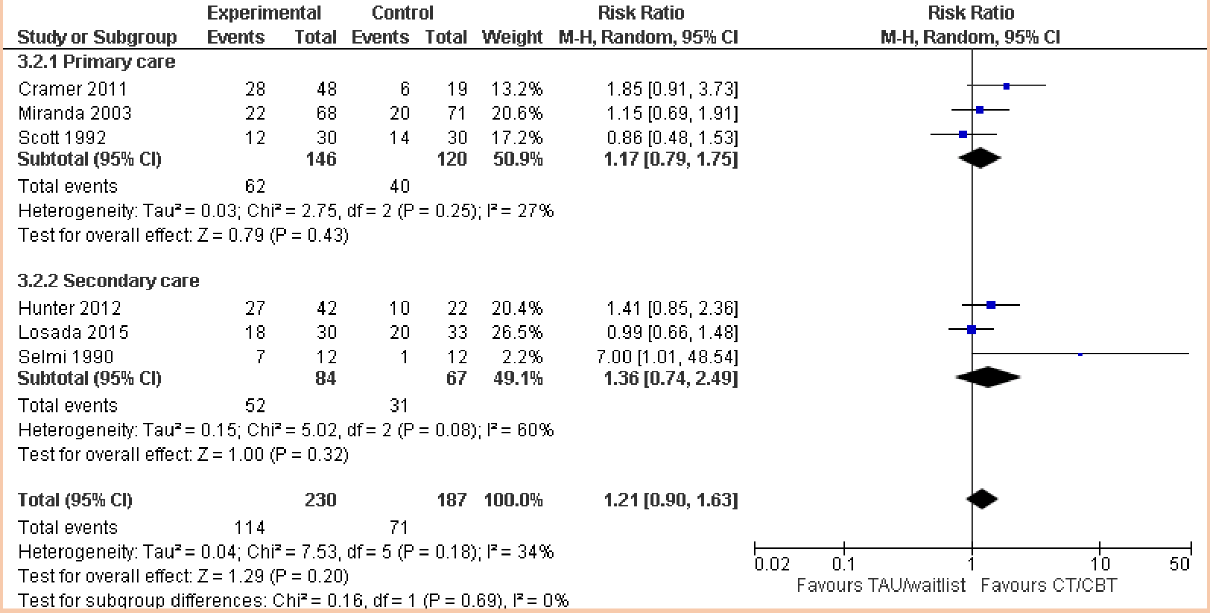
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.2 Secondary care								
Baker 2010	23.28	13.24	71	22.16	12.74	70	8.0%	0.09 [-0.24, 0.42]
Kohtala 2015	12.6	8.9	28	21.2	9.8	29	6.5%	-0.91 [-1.45, -0.36]
Losada 2015	16.3	11.1	42	25.2	11.5	48	7.3%	-0.78 [-1.21, -0.35]
Mohr 2011	15.4	5.5	41	17	5.7	44	7.3%	-0.28 [-0.71, 0.14]
Naeem 2015	4.4	3.8	69	7.6	3.6	68	7.9%	-0.86 [-1.21, -0.51]
Nezu 1989	10.39	5.92	28	21	5.46	11	4.8%	-1.79 [-2.61, -0.98]
Scott 1997	13.5	5.3	18	16.5	6.8	16	5.5%	-0.48 [-1.17, 0.20]
Selmi 1990	11.6	8.2	12	18.5	9.3	12	4.6%	-0.76 [-1.59, 0.07]
Subtotal (95% CI)			**309**			**298**	**51.9%**	**-0.67 [-1.03, -0.30]**

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 30.66$, df = 7 ($P < 0.0001$); $I^2 = 77\%$
Test for overall effect: Z = 3.56 (P = 0.0004)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total (95% CI)			**623**			**567**	**100.0%**	**-0.57 [-0.83, -0.32]**

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 59.87$, df = 14 ($P < 0.00001$); $I^2 = 77\%$
Test for overall effect: Z = 4.42 (P < 0.0001)
Test for subgroup differences: $Chi^2 = 0.48$, df = 1 (P = 0.49), $I^2 = 0\%$

Remission (HAMD-17 <=7/BDI-II<=9/CES-D<=16)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Primary care						
Cramer 2011	28	48	6	19	13.2%	1.85 [0.91, 3.73]
Miranda 2003	22	68	20	71	20.6%	1.15 [0.69, 1.91]
Scott 1992	12	30	14	30	17.2%	0.86 [0.48, 1.53]
Subtotal (95% CI)		**146**		**120**	**50.9%**	**1.17 [0.79, 1.75]**
Total events	62		40			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.75$, df = 2 (P = 0.25); $I^2 = 27\%$
Test for overall effect: Z = 0.79 (P = 0.43)

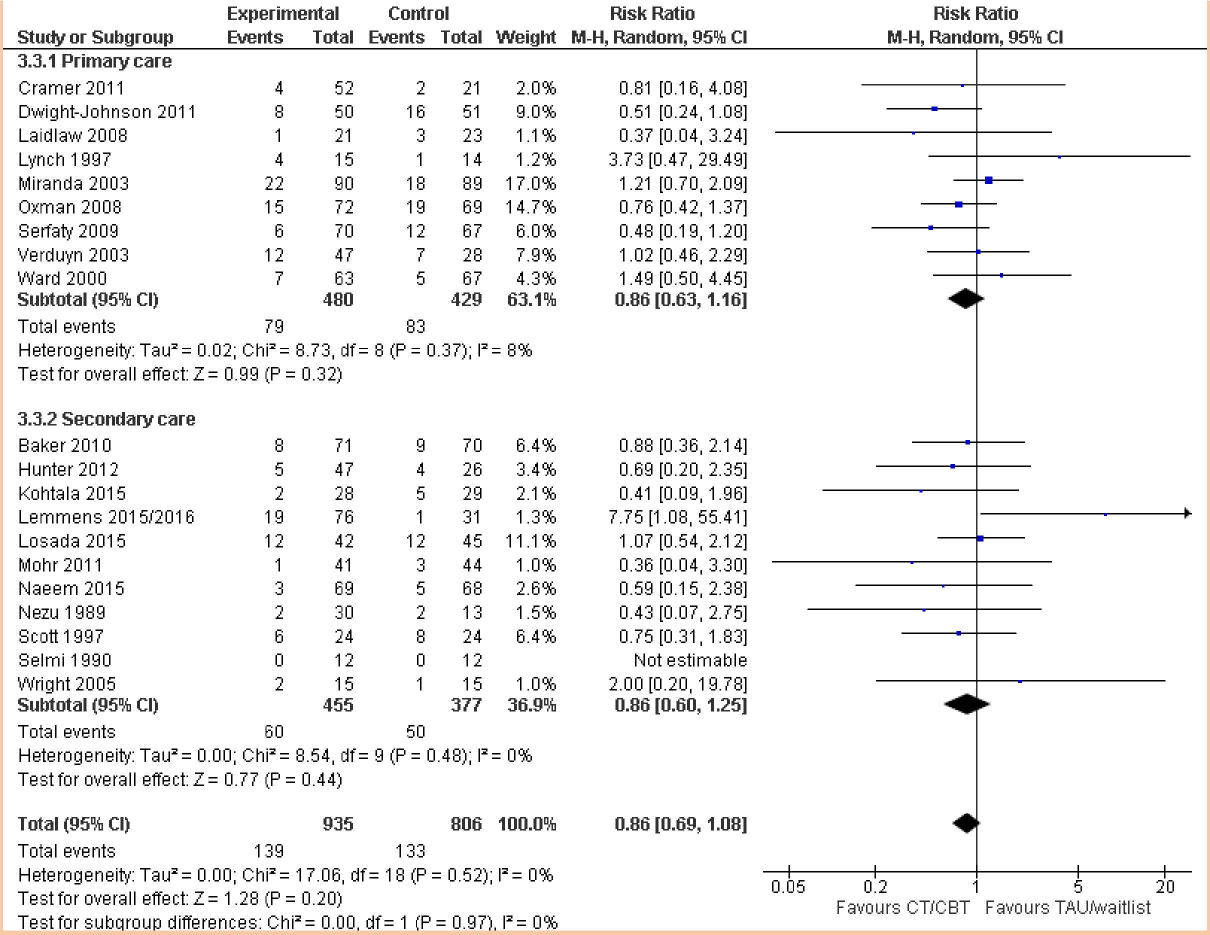
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.2 Secondary care						
Hunter 2012	27	42	10	22	20.4%	1.41 [0.85, 2.36]
Losada 2015	18	30	20	33	26.5%	0.99 [0.66, 1.48]
Selmi 1990	7	12	1	12	2.2%	7.00 [1.01, 48.54]
Subtotal (95% CI)		**84**		**67**	**49.1%**	**1.36 [0.74, 2.49]**
Total events	52		31			

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 5.02$, df = 2 (P = 0.08); $I^2 = 60\%$
Test for overall effect: Z = 1.00 (P = 0.32)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**230**		**187**	**100.0%**	**1.21 [0.90, 1.63]**
Total events	114		71			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 7.53$, df = 5 (P = 0.18); $I^2 = 34\%$
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: $Chi^2 = 0.16$, df = 1 (P = 0.69), $I^2 = 0\%$

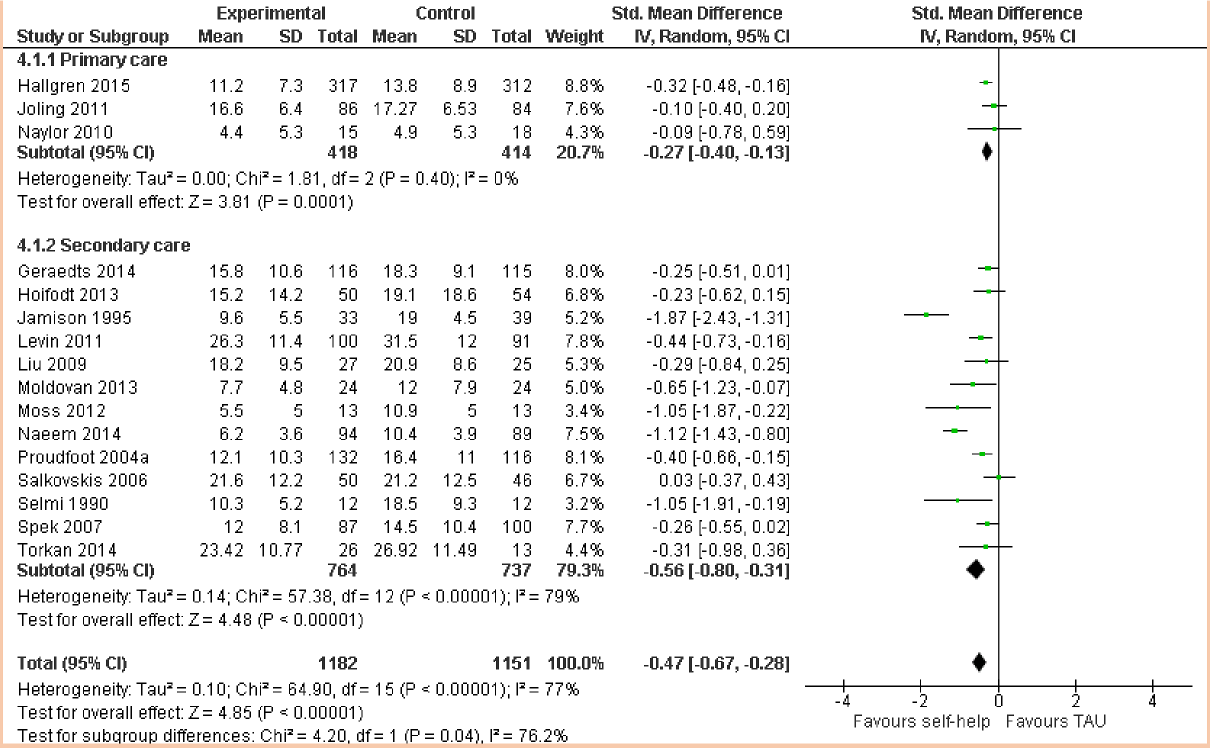
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Primary care						
Cramer 2011	4	52	2	21	2.0%	0.81 [0.16, 4.08]
Dwight-Johnson 2011	8	50	16	51	9.0%	0.51 [0.24, 1.08]
Laidlaw 2008	1	21	3	23	1.1%	0.37 [0.04, 3.24]
Lynch 1997	4	15	1	14	1.2%	3.73 [0.47, 29.49]
Miranda 2003	22	90	18	89	17.0%	1.21 [0.70, 2.09]
Oxman 2008	15	72	19	69	14.7%	0.76 [0.42, 1.37]
Serfaty 2009	6	70	12	67	6.0%	0.48 [0.19, 1.20]
Verduyn 2003	12	47	7	28	7.9%	1.02 [0.46, 2.29]
Ward 2000	7	63	5	67	4.3%	1.49 [0.50, 4.45]
Subtotal (95% CI)		**480**		**429**	**63.1%**	**0.86 [0.63, 1.16]**
Total events	79		83			
Heterogeneity: Tau² = 0.02; Chi² = 8.73, df = 8 (P = 0.37); I² = 8%						
Test for overall effect: Z = 0.99 (P = 0.32)						
3.3.2 Secondary care						
Baker 2010	8	71	9	70	6.4%	0.88 [0.36, 2.14]
Hunter 2012	5	47	4	26	3.4%	0.69 [0.20, 2.35]
Kohtala 2015	2	28	5	29	2.1%	0.41 [0.09, 1.96]
Lemmens 2015/2016	19	76	1	31	1.3%	7.75 [1.08, 55.41]
Losada 2015	12	42	12	45	11.1%	1.07 [0.54, 2.12]
Mohr 2011	1	41	3	44	1.0%	0.36 [0.04, 3.30]
Naeem 2015	3	69	5	68	2.6%	0.59 [0.15, 2.38]
Nezu 1989	2	30	2	13	1.5%	0.43 [0.07, 2.75]
Scott 1997	6	24	8	24	6.4%	0.75 [0.31, 1.83]
Selmi 1990	0	12	0	12		Not estimable
Wright 2005	2	15	1	15	1.0%	2.00 [0.20, 19.78]
Subtotal (95% CI)		**455**		**377**	**36.9%**	**0.86 [0.60, 1.25]**
Total events	60		50			
Heterogeneity: Tau² = 0.00; Chi² = 8.54, df = 9 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		**935**		**806**	**100.0%**	**0.86 [0.69, 1.08]**
Total events	139		133			
Heterogeneity: Tau² = 0.00; Chi² = 17.06, df = 18 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						

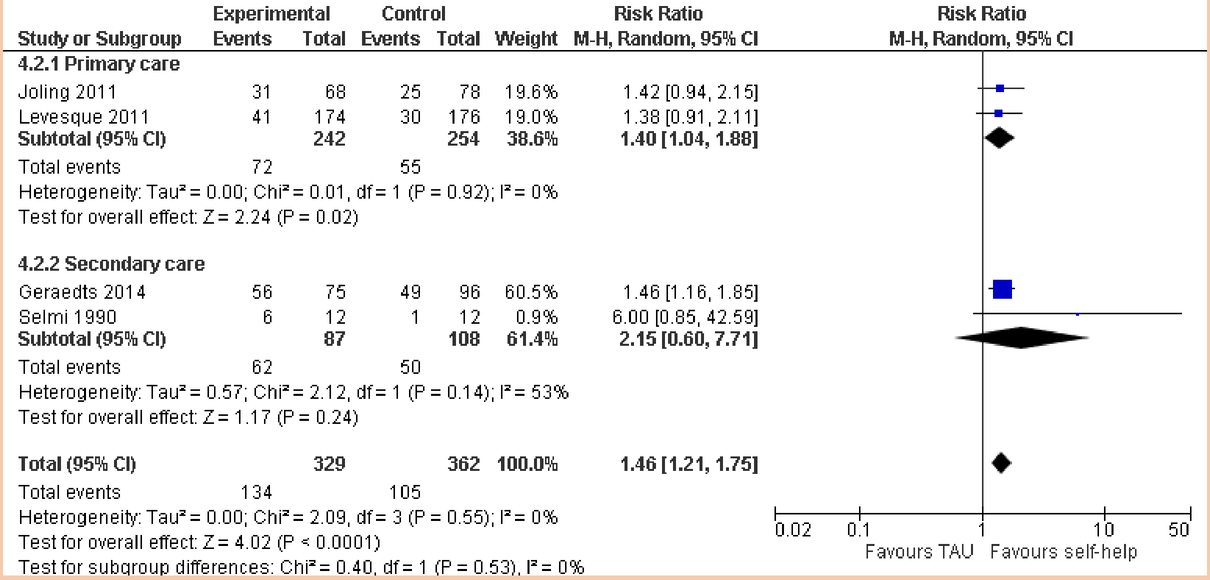
Self-help (without support) versus TAU/waitlist

Depression symptoms at endpoint (MADRS/CES-D/BDI[I or II]/HAMD[17 or 21]/HADS)



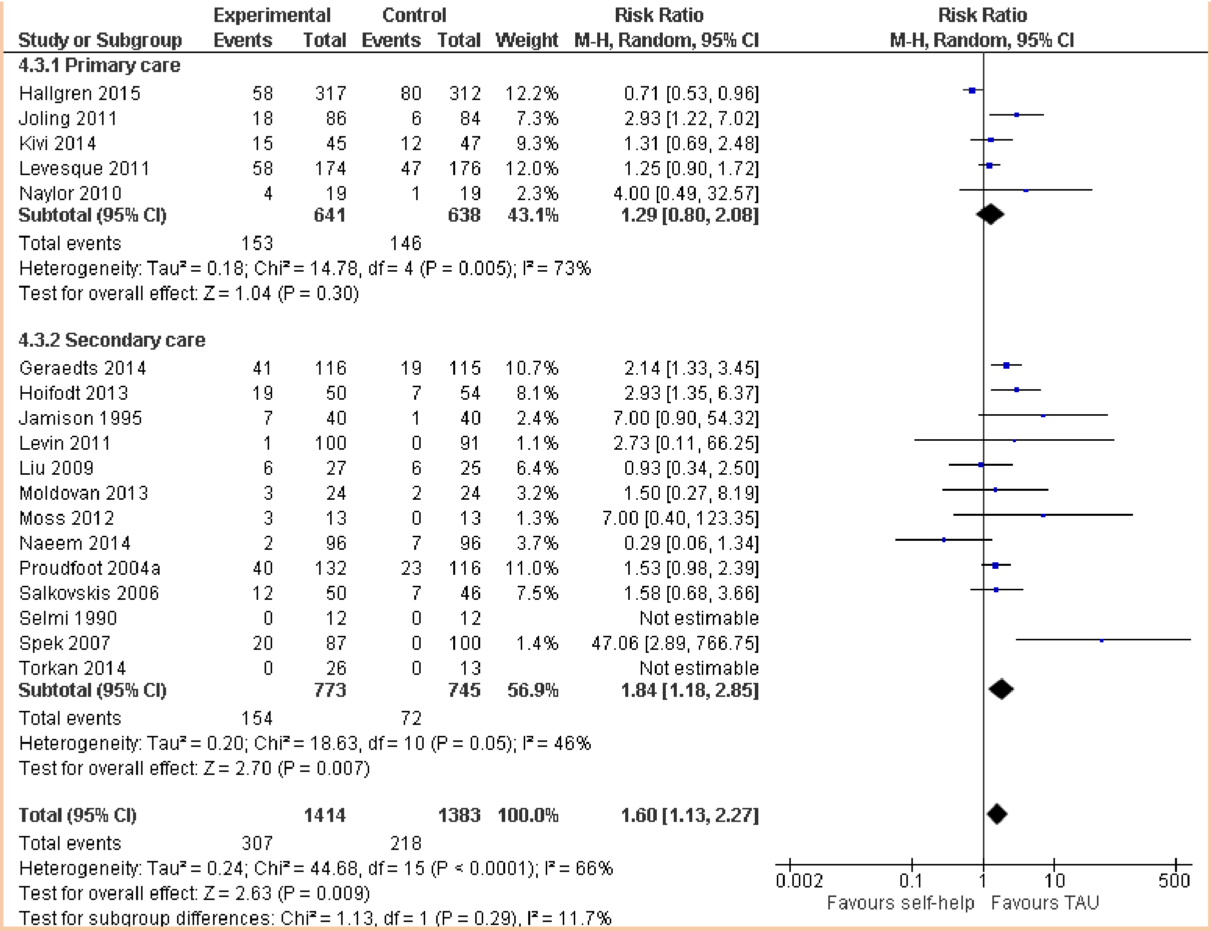
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Primary care								
Hallgren 2015	11.2	7.3	317	13.8	8.9	312	8.8%	-0.32 [-0.48, -0.16]
Joling 2011	16.6	6.4	86	17.27	6.53	84	7.6%	-0.10 [-0.40, 0.20]
Naylor 2010	4.4	5.3	15	4.9	5.3	18	4.3%	-0.09 [-0.78, 0.59]
Subtotal (95% CI)			**418**			**414**	**20.7%**	**-0.27 [-0.40, -0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 2 (P = 0.40); I² = 0%								
Test for overall effect: Z = 3.81 (P = 0.0001)								
4.1.2 Secondary care								
Geraedts 2014	15.8	10.6	116	18.3	9.1	115	8.0%	-0.25 [-0.51, 0.01]
Hoifodt 2013	15.2	14.2	50	19.1	18.6	54	6.8%	-0.23 [-0.62, 0.15]
Jamison 1995	9.6	5.5	33	19	4.5	39	5.2%	-1.87 [-2.43, -1.31]
Levin 2011	26.3	11.4	100	31.5	12	91	7.8%	-0.44 [-0.73, -0.16]
Liu 2009	18.2	9.5	27	20.9	8.6	25	5.3%	-0.29 [-0.84, 0.25]
Moldovan 2013	7.7	4.8	24	12	7.9	24	5.0%	-0.65 [-1.23, -0.07]
Moss 2012	5.5	5	13	10.9	5	13	3.4%	-1.05 [-1.87, -0.22]
Naeem 2014	6.2	3.6	94	10.4	3.9	89	7.5%	-1.12 [-1.43, -0.80]
Proudfoot 2004a	12.1	10.3	132	16.4	11	116	8.1%	-0.40 [-0.66, -0.15]
Salkovskis 2006	21.6	12.2	50	21.2	12.5	46	6.7%	0.03 [-0.37, 0.43]
Selmi 1990	10.3	5.2	12	18.5	9.3	12	3.2%	-1.05 [-1.91, -0.19]
Spek 2007	12	8.1	87	14.5	10.4	100	7.7%	-0.26 [-0.55, 0.02]
Torkan 2014	23.42	10.77	26	26.92	11.49	13	4.4%	-0.31 [-0.98, 0.36]
Subtotal (95% CI)			**764**			**737**	**79.3%**	**-0.56 [-0.80, -0.31]**
Heterogeneity: Tau² = 0.14; Chi² = 57.38, df = 12 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 4.48 (P < 0.00001)								
Total (95% CI)			**1182**			**1151**	**100.0%**	**-0.47 [-0.67, -0.28]**
Heterogeneity: Tau² = 0.10; Chi² = 64.90, df = 15 (P < 0.00001); I² = 77%								
Test for overall effect: Z = 4.85 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.20, df = 1 (P = 0.04), I² = 76.2%								

Remission (CES-D <=16/HAMD-17 <=6)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Primary care						
Joling 2011	31	68	25	78	19.6%	1.42 [0.94, 2.15]
Levesque 2011	41	174	30	176	19.0%	1.38 [0.91, 2.11]
Subtotal (95% CI)		**242**		**254**	**38.6%**	**1.40 [1.04, 1.88]**
Total events	72		55			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.24 (P = 0.02)						
4.2.2 Secondary care						
Geraedts 2014	56	75	49	96	60.5%	1.46 [1.16, 1.85]
Selmi 1990	6	12	1	12	0.9%	6.00 [0.85, 42.59]
Subtotal (95% CI)		**87**		**108**	**61.4%**	**2.15 [0.60, 7.71]**
Total events	62		50			
Heterogeneity: Tau² = 0.57; Chi² = 2.12, df = 1 (P = 0.14); I² = 53%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**329**		**362**	**100.0%**	**1.46 [1.21, 1.75]**
Total events	134		105			
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%						
Test for overall effect: Z = 4.02 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%						

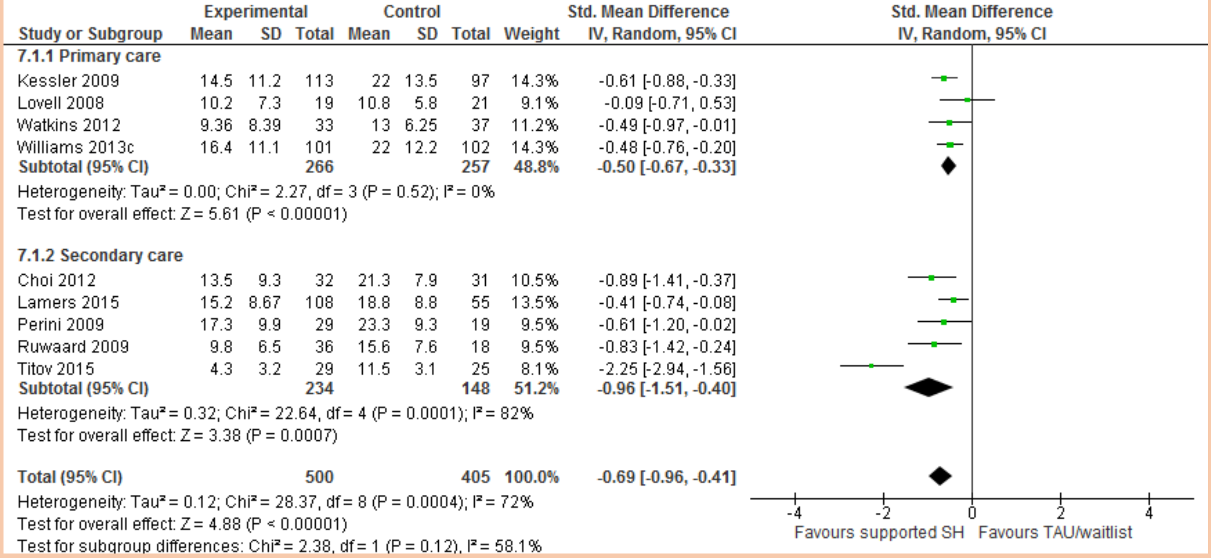
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Primary care						
Hallgren 2015	58	317	80	312	12.2%	0.71 [0.53, 0.96]
Joling 2011	18	86	6	84	7.3%	2.93 [1.22, 7.02]
Kivi 2014	15	45	12	47	9.3%	1.31 [0.69, 2.48]
Levesque 2011	58	174	47	176	12.0%	1.25 [0.90, 1.72]
Naylor 2010	4	19	1	19	2.3%	4.00 [0.49, 32.57]
Subtotal (95% CI)		**641**		**638**	**43.1%**	**1.29 [0.80, 2.08]**
Total events	153		146			
Heterogeneity: Tau² = 0.18; Chi² = 14.78, df = 4 (P = 0.005); I² = 73%						
Test for overall effect: Z = 1.04 (P = 0.30)						
4.3.2 Secondary care						
Geraedts 2014	41	116	19	115	10.7%	2.14 [1.33, 3.45]
Hoifodt 2013	19	50	7	54	8.1%	2.93 [1.35, 6.37]
Jamison 1995	7	40	1	40	2.4%	7.00 [0.90, 54.32]
Levin 2011	1	100	0	91	1.1%	2.73 [0.11, 66.25]
Liu 2009	6	27	6	25	6.4%	0.93 [0.34, 2.50]
Moldovan 2013	3	24	2	24	3.2%	1.50 [0.27, 8.19]
Moss 2012	3	13	0	13	1.3%	7.00 [0.40, 123.35]
Naeem 2014	2	96	7	96	3.7%	0.29 [0.06, 1.34]
Proudfoot 2004a	40	132	23	116	11.0%	1.53 [0.98, 2.39]
Salkovskis 2006	12	50	7	46	7.5%	1.58 [0.68, 3.66]
Selmi 1990	0	12	0	12		Not estimable
Spek 2007	20	87	0	100	1.4%	47.06 [2.89, 766.75]
Torkan 2014	0	26	0	13		Not estimable
Subtotal (95% CI)		**773**		**745**	**56.9%**	**1.84 [1.18, 2.85]**
Total events	154		72			
Heterogeneity: Tau² = 0.20; Chi² = 18.63, df = 10 (P = 0.05); I² = 46%						
Test for overall effect: Z = 2.70 (P = 0.007)						
Total (95% CI)		**1414**		**1383**	**100.0%**	**1.60 [1.13, 2.27]**
Total events	307		218			
Heterogeneity: Tau² = 0.24; Chi² = 44.68, df = 15 (P < 0.0001); I² = 66%						
Test for overall effect: Z = 2.63 (P = 0.009)						
Test for subgroup differences: Chi² = 1.13, df = 1 (P = 0.29), I² = 11.7%						

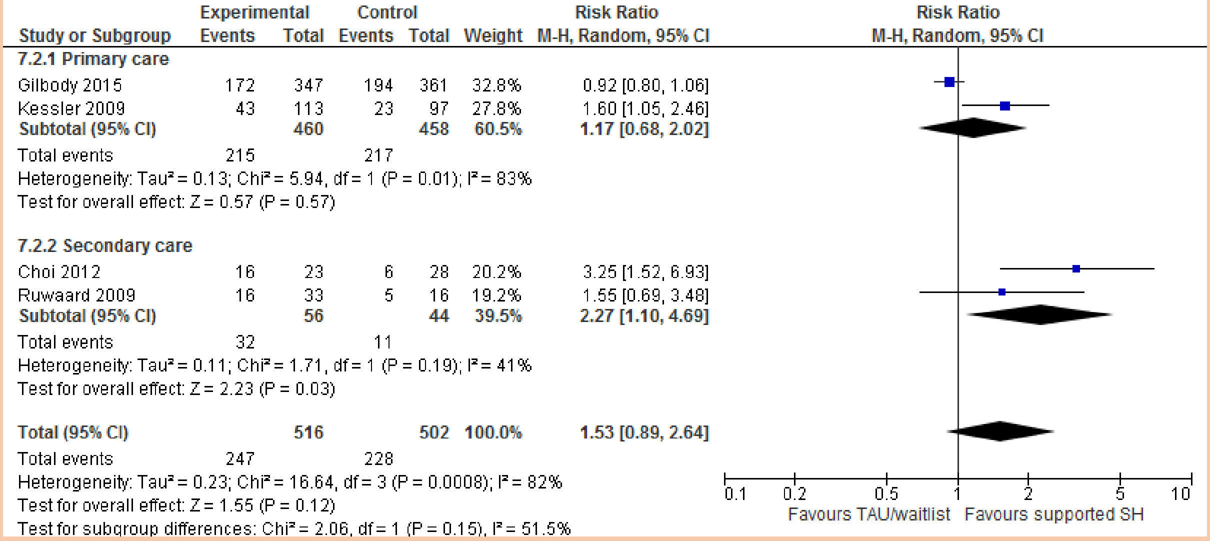
Self-help with support versus TAU/waitlist

Depression symptoms at endpoint (HAMD-17/PHQ-9/BDI[I, II or CH]/CES-D)



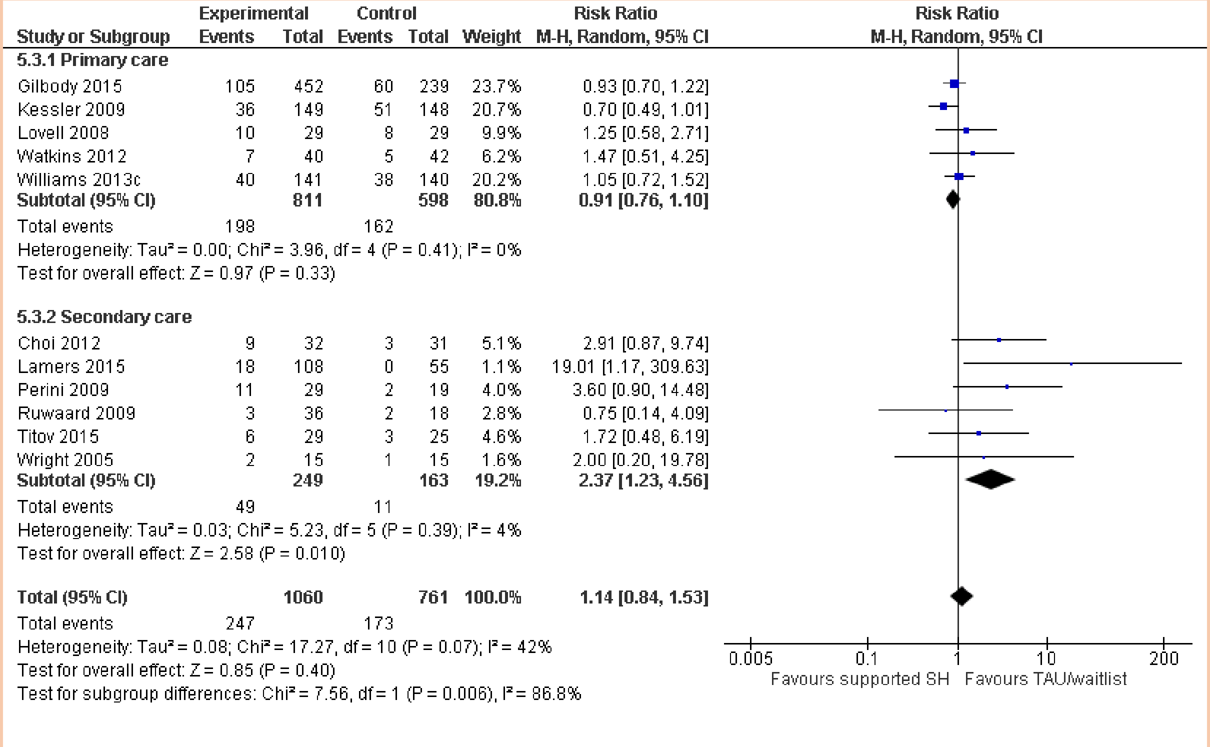
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.1.1 Primary care								
Kessler 2009	14.5	11.2	113	22	13.5	97	14.3%	-0.61 [-0.88, -0.33]
Lovell 2008	10.2	7.3	19	10.8	5.8	21	9.1%	-0.09 [-0.71, 0.53]
Watkins 2012	9.36	8.39	33	13	6.25	37	11.2%	-0.49 [-0.97, -0.01]
Williams 2013c	16.4	11.1	101	22	12.2	102	14.3%	-0.48 [-0.76, -0.20]
Subtotal (95% CI)			**266**			**257**	**48.8%**	**-0.50 [-0.67, -0.33]**
Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 3 (P = 0.52); I² = 0%								
Test for overall effect: Z = 5.61 (P < 0.00001)								
7.1.2 Secondary care								
Choi 2012	13.5	9.3	32	21.3	7.9	31	10.5%	-0.89 [-1.41, -0.37]
Lamers 2015	15.2	8.67	108	18.8	8.8	55	13.5%	-0.41 [-0.74, -0.08]
Perini 2009	17.3	9.9	29	23.3	9.3	19	9.5%	-0.61 [-1.20, -0.02]
Ruwaard 2009	9.8	6.5	36	15.6	7.6	18	9.5%	-0.83 [-1.42, -0.24]
Titov 2015	4.3	3.2	29	11.5	3.1	25	8.1%	-2.25 [-2.94, -1.56]
Subtotal (95% CI)			**234**			**148**	**51.2%**	**-0.96 [-1.51, -0.40]**
Heterogeneity: Tau² = 0.32; Chi² = 22.64, df = 4 (P = 0.0001); I² = 82%								
Test for overall effect: Z = 3.38 (P = 0.0007)								
Total (95% CI)			**500**			**405**	**100.0%**	**-0.69 [-0.96, -0.41]**
Heterogeneity: Tau² = 0.12; Chi² = 28.37, df = 8 (P = 0.0004); I² = 72%								
Test for overall effect: Z = 4.88 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.38, df = 1 (P = 0.12), I² = 58.1%								

Remission (PHQ-9/BDI <=9/<=16/<=10)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 Primary care						
Gilbody 2015	172	347	194	361	32.8%	0.92 [0.80, 1.06]
Kessler 2009	43	113	23	97	27.8%	1.60 [1.05, 2.46]
Subtotal (95% CI)		**460**		**458**	**60.5%**	**1.17 [0.68, 2.02]**
Total events	215		217			
Heterogeneity: Tau² = 0.13; Chi² = 5.94, df = 1 (P = 0.01); I² = 83%						
Test for overall effect: Z = 0.57 (P = 0.57)						
7.2.2 Secondary care						
Choi 2012	16	23	6	28	20.2%	3.25 [1.52, 6.93]
Ruwaard 2009	16	33	5	16	19.2%	1.55 [0.69, 3.48]
Subtotal (95% CI)		**56**		**44**	**39.5%**	**2.27 [1.10, 4.69]**
Total events	32		11			
Heterogeneity: Tau² = 0.11; Chi² = 1.71, df = 1 (P = 0.19); I² = 41%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Total (95% CI)		**516**		**502**	**100.0%**	**1.53 [0.89, 2.64]**
Total events	247		228			
Heterogeneity: Tau² = 0.23; Chi² = 16.64, df = 3 (P = 0.0008); I² = 82%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 2.06, df = 1 (P = 0.15), I² = 51.5%						

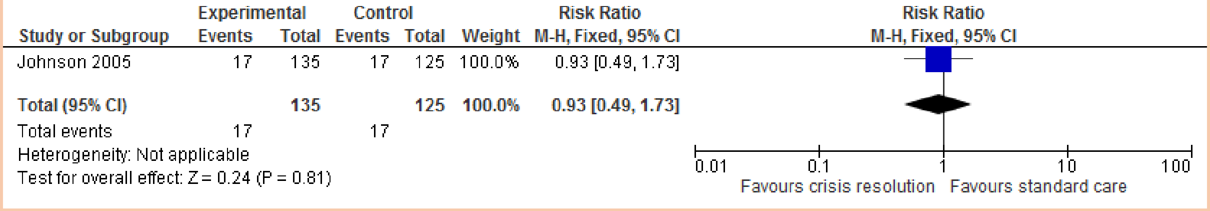
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 Primary care						
Gilbody 2015	105	452	60	239	23.7%	0.93 [0.70, 1.22]
Kessler 2009	36	149	51	148	20.7%	0.70 [0.49, 1.01]
Lovell 2008	10	29	8	29	9.9%	1.25 [0.58, 2.71]
Watkins 2012	7	40	5	42	6.2%	1.47 [0.51, 4.25]
Williams 2013c	40	141	38	140	20.2%	1.05 [0.72, 1.52]
Subtotal (95% CI)		**811**		**598**	**80.8%**	**0.91 [0.76, 1.10]**
Total events	198		162			
Heterogeneity: Tau² = 0.00; Chi² = 3.96, df = 4 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
5.3.2 Secondary care						
Choi 2012	9	32	3	31	5.1%	2.91 [0.87, 9.74]
Lamers 2015	18	108	0	55	1.1%	19.01 [1.17, 309.63]
Perini 2009	11	29	2	19	4.0%	3.60 [0.90, 14.48]
Ruwaard 2009	3	36	2	18	2.8%	0.75 [0.14, 4.09]
Titov 2015	6	29	3	25	4.6%	1.72 [0.48, 6.19]
Wright 2005	2	15	1	15	1.6%	2.00 [0.20, 19.78]
Subtotal (95% CI)		**249**		**163**	**19.2%**	**2.37 [1.23, 4.56]**
Total events	49		11			
Heterogeneity: Tau² = 0.03; Chi² = 5.23, df = 5 (P = 0.39); I² = 4%						
Test for overall effect: Z = 2.58 (P = 0.010)						
Total (95% CI)		**1060**		**761**	**100.0%**	**1.14 [0.84, 1.53]**
Total events	247		173			
Heterogeneity: Tau² = 0.08; Chi² = 17.27, df = 10 (P = 0.07); I² = 42%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Chi² = 7.56, df = 1 (P = 0.006), I² = 86.8%						

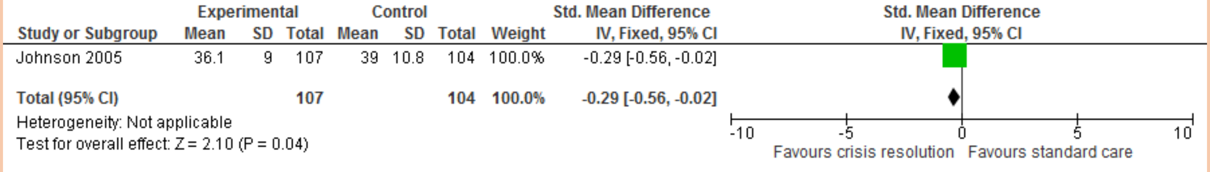
Crisis resolution team care versus standard care

Lost to follow-up by end of study (12 months)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Johnson 2005	17	135	17	125	100.0%	0.93 [0.49, 1.73]
Total (95% CI)		**135**		**125**	**100.0%**	**0.93 [0.49, 1.73]**
Total events	17		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						

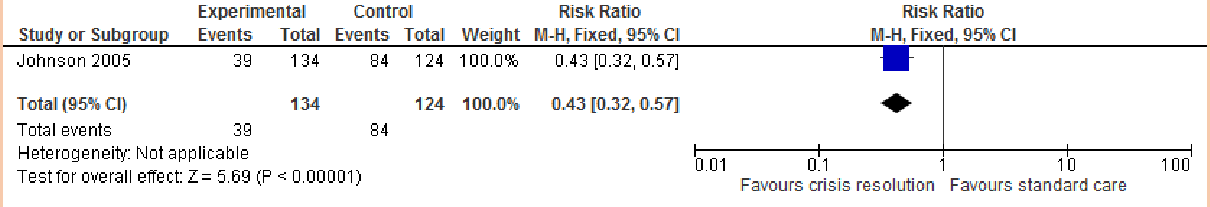
Symptom severity (BPRS) 8 weeks after crisis



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Johnson 2005	36.1	9	107	39	10.8	104	100.0%	-0.29 [-0.56, -0.02]
Total (95% CI)			**107**			**104**	**100.0%**	**-0.29 [-0.56, -0.02]**

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

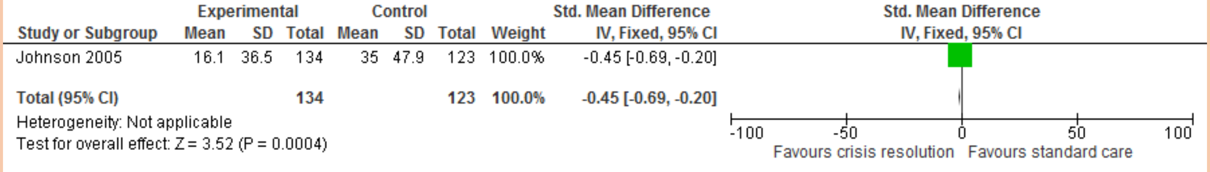
Admission as inpatient (6 months after crisis)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Johnson 2005	39	134	84	124	100.0%	0.43 [0.32, 0.57]
Total (95% CI)		**134**		**124**	**100.0%**	**0.43 [0.32, 0.57]**
Total events	39		84			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.69 (P < 0.00001)

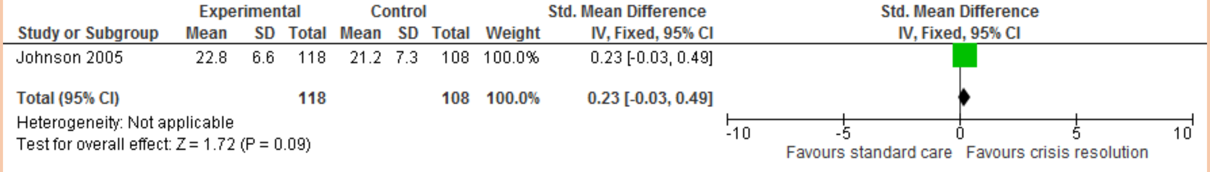
Bed days in hospital (6 months after crisis)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Johnson 2005	16.1	36.5	134	35	47.9	123	100.0%	-0.45 [-0.69, -0.20]
Total (95% CI)			**134**			**123**	**100.0%**	**-0.45 [-0.69, -0.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.52 (P = 0.0004)

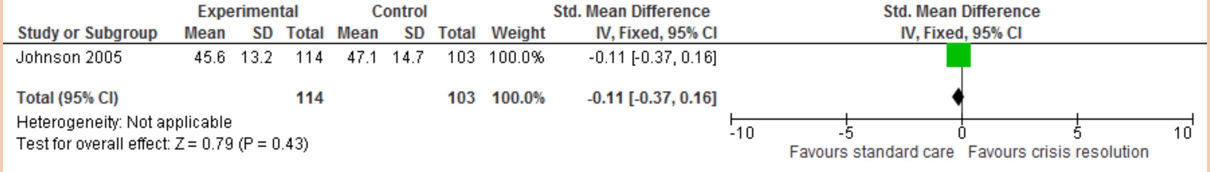
Patient satisfaction (CSQ-8) 8 weeks after crisis



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Johnson 2005	22.8	6.6	118	21.2	7.3	108	100.0%	0.23 [-0.03, 0.49]
Total (95% CI)			**118**			**108**	**100.0%**	**0.23 [-0.03, 0.49]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)

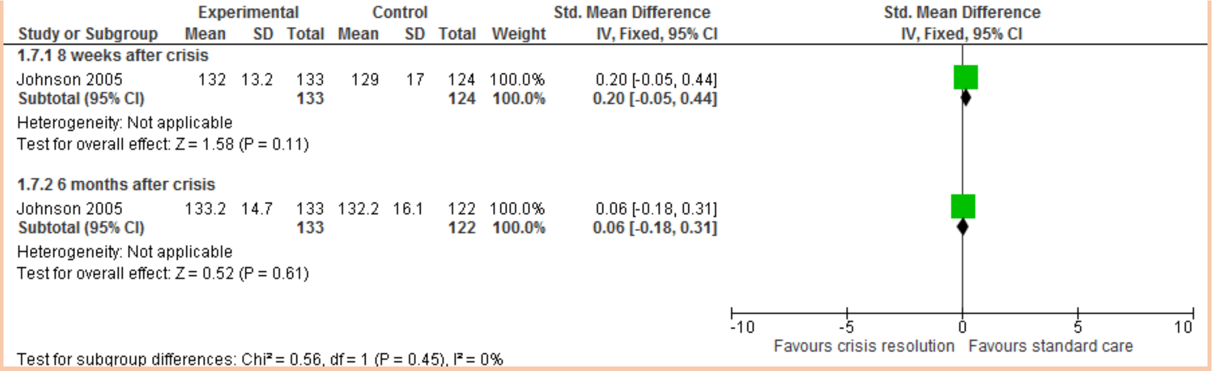
Quality of life (MANSA) 8 weeks after crisis



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Johnson 2005	45.6	13.2	114	47.1	14.7	103	100.0%	-0.11 [-0.37, 0.16]
Total (95% CI)			**114**			**103**	**100.0%**	**-0.11 [-0.37, 0.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

Social functioning (LSP)

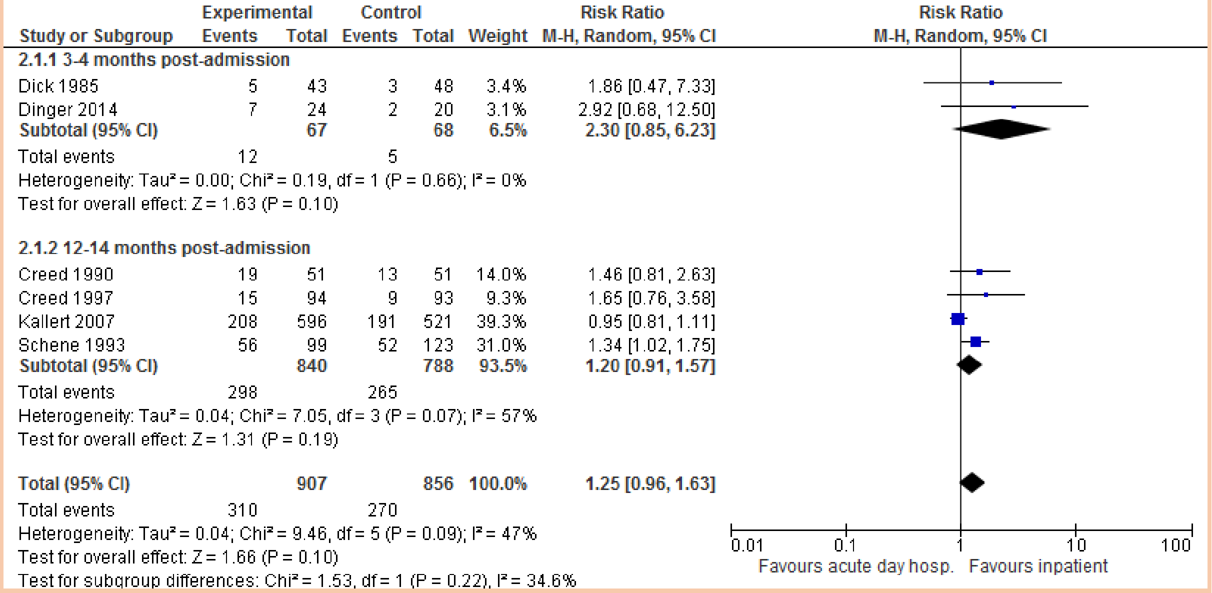


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.7.1 8 weeks after crisis								
Johnson 2005	132	13.2	133	129	17	124	100.0%	0.20 [-0.05, 0.44]
Subtotal (95% CI)			**133**			**124**	**100.0%**	**0.20 [-0.05, 0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
1.7.2 6 months after crisis								
Johnson 2005	133.2	14.7	133	132.2	16.1	122	100.0%	0.06 [-0.18, 0.31]
Subtotal (95% CI)			**133**			**122**	**100.0%**	**0.06 [-0.18, 0.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.61)								

Test for subgroup differences: Chi^2 = 0.56, df = 1 (P = 0.45), I^2 = 0%

Acute day hospital care versus inpatient care

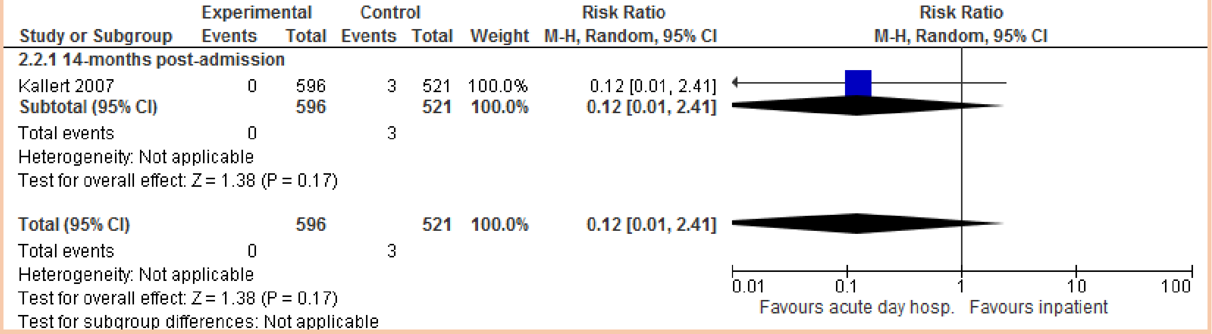
Lost to follow-up (by end of study)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 3-4 months post-admission						
Dick 1985	5	43	3	48	3.4%	1.86 [0.47, 7.33]
Dinger 2014	7	24	2	20	3.1%	2.92 [0.68, 12.50]
Subtotal (95% CI)		**67**		**68**	**6.5%**	**2.30 [0.85, 6.23]**
Total events	12		5			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.19, df = 1 (P = 0.66); I^2 = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
2.1.2 12-14 months post-admission						
Creed 1990	19	51	13	51	14.0%	1.46 [0.81, 2.63]
Creed 1997	15	94	9	93	9.3%	1.65 [0.76, 3.58]
Kallert 2007	208	596	191	521	39.3%	0.95 [0.81, 1.11]
Schene 1993	56	99	52	123	31.0%	1.34 [1.02, 1.75]
Subtotal (95% CI)		**840**		**788**	**93.5%**	**1.20 [0.91, 1.57]**
Total events	298		265			
Heterogeneity: Tau^2 = 0.04; Chi^2 = 7.05, df = 3 (P = 0.07); I^2 = 57%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**907**		**856**	**100.0%**	**1.25 [0.96, 1.63]**
Total events	310		270			
Heterogeneity: Tau^2 = 0.04; Chi^2 = 9.46, df = 5 (P = 0.09); I^2 = 47%						
Test for overall effect: Z = 1.66 (P = 0.10)						

Test for subgroup differences: Chi^2 = 1.53, df = 1 (P = 0.22), I^2 = 34.6%

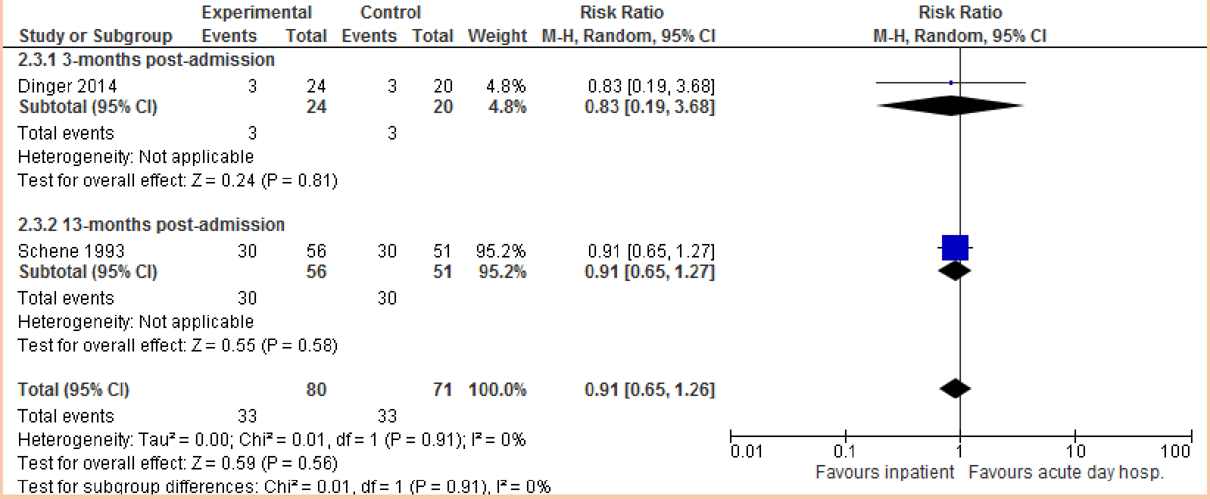
Death (suicide)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 14-months post-admission						
Kallert 2007	0	596	3	521	100.0%	0.12 [0.01, 2.41]
Subtotal (95% CI)		**596**		**521**	**100.0%**	**0.12 [0.01, 2.41]**
Total events	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)		**596**		**521**	**100.0%**	**0.12 [0.01, 2.41]**
Total events	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						

Test for subgroup differences: Not applicable

Remission (HAM-D<7/Present State Examination: Index of Definition $\leq$4)

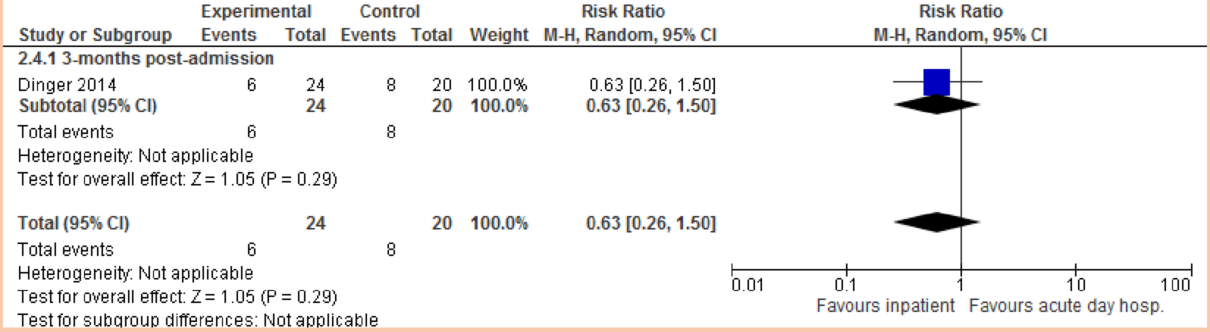


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 3-months post-admission						
Dinger 2014	3	24	3	20	4.8%	0.83 [0.19, 3.68]
Subtotal (95% CI)		**24**		**20**	**4.8%**	**0.83 [0.19, 3.68]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
2.3.2 13-months post-admission						
Schene 1993	30	56	30	51	95.2%	0.91 [0.65, 1.27]
Subtotal (95% CI)		**56**		**51**	**95.2%**	**0.91 [0.65, 1.27]**
Total events	30		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
Total (95% CI)		**80**		**71**	**100.0%**	**0.91 [0.65, 1.26]**
Total events	33		33			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours inpatient
Favours acute day hosp.

Response (at least 47% improvement on HAM-D)

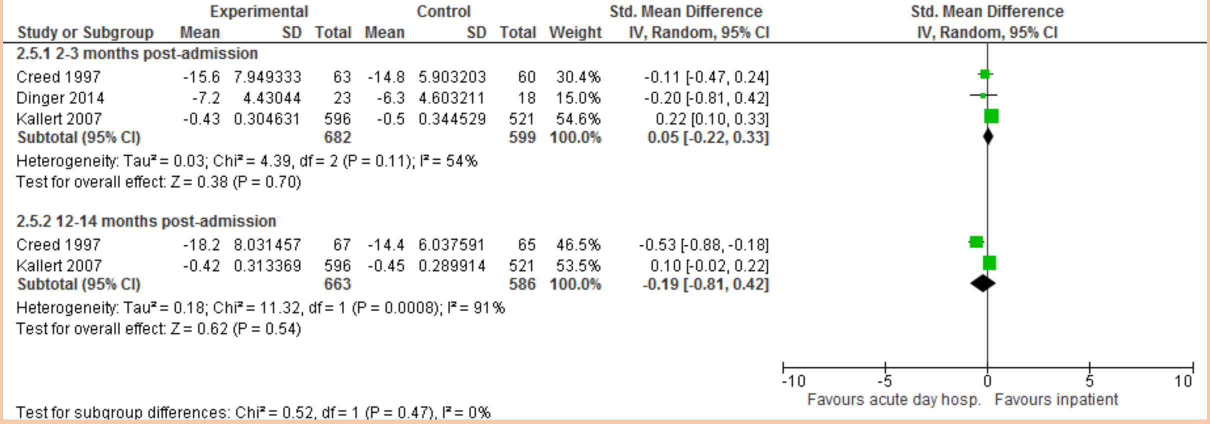


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 3-months post-admission						
Dinger 2014	6	24	8	20	100.0%	0.63 [0.26, 1.50]
Subtotal (95% CI)		**24**		**20**	**100.0%**	**0.63 [0.26, 1.50]**
Total events	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**24**		**20**	**100.0%**	**0.63 [0.26, 1.50]**
Total events	6		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours inpatient
Favours acute day hosp.

Symptom severity (BPRS/CPRS/HAM-D change score)

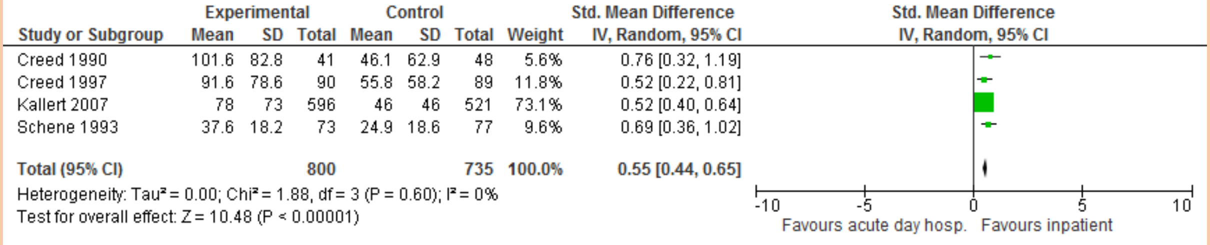


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 2-3 months post-admission								
Creed 1997	-15.6	7.949333	63	-14.8	5.903203	60	30.4%	-0.11 [-0.47, 0.24]
Dinger 2014	-7.2	4.43044	23	-6.3	4.603211	18	15.0%	-0.20 [-0.81, 0.42]
Kallert 2007	-0.43	0.304631	596	-0.5	0.344529	521	54.6%	0.22 [0.10, 0.33]
Subtotal (95% CI)			**682**			**599**	**100.0%**	**0.05 [-0.22, 0.33]**
Heterogeneity: Tau² = 0.03; Chi² = 4.39, df = 2 (P = 0.11); I² = 54%								
Test for overall effect: Z = 0.38 (P = 0.70)								
2.5.2 12-14 months post-admission								
Creed 1997	-18.2	8.031457	67	-14.4	6.037591	65	46.5%	-0.53 [-0.88, -0.18]
Kallert 2007	-0.42	0.313369	596	-0.45	0.289914	521	53.5%	0.10 [-0.02, 0.22]
Subtotal (95% CI)			**663**			**586**	**100.0%**	**-0.19 [-0.81, 0.42]**
Heterogeneity: Tau² = 0.18; Chi² = 11.32, df = 1 (P = 0.0008); I² = 91%								
Test for overall effect: Z = 0.62 (P = 0.54)								

Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours acute day hosp.
Favours inpatient

Duration of index admission

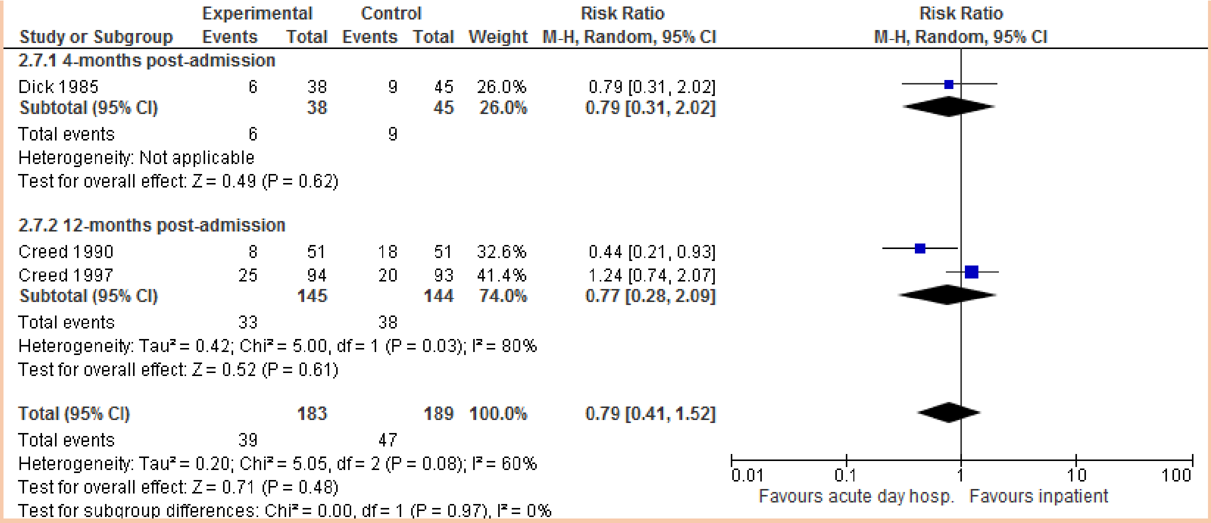


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Creed 1990	101.6	82.8	41	46.1	62.9	48	5.6%	0.76 [0.32, 1.19]
Creed 1997	91.6	78.6	90	55.8	58.2	89	11.8%	0.52 [0.22, 0.81]
Kallert 2007	78	73	596	46	46	521	73.1%	0.52 [0.40, 0.64]
Schene 1993	37.6	18.2	73	24.9	18.6	77	9.6%	0.69 [0.36, 1.02]
Total (95% CI)			**800**			**735**	**100.0%**	**0.55 [0.44, 0.65]**

Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 10.48 (P < 0.00001)

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours acute day hosp.
Favours inpatient

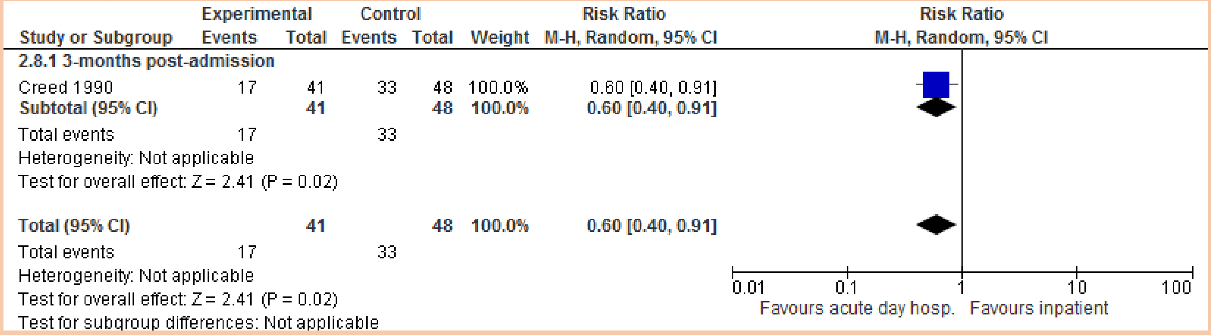
Readmission



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 4-months post-admission						
Dick 1985	6	38	9	45	26.0%	0.79 [0.31, 2.02]
Subtotal (95% CI)		**38**		**45**	**26.0%**	**0.79 [0.31, 2.02]**
Total events	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
2.7.2 12-months post-admission						
Creed 1990	8	51	18	51	32.6%	0.44 [0.21, 0.93]
Creed 1997	25	94	20	93	41.4%	1.24 [0.74, 2.07]
Subtotal (95% CI)		**145**		**144**	**74.0%**	**0.77 [0.28, 2.09]**
Total events	33		38			
Heterogeneity: Tau² = 0.42; Chi² = 5.00, df = 1 (P = 0.03); I² = 80%						
Test for overall effect: Z = 0.52 (P = 0.61)						
Total (95% CI)		**183**		**189**	**100.0%**	**0.79 [0.41, 1.52]**
Total events	39		47			
Heterogeneity: Tau² = 0.20; Chi² = 5.05, df = 2 (P = 0.08); I² = 60%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acute day hosp.
Favours inpatient

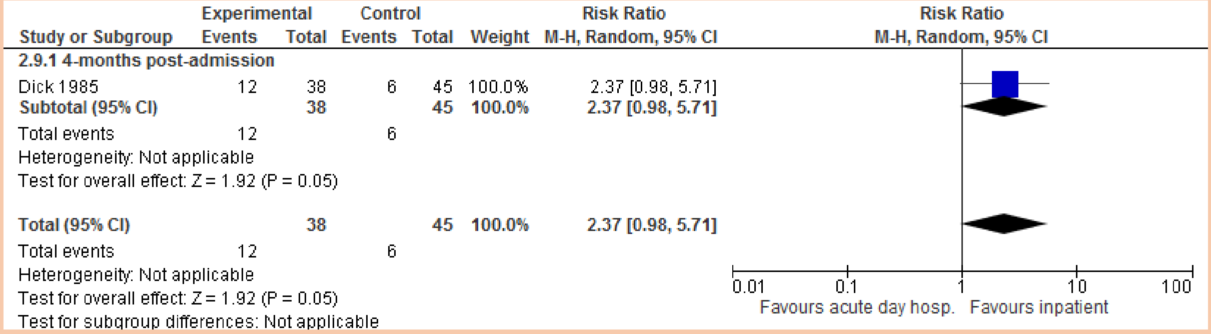
Discharge



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 3-months post-admission						
Creed 1990	17	41	33	48	100.0%	0.60 [0.40, 0.91]
Subtotal (95% CI)		**41**		**48**	**100.0%**	**0.60 [0.40, 0.91]**
Total events	17		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.41 (P = 0.02)						
Total (95% CI)		**41**		**48**	**100.0%**	**0.60 [0.40, 0.91]**
Total events	17		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acute day hosp.
Favours inpatient

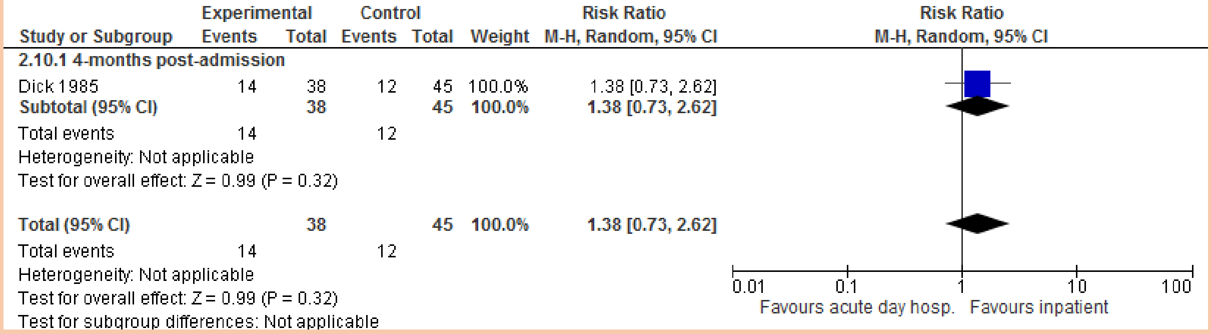
Service utilisation: Emergency contacts



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 4-months post-admission						
Dick 1985	12	38	6	45	100.0%	2.37 [0.98, 5.71]
Subtotal (95% CI)		**38**		**45**	**100.0%**	**2.37 [0.98, 5.71]**
Total events	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						
Total (95% CI)		**38**		**45**	**100.0%**	**2.37 [0.98, 5.71]**
Total events	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acute day hosp.
Favours inpatient

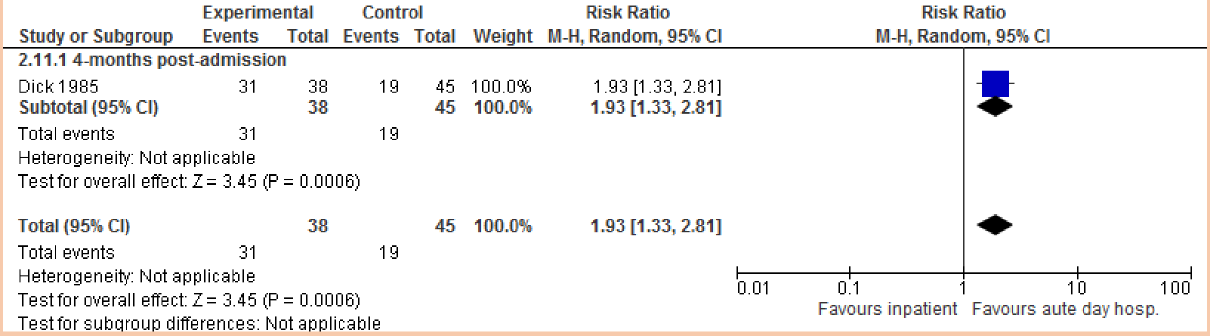
Service utilisation: Outpatient contact



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 4-months post-admission						
Dick 1985	14	38	12	45	100.0%	1.38 [0.73, 2.62]
Subtotal (95% CI)		**38**		**45**	**100.0%**	**1.38 [0.73, 2.62]**
Total events	14		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**38**		**45**	**100.0%**	**1.38 [0.73, 2.62]**
Total events	14		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acute day hosp.
Favours inpatient

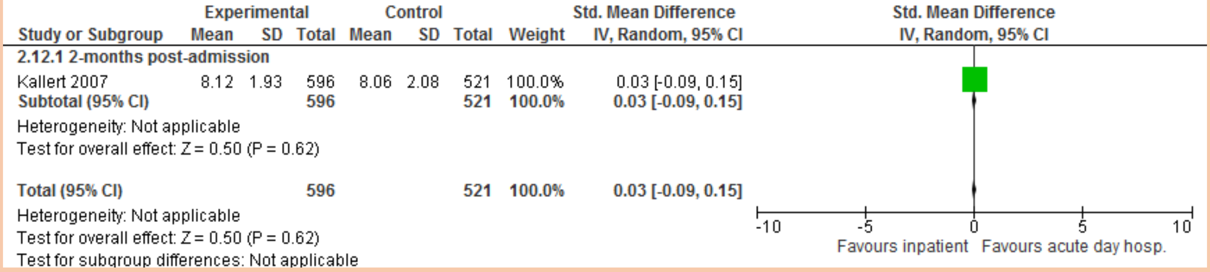
Satisfaction (number of participants satisfied or very satisfied with their treatment)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 4-months post-admission						
Dick 1985	31	38	19	45	100.0%	1.93 [1.33, 2.81]
Subtotal (95% CI)		**38**		**45**	**100.0%**	**1.93 [1.33, 2.81]**
Total events	31		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Total (95% CI)		**38**		**45**	**100.0%**	**1.93 [1.33, 2.81]**
Total events	31		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours inpatient
Favours aute day hosp.

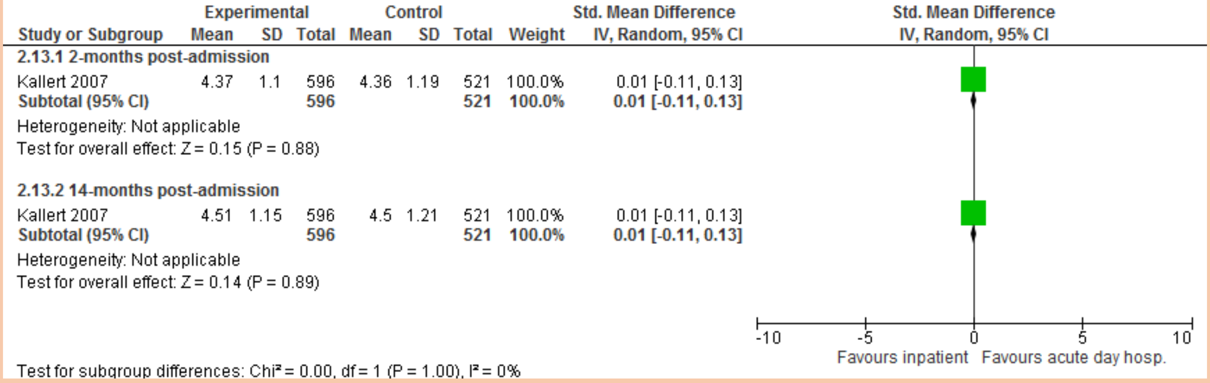
Satisfaction (CAT)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.12.1 2-months post-admission								
Kallert 2007	8.12	1.93	596	8.06	2.08	521	100.0%	0.03 [-0.09, 0.15]
Subtotal (95% CI)			**596**			**521**	**100.0%**	**0.03 [-0.09, 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.62)								
Total (95% CI)			**596**			**521**	**100.0%**	**0.03 [-0.09, 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.50 (P = 0.62)								
Test for subgroup differences: Not applicable								

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours inpatient
Favours acute day hosp.

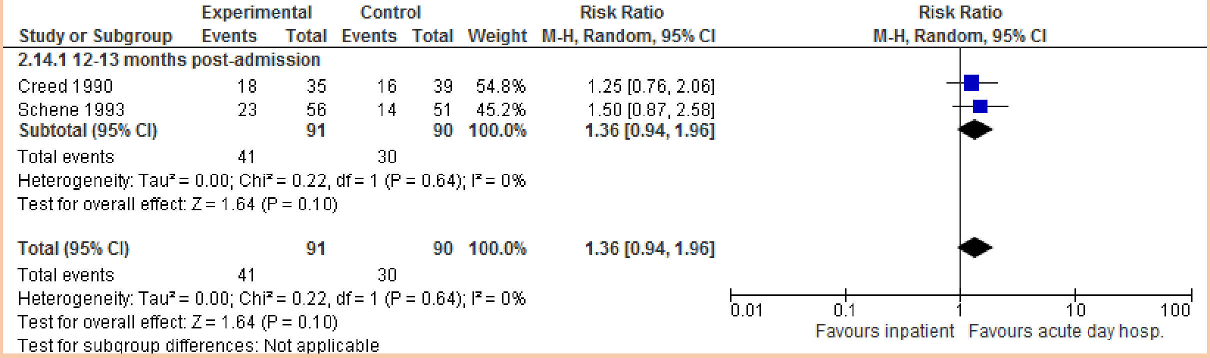
Quality of life (MANSA)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.13.1 2-months post-admission								
Kallert 2007	4.37	1.1	596	4.36	1.19	521	100.0%	0.01 [-0.11, 0.13]
Subtotal (95% CI)			**596**			**521**	**100.0%**	**0.01 [-0.11, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.15 (P = 0.88)								
2.13.2 14-months post-admission								
Kallert 2007	4.51	1.15	596	4.5	1.21	521	100.0%	0.01 [-0.11, 0.13]
Subtotal (95% CI)			**596**			**521**	**100.0%**	**0.01 [-0.11, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours inpatient
Favours acute day hosp.

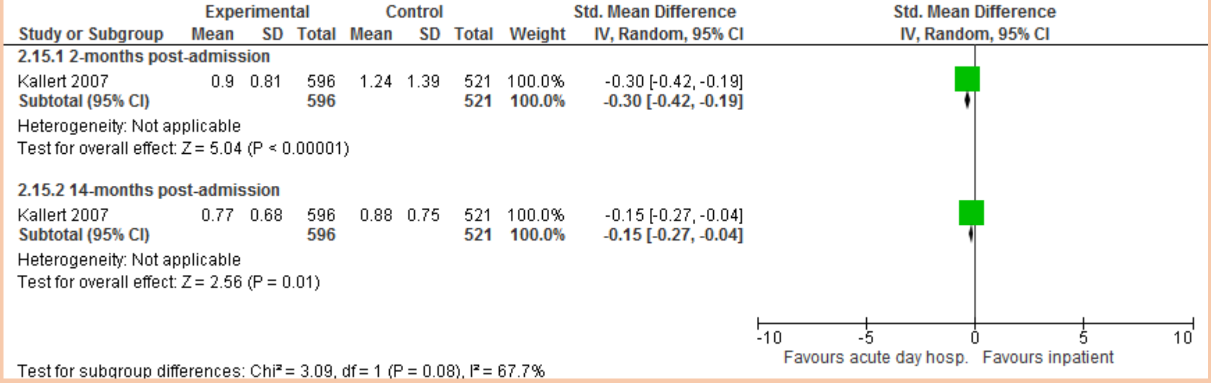
Social functioning response (2 role disabilities or less on Groningen Social Disabilities Schedule [GSDS]/number of participants living in the community and social functioning at previous level [according to the social performance and behaviour assessment schedule])



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 12-13 months post-admission						
Creed 1990	18	35	16	39	54.8%	1.25 [0.76, 2.06]
Schene 1993	23	56	14	51	45.2%	1.50 [0.87, 2.58]
Subtotal (95% CI)		**91**		**90**	**100.0%**	**1.36 [0.94, 1.96]**
Total events	41		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
Total (95% CI)		**91**		**90**	**100.0%**	**1.36 [0.94, 1.96]**
Total events	41		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours inpatient
Favours acute day hosp.

Social functioning impairment (GSDS-II)

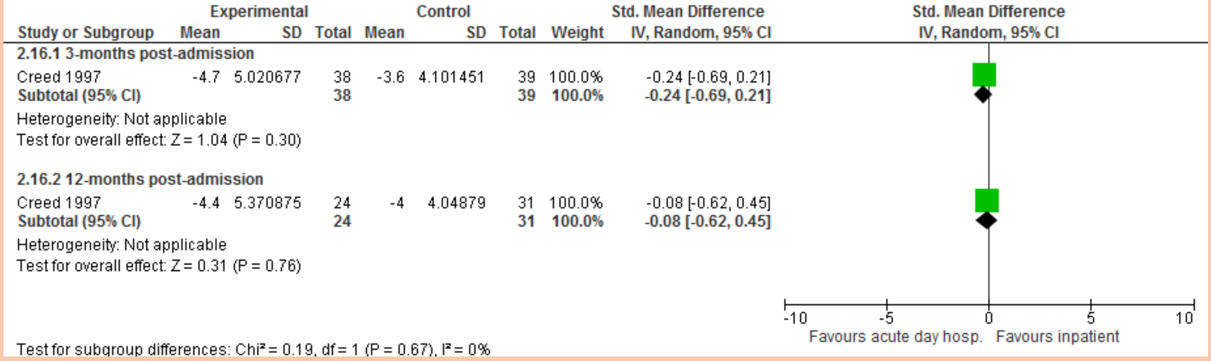


	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
2.15.1 2-months post-admission								
Kallert 2007	0.9	0.81	596	1.24	1.39	521	100.0%	-0.30 [-0.42, -0.19]
Subtotal (95% CI)			**596**			**521**	**100.0%**	**-0.30 [-0.42, -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.04 (P < 0.00001)								
2.15.2 14-months post-admission								
Kallert 2007	0.77	0.68	596	0.88	0.75	521	100.0%	-0.15 [-0.27, -0.04]
Subtotal (95% CI)			**596**			**521**	**100.0%**	**-0.15 [-0.27, -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.56 (P = 0.01)								

Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 67.7%

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours acute day hosp.
Favours inpatient

Carer distress (GHQ change score)



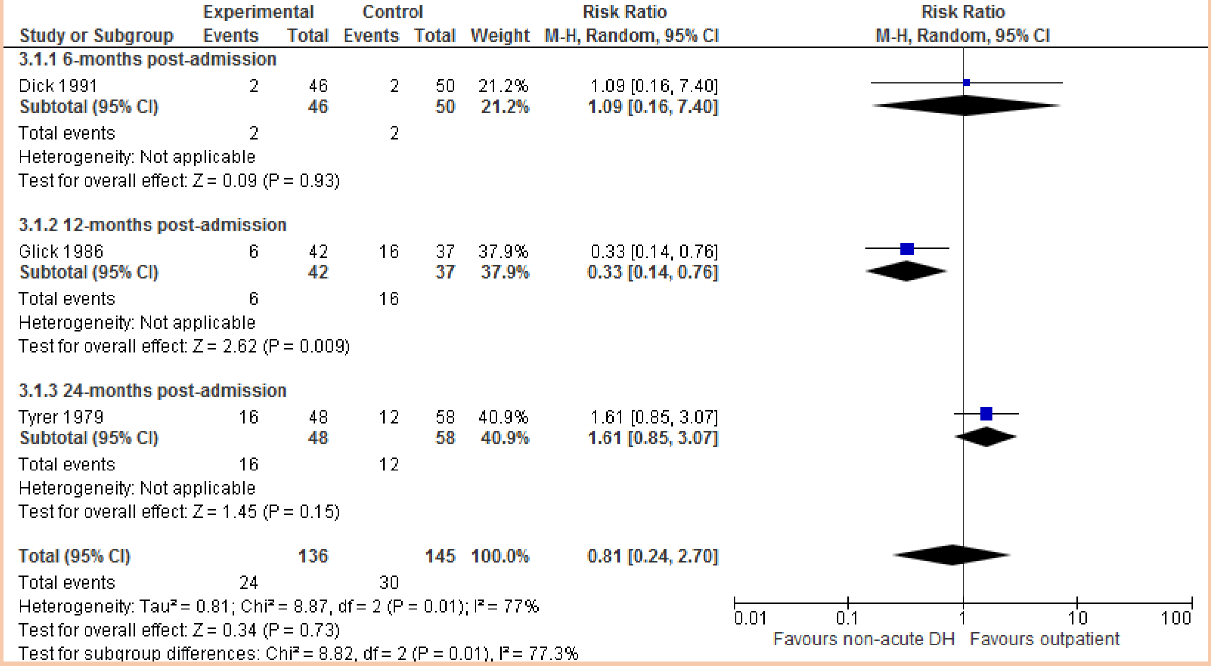
	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
2.16.1 3-months post-admission								
Creed 1997	-4.7	5.020677	38	-3.6	4.101451	39	100.0%	-0.24 [-0.69, 0.21]
Subtotal (95% CI)			**38**			**39**	**100.0%**	**-0.24 [-0.69, 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.04 (P = 0.30)								
2.16.2 12-months post-admission								
Creed 1997	-4.4	5.370875	24	-4	4.04879	31	100.0%	-0.08 [-0.62, 0.45]
Subtotal (95% CI)			**24**			**31**	**100.0%**	**-0.08 [-0.62, 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								

Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours acute day hosp.
Favours inpatient

Non-acute day hospital care versus outpatient care

Lost to follow-up (by end of study)

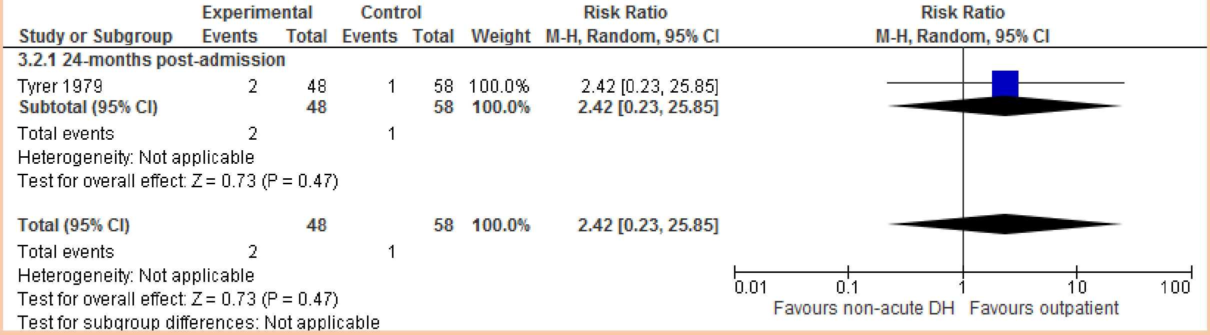


	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
3.1.1 6-months post-admission						
Dick 1991	2	46	2	50	21.2%	1.09 [0.16, 7.40]
Subtotal (95% CI)		**46**		**50**	**21.2%**	**1.09 [0.16, 7.40]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
3.1.2 12-months post-admission						
Glick 1986	6	42	16	37	37.9%	0.33 [0.14, 0.76]
Subtotal (95% CI)		**42**		**37**	**37.9%**	**0.33 [0.14, 0.76]**
Total events	6		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.62 (P = 0.009)						
3.1.3 24-months post-admission						
Tyrer 1979	16	48	12	58	40.9%	1.61 [0.85, 3.07]
Subtotal (95% CI)		**48**		**58**	**40.9%**	**1.61 [0.85, 3.07]**
Total events	16		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**136**		**145**	**100.0%**	**0.81 [0.24, 2.70]**
Total events	24		30			

Heterogeneity: Tau² = 0.81; Chi² = 8.87, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Chi² = 8.82, df = 2 (P = 0.01), I² = 77.3%

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours non-acute DH
Favours outpatient

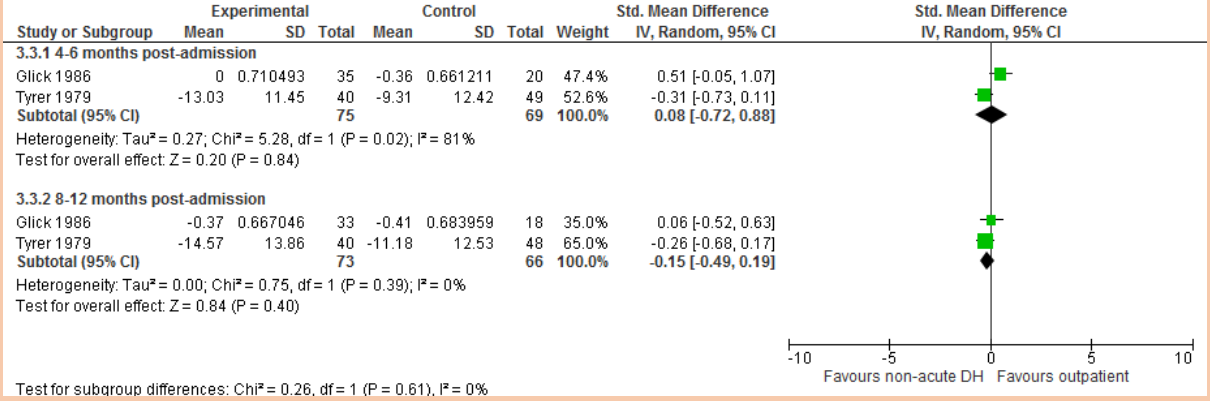
Death (all causes)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 24-months post-admission						
Tyrer 1979	2	48	1	58	100.0%	2.42 [0.23, 25.85]
Subtotal (95% CI)		**48**		**58**	**100.0%**	**2.42 [0.23, 25.85]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**48**		**58**	**100.0%**	**2.42 [0.23, 25.85]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours non-acute DH
Favours outpatient

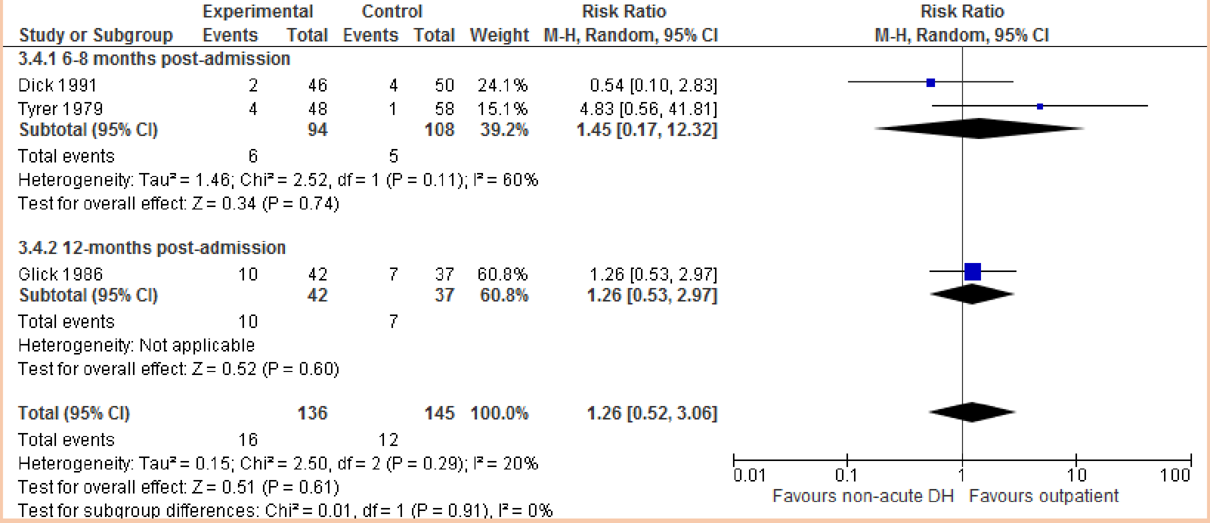
Symptom severity (Psychiatric Evaluation Form/Present State Examination; change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.1 4-6 months post-admission								
Glick 1986	0	0.710493	35	-0.36	0.661211	20	47.4%	0.51 [-0.05, 1.07]
Tyrer 1979	-13.03	11.45	40	-9.31	12.42	49	52.6%	-0.31 [-0.73, 0.11]
Subtotal (95% CI)			**75**			**69**	**100.0%**	**0.08 [-0.72, 0.88]**
Heterogeneity: Tau² = 0.27; Chi² = 5.28, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 0.20 (P = 0.84)								
3.3.2 8-12 months post-admission								
Glick 1986	-0.37	0.667046	33	-0.41	0.683959	18	35.0%	0.06 [-0.52, 0.63]
Tyrer 1979	-14.57	13.86	40	-11.18	12.53	48	65.0%	-0.26 [-0.68, 0.17]
Subtotal (95% CI)			**73**			**66**	**100.0%**	**-0.15 [-0.49, 0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 0.84 (P = 0.40)								
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%								

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours non-acute DH
Favours outpatient

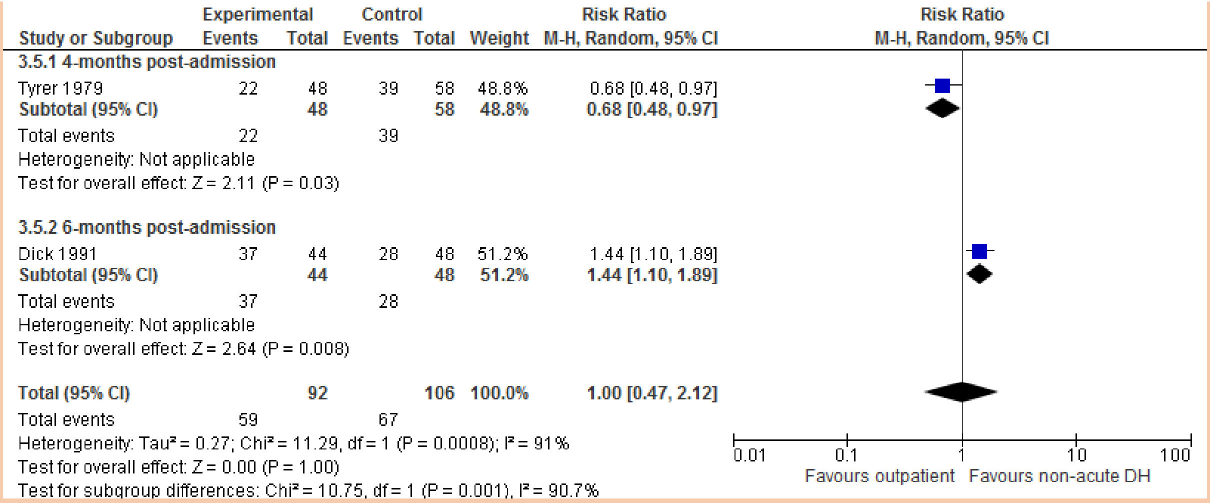
Admission as inpatient



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 6-8 months post-admission						
Dick 1991	2	46	4	50	24.1%	0.54 [0.10, 2.83]
Tyrer 1979	4	48	1	58	15.1%	4.83 [0.56, 41.81]
Subtotal (95% CI)		**94**		**108**	**39.2%**	**1.45 [0.17, 12.32]**
Total events	6		5			
Heterogeneity: Tau² = 1.46; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 0.34 (P = 0.74)						
3.4.2 12-months post-admission						
Glick 1986	10	42	7	37	60.8%	1.26 [0.53, 2.97]
Subtotal (95% CI)		**42**		**37**	**60.8%**	**1.26 [0.53, 2.97]**
Total events	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
Total (95% CI)		**136**		**145**	**100.0%**	**1.26 [0.52, 3.06]**
Total events	16		12			
Heterogeneity: Tau² = 0.15; Chi² = 2.50, df = 2 (P = 0.29); I² = 20%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours non-acute DH
Favours outpatient

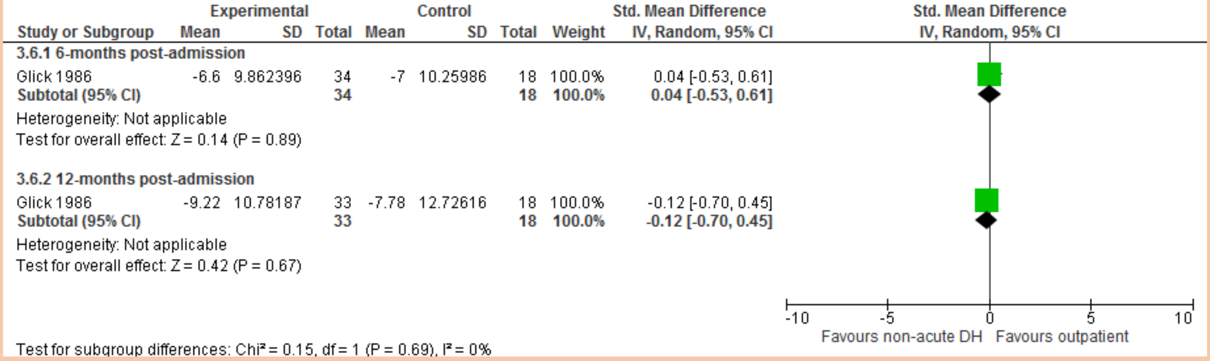
Satisfaction (number of participants satisfied or very satisfied with their treatment)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 4-months post-admission						
Tyrer 1979	22	48	39	58	48.8%	0.68 [0.48, 0.97]
Subtotal (95% CI)		**48**		**58**	**48.8%**	**0.68 [0.48, 0.97]**
Total events	22		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.11 (P = 0.03)						
3.5.2 6-months post-admission						
Dick 1991	37	44	28	48	51.2%	1.44 [1.10, 1.89]
Subtotal (95% CI)		**44**		**48**	**51.2%**	**1.44 [1.10, 1.89]**
Total events	37		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.64 (P = 0.008)						
Total (95% CI)		**92**		**106**	**100.0%**	**1.00 [0.47, 2.12]**
Total events	59		67			
Heterogeneity: Tau² = 0.27; Chi² = 11.29, df = 1 (P = 0.0008); I² = 91%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 10.75, df = 1 (P = 0.001), I² = 90.7%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours outpatient
Favours non-acute DH

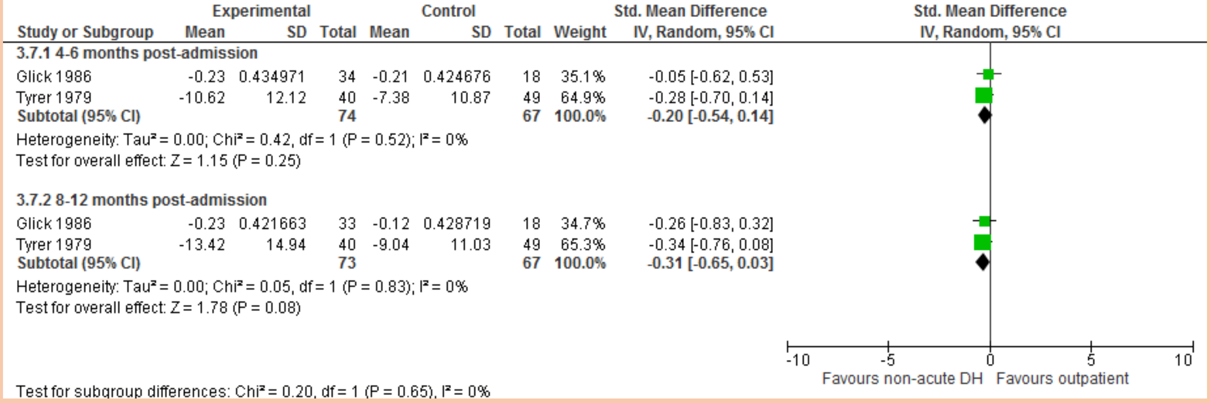
Global functioning (GAS; change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.6.1 6-months post-admission								
Glick 1986	-6.6	9.862396	34	-7	10.25986	18	100.0%	0.04 [-0.53, 0.61]
Subtotal (95% CI)			**34**			**18**	**100.0%**	**0.04 [-0.53, 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								
3.6.2 12-months post-admission								
Glick 1986	-9.22	10.78187	33	-7.78	12.72616	18	100.0%	-0.12 [-0.70, 0.45]
Subtotal (95% CI)			**33**			**18**	**100.0%**	**-0.12 [-0.70, 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.69), I² = 0%								

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours non-acute DH
Favours outpatient

Social functioning (SAS-SR/SFS; change score)

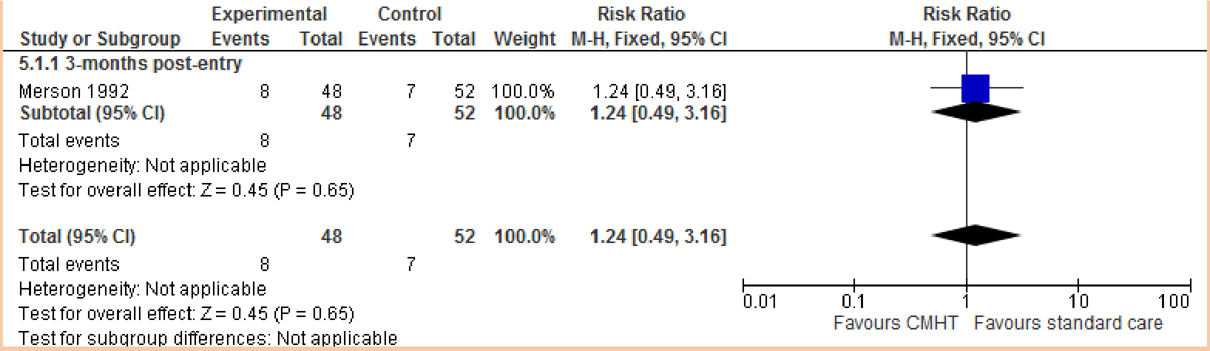


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.7.1 4-6 months post-admission								
Glick 1986	-0.23	0.434971	34	-0.21	0.424676	18	35.1%	-0.05 [-0.62, 0.53]
Tyrer 1979	-10.62	12.12	40	-7.38	10.87	49	64.9%	-0.28 [-0.70, 0.14]
Subtotal (95% CI)			**74**			**67**	**100.0%**	**-0.20 [-0.54, 0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 1.15 (P = 0.25)								
3.7.2 8-12 months post-admission								
Glick 1986	-0.23	0.421663	33	-0.12	0.428719	18	34.7%	-0.26 [-0.83, 0.32]
Tyrer 1979	-13.42	14.94	40	-9.04	11.03	49	65.3%	-0.34 [-0.76, 0.08]
Subtotal (95% CI)			**73**			**67**	**100.0%**	**-0.31 [-0.65, 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 1.78 (P = 0.08)								
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%								

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours non-acute DH
Favours outpatient

Community mental health teams (CMHTs) versus standard care

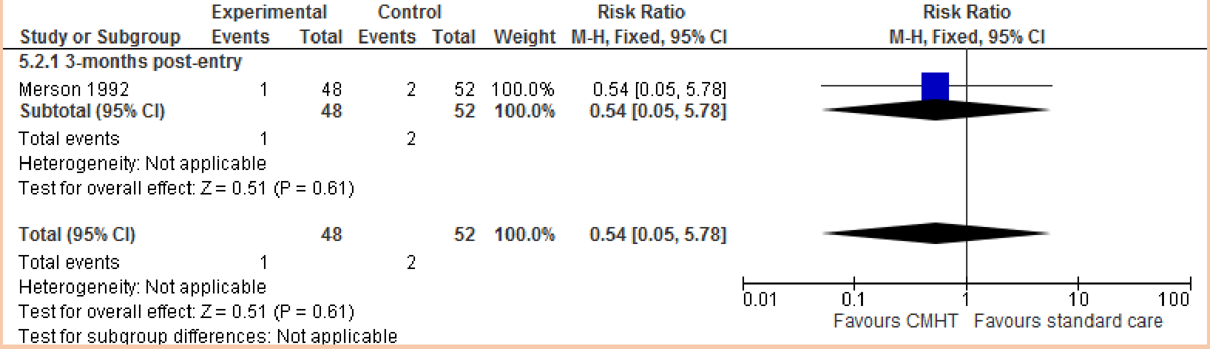
Lost to follow-up (by end of study)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 3-months post-entry						
Merson 1992	8	48	7	52	100.0%	1.24 [0.49, 3.16]
Subtotal (95% CI)		**48**		**52**	**100.0%**	**1.24 [0.49, 3.16]**
Total events	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**48**		**52**	**100.0%**	**1.24 [0.49, 3.16]**
Total events	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours CMHT
Favours standard care

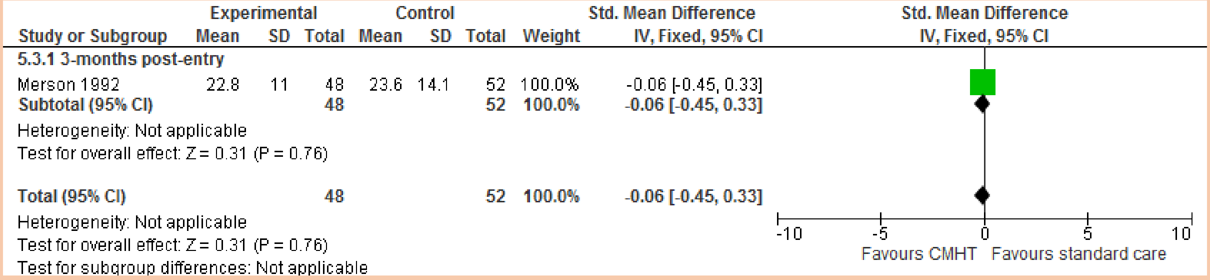
Death (all causes)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 3-months post-entry						
Merson 1992	1	48	2	52	100.0%	0.54 [0.05, 5.78]
Subtotal (95% CI)		**48**		**52**	**100.0%**	**0.54 [0.05, 5.78]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**48**		**52**	**100.0%**	**0.54 [0.05, 5.78]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours CMHT
Favours standard care

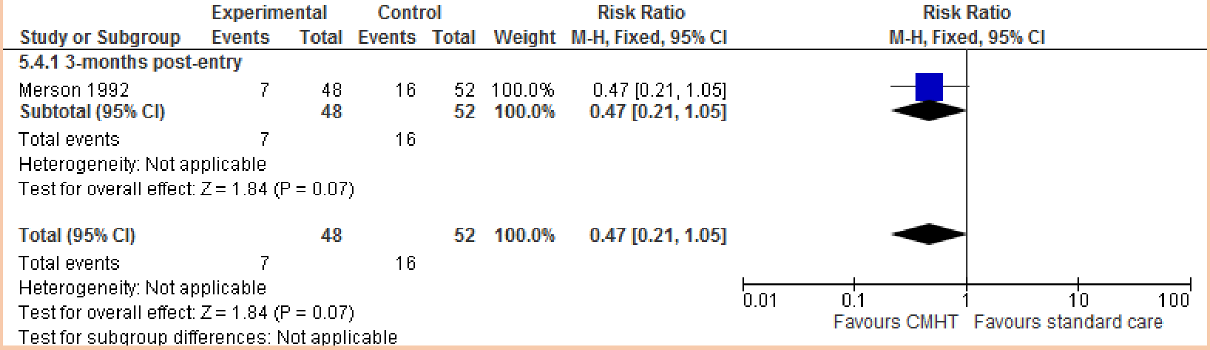
Symptom severity (CPRS at endpoint)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
5.3.1 3-months post-entry								
Merson 1992	22.8	11	48	23.6	14.1	52	100.0%	-0.06 [-0.45, 0.33]
Subtotal (95% CI)			**48**			**52**	**100.0%**	**-0.06 [-0.45, 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
Total (95% CI)			**48**			**52**	**100.0%**	**-0.06 [-0.45, 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
Test for subgroup differences: Not applicable								

Std. Mean Difference
IV, Fixed, 95% CI
-10
-5
0
5
10
Favours CMHT
Favours standard care

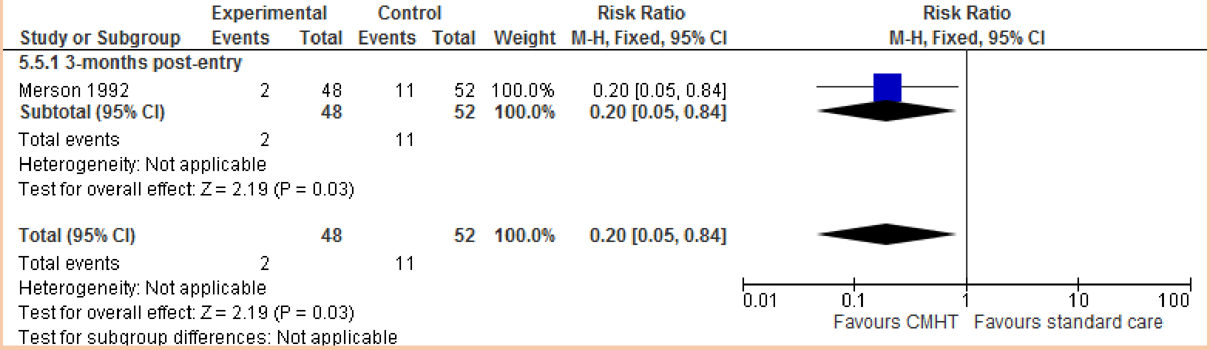
Admission as inpatient



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 3-months post-entry						
Merson 1992	7	48	16	52	100.0%	0.47 [0.21, 1.05]
Subtotal (95% CI)		**48**		**52**	**100.0%**	**0.47 [0.21, 1.05]**
Total events	7		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
Total (95% CI)		**48**		**52**	**100.0%**	**0.47 [0.21, 1.05]**
Total events	7		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours CMHT
Favours standard care

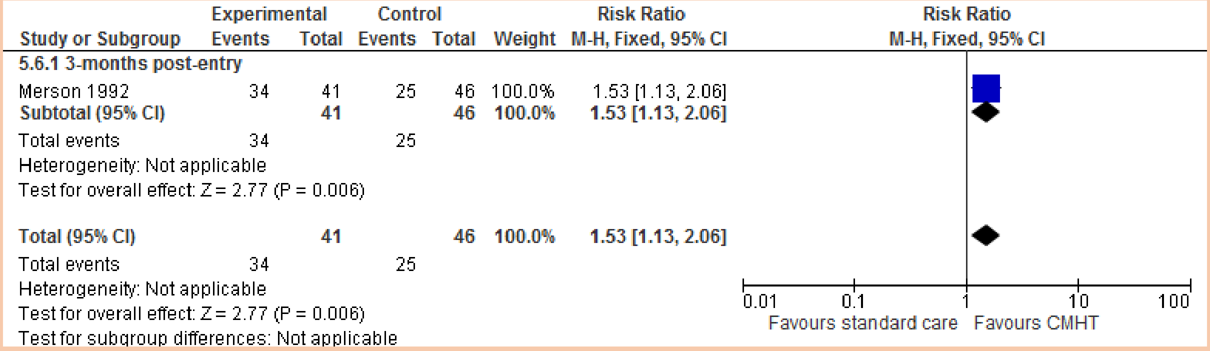
Admission as inpatient for >10 days



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.5.1 3-months post-entry						
Merson 1992	2	48	11	52	100.0%	0.20 [0.05, 0.84]
Subtotal (95% CI)		**48**		**52**	**100.0%**	**0.20 [0.05, 0.84]**
Total events	2		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.19 (P = 0.03)						
Total (95% CI)		**48**		**52**	**100.0%**	**0.20 [0.05, 0.84]**
Total events	2		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours CMHT
Favours standard care

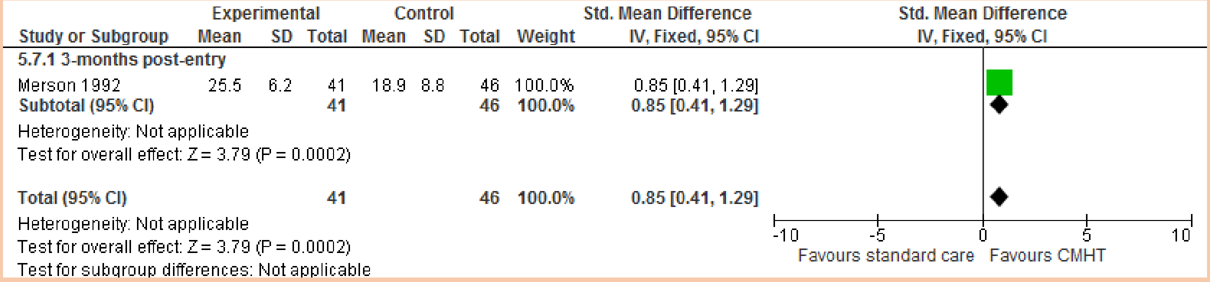
Satisfaction (number of participants satisfied with their treatment)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 3-months post-entry						
Merson 1992	34	41	25	46	100.0%	1.53 [1.13, 2.06]
Subtotal (95% CI)		**41**		**46**	**100.0%**	**1.53 [1.13, 2.06]**
Total events	34		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.77 (P = 0.006)						
Total (95% CI)		**41**		**46**	**100.0%**	**1.53 [1.13, 2.06]**
Total events	34		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.77 (P = 0.006)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours standard care
Favours CMHT

Satisfaction (service satisfaction score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
5.7.1 3-months post-entry								
Merson 1992	25.5	6.2	41	18.9	8.8	46	100.0%	0.85 [0.41, 1.29]
Subtotal (95% CI)			**41**			**46**	**100.0%**	**0.85 [0.41, 1.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.79 (P = 0.0002)								
Total (95% CI)			**41**			**46**	**100.0%**	**0.85 [0.41, 1.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.79 (P = 0.0002)								
Test for subgroup differences: Not applicable								

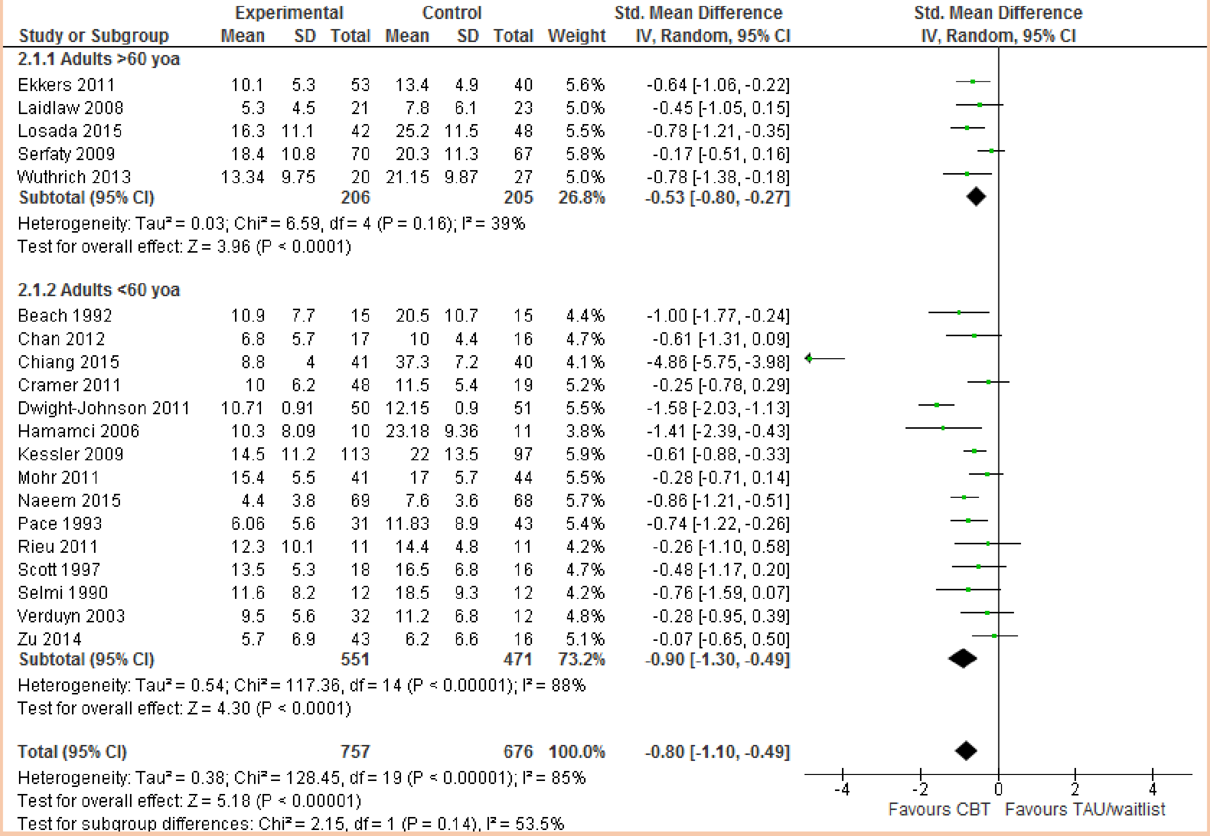
Std. Mean Difference
IV, Fixed, 95% CI
-10
-5
0
5
10
Favours standard care
Favours CMHT

First-line treatment (chapter 7) - NMA subgroup analysis for special populations

Older adults

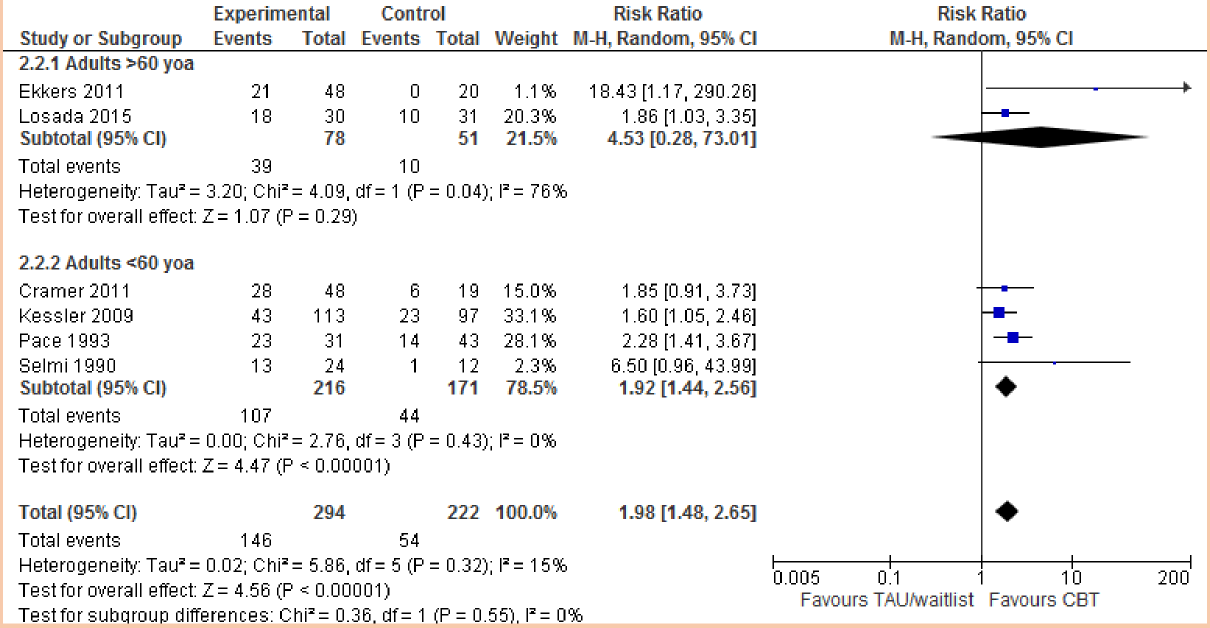
CBT versus TAU/waitlist

Depression symptomatology at endpoint



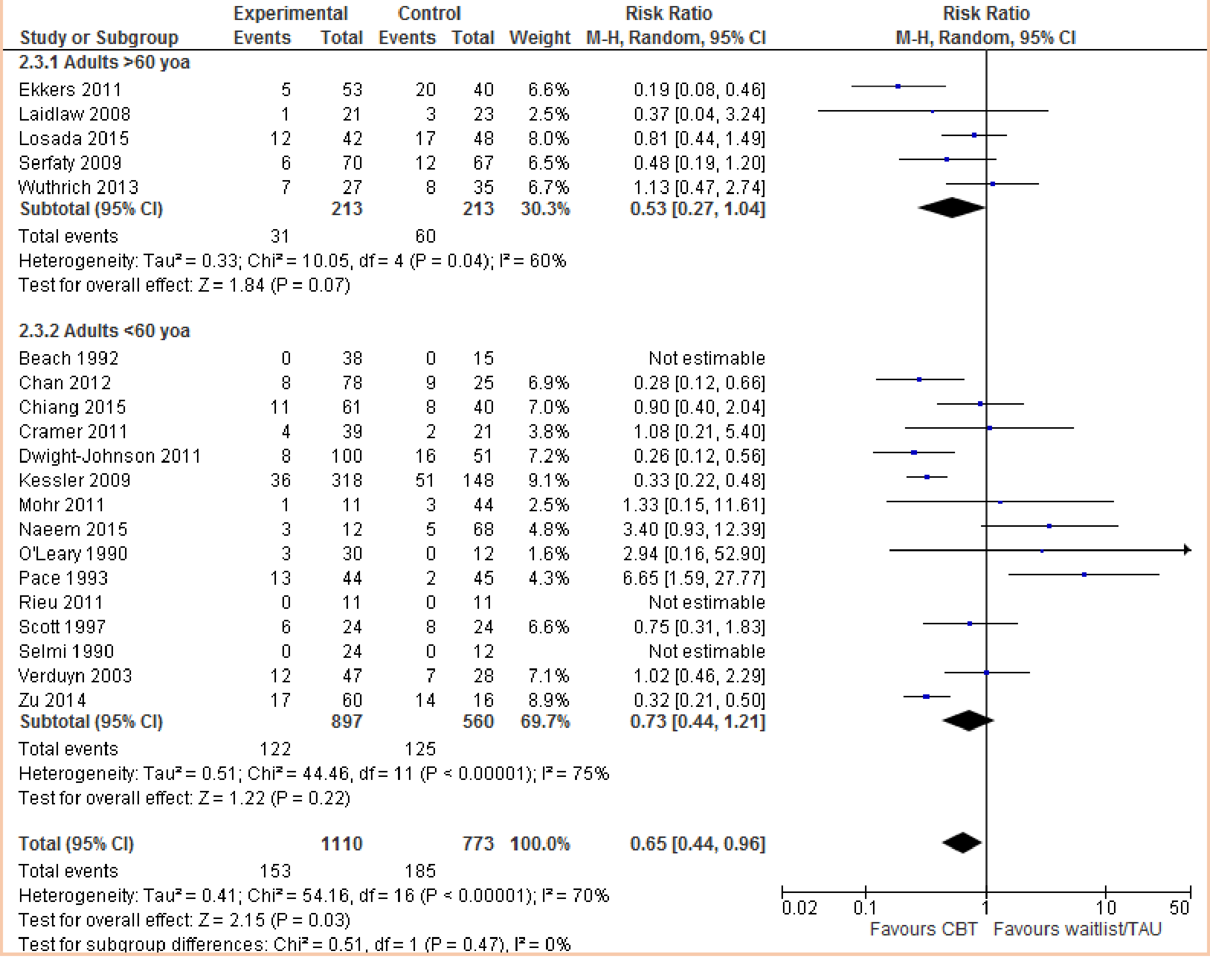
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Adults >60 yoa								
Ekkers 2011	10.1	5.3	53	13.4	4.9	40	5.6%	-0.64 [-1.06, -0.22]
Laidlaw 2008	5.3	4.5	21	7.8	6.1	23	5.0%	-0.45 [-1.05, 0.15]
Losada 2015	16.3	11.1	42	25.2	11.5	48	5.5%	-0.78 [-1.21, -0.35]
Serfaty 2009	18.4	10.8	70	20.3	11.3	67	5.8%	-0.17 [-0.51, 0.16]
Wuthrich 2013	13.34	9.75	20	21.15	9.87	27	5.0%	-0.78 [-1.38, -0.18]
Subtotal (95% CI)			**206**			**205**	**26.8%**	**-0.53 [-0.80, -0.27]**
Heterogeneity: Tau² = 0.03; Chi² = 6.59, df = 4 (P = 0.16); I² = 39%								
Test for overall effect: Z = 3.96 (P < 0.0001)								
2.1.2 Adults <60 yoa								
Beach 1992	10.9	7.7	15	20.5	10.7	15	4.4%	-1.00 [-1.77, -0.24]
Chan 2012	6.8	5.7	17	10	4.4	16	4.7%	-0.61 [-1.31, 0.09]
Chiang 2015	8.8	4	41	37.3	7.2	40	4.1%	-4.86 [-5.75, -3.98]
Cramer 2011	10	6.2	48	11.5	5.4	19	5.2%	-0.25 [-0.78, 0.29]
Dwight-Johnson 2011	10.71	0.91	50	12.15	0.9	51	5.5%	-1.58 [-2.03, -1.13]
Hamamci 2006	10.3	8.09	10	23.18	9.36	11	3.8%	-1.41 [-2.39, -0.43]
Kessler 2009	14.5	11.2	113	22	13.5	97	5.9%	-0.61 [-0.88, -0.33]
Mohr 2011	15.4	5.5	41	17	5.7	44	5.5%	-0.28 [-0.71, 0.14]
Naeem 2015	4.4	3.8	69	7.6	3.6	68	5.7%	-0.86 [-1.21, -0.51]
Pace 1993	6.06	5.6	31	11.83	8.9	43	5.4%	-0.74 [-1.22, -0.26]
Rieu 2011	12.3	10.1	11	14.4	4.8	11	4.2%	-0.26 [-1.10, 0.58]
Scott 1997	13.5	5.3	18	16.5	6.8	16	4.7%	-0.48 [-1.17, 0.20]
Selmi 1990	11.6	8.2	12	18.5	9.3	12	4.2%	-0.76 [-1.59, 0.07]
Verduyn 2003	9.5	5.6	32	11.2	6.8	12	4.8%	-0.28 [-0.95, 0.39]
Zu 2014	5.7	6.9	43	6.2	6.6	16	5.1%	-0.07 [-0.65, 0.50]
Subtotal (95% CI)			**551**			**471**	**73.2%**	**-0.90 [-1.30, -0.49]**
Heterogeneity: Tau² = 0.54; Chi² = 117.36, df = 14 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 4.30 (P < 0.0001)								
Total (95% CI)			**757**			**676**	**100.0%**	**-0.80 [-1.10, -0.49]**
Heterogeneity: Tau² = 0.38; Chi² = 128.45, df = 19 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 5.18 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.15, df = 1 (P = 0.14), I² = 53.5%								

Remission at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Adults >60 yoa						
Ekkers 2011	21	48	0	20	1.1%	18.43 [1.17, 290.26]
Losada 2015	18	30	10	31	20.3%	1.86 [1.03, 3.35]
Subtotal (95% CI)		**78**		**51**	**21.5%**	**4.53 [0.28, 73.01]**
Total events	39		10			
Heterogeneity: Tau² = 3.20; Chi² = 4.09, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 1.07 (P = 0.29)						
2.2.2 Adults <60 yoa						
Cramer 2011	28	48	6	19	15.0%	1.85 [0.91, 3.73]
Kessler 2009	43	113	23	97	33.1%	1.60 [1.05, 2.46]
Pace 1993	23	31	14	43	28.1%	2.28 [1.41, 3.67]
Selmi 1990	13	24	1	12	2.3%	6.50 [0.96, 43.99]
Subtotal (95% CI)		**216**		**171**	**78.5%**	**1.92 [1.44, 2.56]**
Total events	107		44			
Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 4.47 (P < 0.00001)						
Total (95% CI)		**294**		**222**	**100.0%**	**1.98 [1.48, 2.65]**
Total events	146		54			
Heterogeneity: Tau² = 0.02; Chi² = 5.86, df = 5 (P = 0.32); I² = 15%						
Test for overall effect: Z = 4.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%						

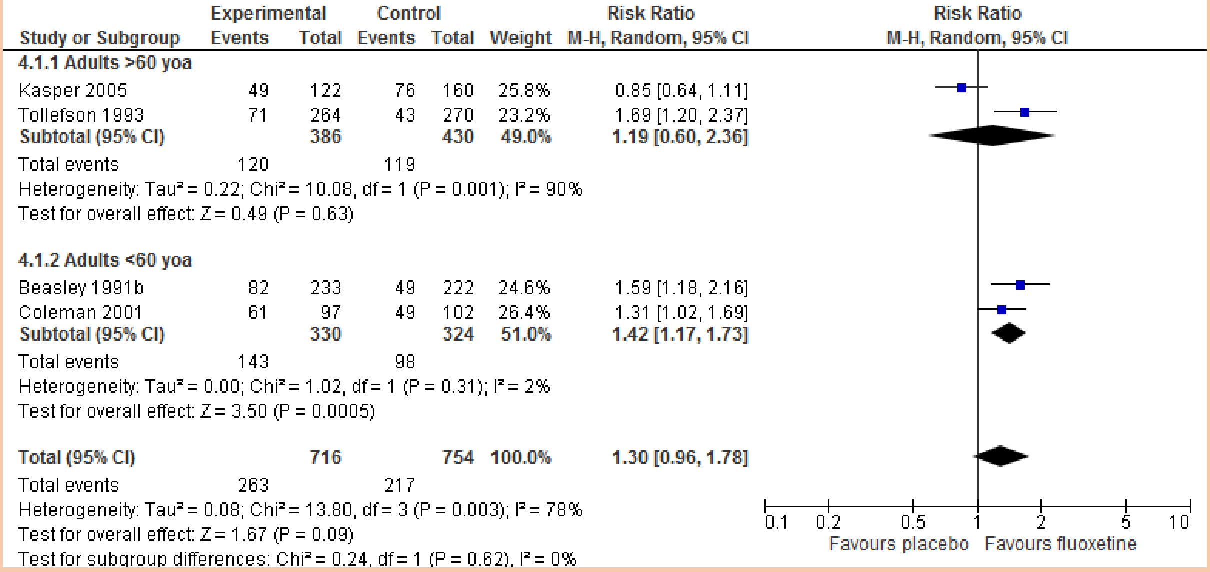
Discontinuation any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Adults >60 yoa						
Ekkers 2011	5	53	20	40	6.6%	0.19 [0.08, 0.46]
Laidlaw 2008	1	21	3	23	2.5%	0.37 [0.04, 3.24]
Losada 2015	12	42	17	48	8.0%	0.81 [0.44, 1.49]
Serfaty 2009	6	70	12	67	6.5%	0.48 [0.19, 1.20]
Wuthrich 2013	7	27	8	35	6.7%	1.13 [0.47, 2.74]
Subtotal (95% CI)		**213**		**213**	**30.3%**	**0.53 [0.27, 1.04]**
Total events	31		60			
Heterogeneity: Tau² = 0.33; Chi² = 10.05, df = 4 (P = 0.04); I² = 60%						
Test for overall effect: Z = 1.84 (P = 0.07)						
2.3.2 Adults <60 yoa						
Beach 1992	0	38	0	15		Not estimable
Chan 2012	8	78	9	25	6.9%	0.28 [0.12, 0.66]
Chiang 2015	11	61	8	40	7.0%	0.90 [0.40, 2.04]
Cramer 2011	4	39	2	21	3.8%	1.08 [0.21, 5.40]
Dwight-Johnson 2011	8	100	16	51	7.2%	0.26 [0.12, 0.56]
Kessler 2009	36	318	51	148	9.1%	0.33 [0.22, 0.48]
Mohr 2011	1	11	3	44	2.5%	1.33 [0.15, 11.61]
Naeem 2015	3	12	5	68	4.8%	3.40 [0.93, 12.39]
O'Leary 1990	3	30	0	12	1.6%	2.94 [0.16, 52.90]
Pace 1993	13	44	2	45	4.3%	6.65 [1.59, 27.77]
Rieu 2011	0	11	0	11		Not estimable
Scott 1997	6	24	8	24	6.6%	0.75 [0.31, 1.83]
Selmi 1990	0	24	0	12		Not estimable
Verduyn 2003	12	47	7	28	7.1%	1.02 [0.46, 2.29]
Zu 2014	17	60	14	16	8.9%	0.32 [0.21, 0.50]
Subtotal (95% CI)		**897**		**560**	**69.7%**	**0.73 [0.44, 1.21]**
Total events	122		125			
Heterogeneity: Tau² = 0.51; Chi² = 44.46, df = 11 (P < 0.00001); I² = 75%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**1110**		**773**	**100.0%**	**0.65 [0.44, 0.96]**
Total events	153		185			
Heterogeneity: Tau² = 0.41; Chi² = 54.16, df = 16 (P < 0.00001); I² = 70%						
Test for overall effect: Z = 2.15 (P = 0.03)						
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.47), I² = 0%						

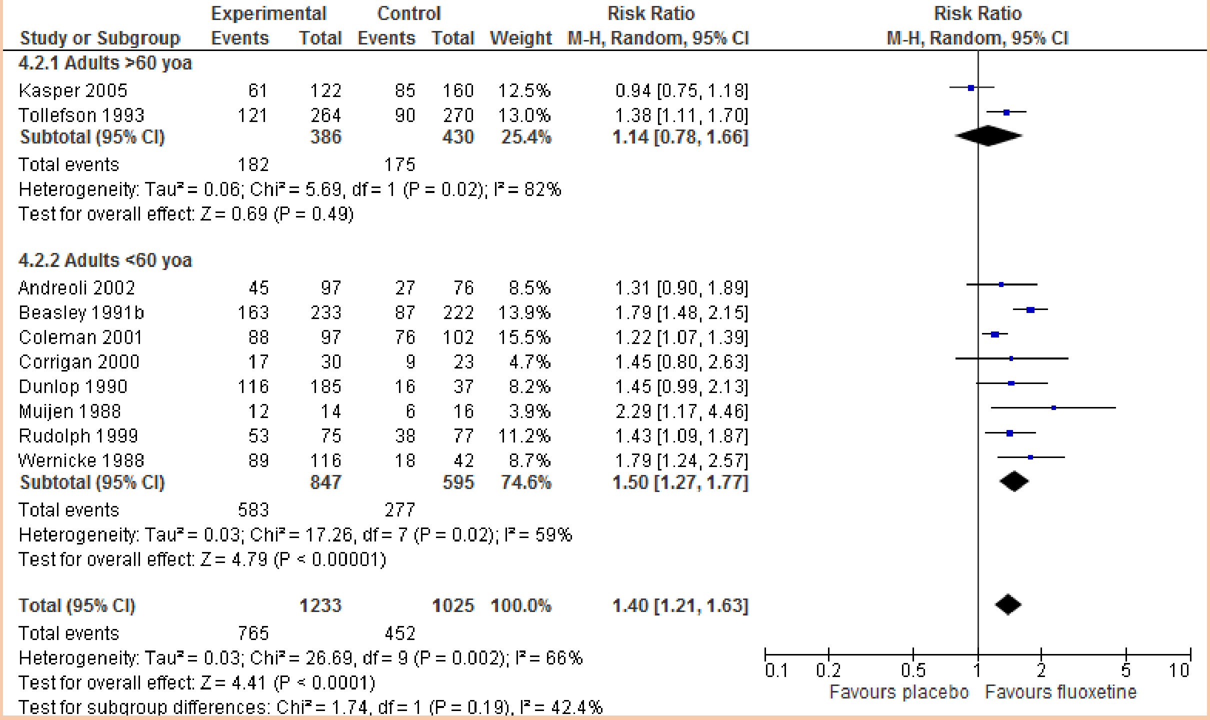
Fluoxetine versus placebo

Remission at endpoint



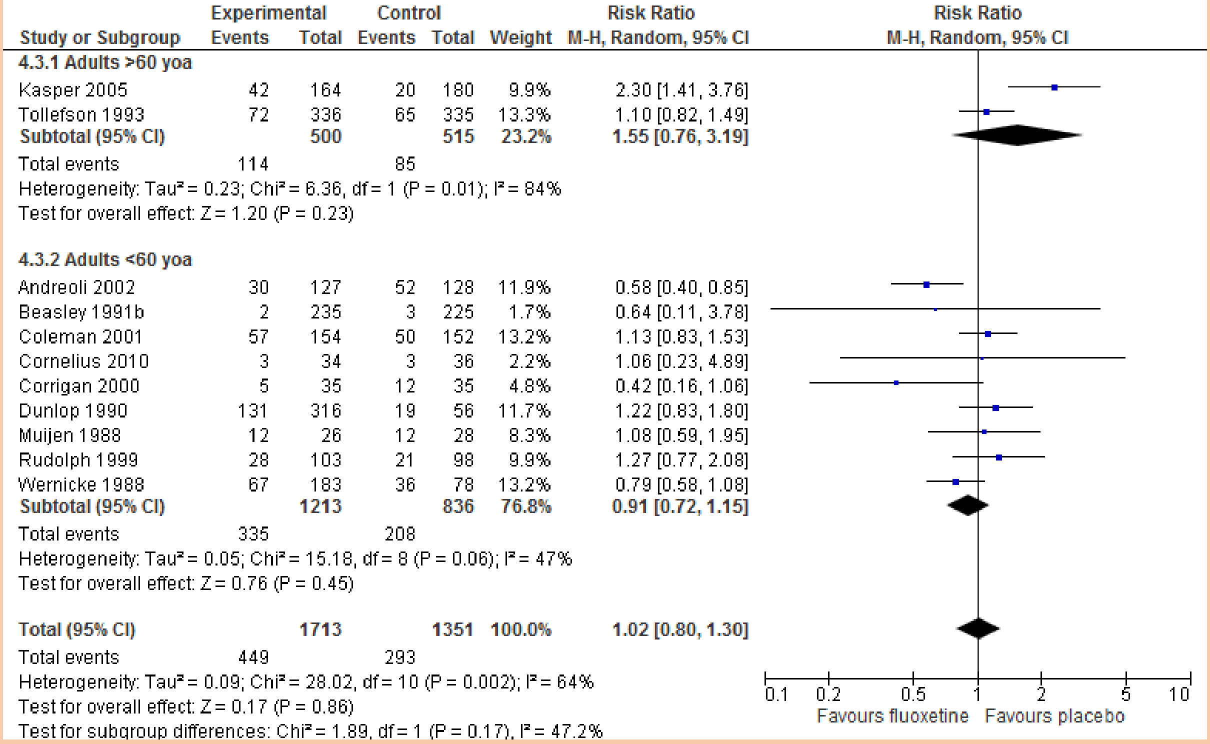
Study or Subgroup	Experimental		Control			Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
4.1.1 Adults >60 yoa						
Kasper 2005	49	122	76	160	25.8%	0.85 [0.64, 1.11]
Tollefson 1993	71	264	43	270	23.2%	1.69 [1.20, 2.37]
Subtotal (95% CI)		**386**		**430**	**49.0%**	**1.19 [0.60, 2.36]**
Total events	120		119			
Heterogeneity: Tau^2 = 0.22; Chi^2 = 10.08, df = 1 (P = 0.001); I^2 = 90%						
Test for overall effect: Z = 0.49 (P = 0.63)						
4.1.2 Adults <60 yoa						
Beasley 1991b	82	233	49	222	24.6%	1.59 [1.18, 2.16]
Coleman 2001	61	97	49	102	26.4%	1.31 [1.02, 1.69]
Subtotal (95% CI)		**330**		**324**	**51.0%**	**1.42 [1.17, 1.73]**
Total events	143		98			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.02, df = 1 (P = 0.31); I^2 = 2%						
Test for overall effect: Z = 3.50 (P = 0.0005)						
Total (95% CI)		**716**		**754**	**100.0%**	**1.30 [0.96, 1.78]**
Total events	263		217			
Heterogeneity: Tau^2 = 0.08; Chi^2 = 13.80, df = 3 (P = 0.003); I^2 = 78%						
Test for overall effect: Z = 1.67 (P = 0.09)						
Test for subgroup differences: Chi^2 = 0.24, df = 1 (P = 0.62), I^2 = 0%						

Response at endpoint



Study or Subgroup	Experimental		Control			Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
4.2.1 Adults >60 yoa						
Kasper 2005	61	122	85	160	12.5%	0.94 [0.75, 1.18]
Tollefson 1993	121	264	90	270	13.0%	1.38 [1.11, 1.70]
Subtotal (95% CI)		**386**		**430**	**25.4%**	**1.14 [0.78, 1.66]**
Total events	182		175			
Heterogeneity: Tau^2 = 0.06; Chi^2 = 5.69, df = 1 (P = 0.02); I^2 = 82%						
Test for overall effect: Z = 0.69 (P = 0.49)						
4.2.2 Adults <60 yoa						
Andreoli 2002	45	97	27	76	8.5%	1.31 [0.90, 1.89]
Beasley 1991b	163	233	87	222	13.9%	1.79 [1.48, 2.15]
Coleman 2001	88	97	76	102	15.5%	1.22 [1.07, 1.39]
Corrigan 2000	17	30	9	23	4.7%	1.45 [0.80, 2.63]
Dunlop 1990	116	185	16	37	8.2%	1.45 [0.99, 2.13]
Muijen 1988	12	14	6	16	3.9%	2.29 [1.17, 4.46]
Rudolph 1999	53	75	38	77	11.2%	1.43 [1.09, 1.87]
Wernicke 1988	89	116	18	42	8.7%	1.79 [1.24, 2.57]
Subtotal (95% CI)		**847**		**595**	**74.6%**	**1.50 [1.27, 1.77]**
Total events	583		277			
Heterogeneity: Tau^2 = 0.03; Chi^2 = 17.26, df = 7 (P = 0.02); I^2 = 59%						
Test for overall effect: Z = 4.79 (P < 0.00001)						
Total (95% CI)		**1233**		**1025**	**100.0%**	**1.40 [1.21, 1.63]**
Total events	765		452			
Heterogeneity: Tau^2 = 0.03; Chi^2 = 26.69, df = 9 (P = 0.002); I^2 = 66%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
Test for subgroup differences: Chi^2 = 1.74, df = 1 (P = 0.19), I^2 = 42.4%						

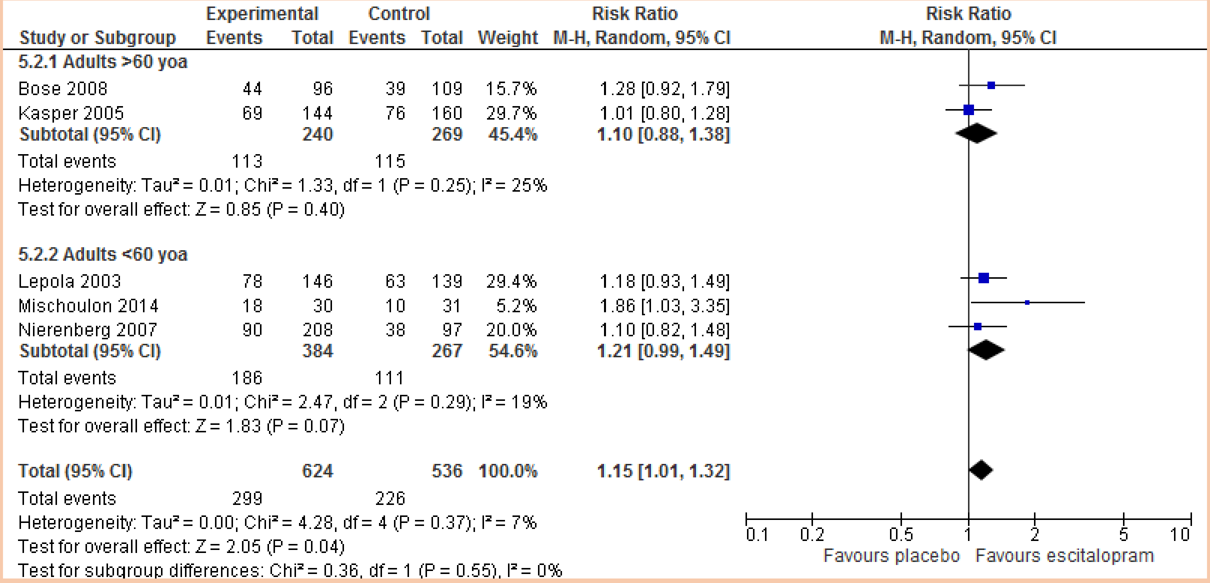
Discontinuation any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Adults >60 yoa						
Kasper 2005	42	164	20	180	9.9%	2.30 [1.41, 3.76]
Tollefson 1993	72	336	65	335	13.3%	1.10 [0.82, 1.49]
Subtotal (95% CI)		**500**		**515**	**23.2%**	**1.55 [0.76, 3.19]**
Total events	114		85			
Heterogeneity: Tau^2 = 0.23; Chi^2 = 6.36, df = 1 (P = 0.01); I^2 = 84%						
Test for overall effect: Z = 1.20 (P = 0.23)						
4.3.2 Adults <60 yoa						
Andreoli 2002	30	127	52	128	11.9%	0.58 [0.40, 0.85]
Beasley 1991b	2	235	3	225	1.7%	0.64 [0.11, 3.78]
Coleman 2001	57	154	50	152	13.2%	1.13 [0.83, 1.53]
Cornelius 2010	3	34	3	36	2.2%	1.06 [0.23, 4.89]
Corrigan 2000	5	35	12	35	4.8%	0.42 [0.16, 1.06]
Dunlop 1990	131	316	19	56	11.7%	1.22 [0.83, 1.80]
Muijen 1988	12	26	12	28	8.3%	1.08 [0.59, 1.95]
Rudolph 1999	28	103	21	98	9.9%	1.27 [0.77, 2.08]
Wernicke 1988	67	183	36	78	13.2%	0.79 [0.58, 1.08]
Subtotal (95% CI)		**1213**		**836**	**76.8%**	**0.91 [0.72, 1.15]**
Total events	335		208			
Heterogeneity: Tau^2 = 0.05; Chi^2 = 15.18, df = 8 (P = 0.06); I^2 = 47%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**1713**		**1351**	**100.0%**	**1.02 [0.80, 1.30]**
Total events	449		293			
Heterogeneity: Tau^2 = 0.09; Chi^2 = 28.02, df = 10 (P = 0.002); I^2 = 64%						
Test for overall effect: Z = 0.17 (P = 0.86)						
Test for subgroup differences: Chi^2 = 1.89, df = 1 (P = 0.17), I^2 = 47.2%						

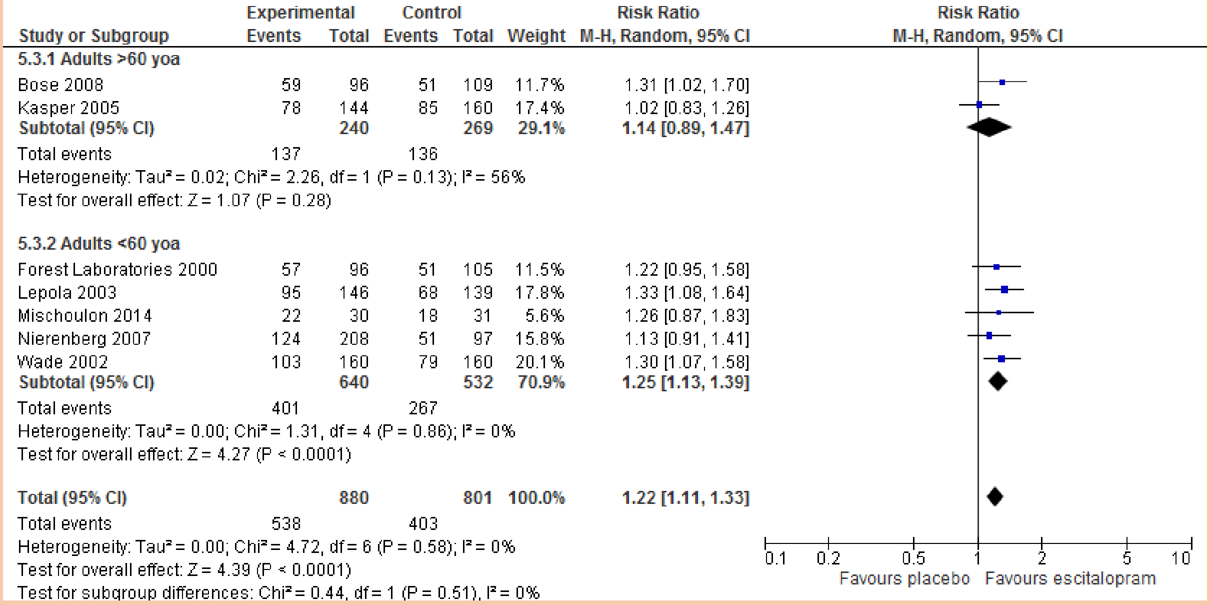
Escitalopram versus placebo

Remission at endpoint



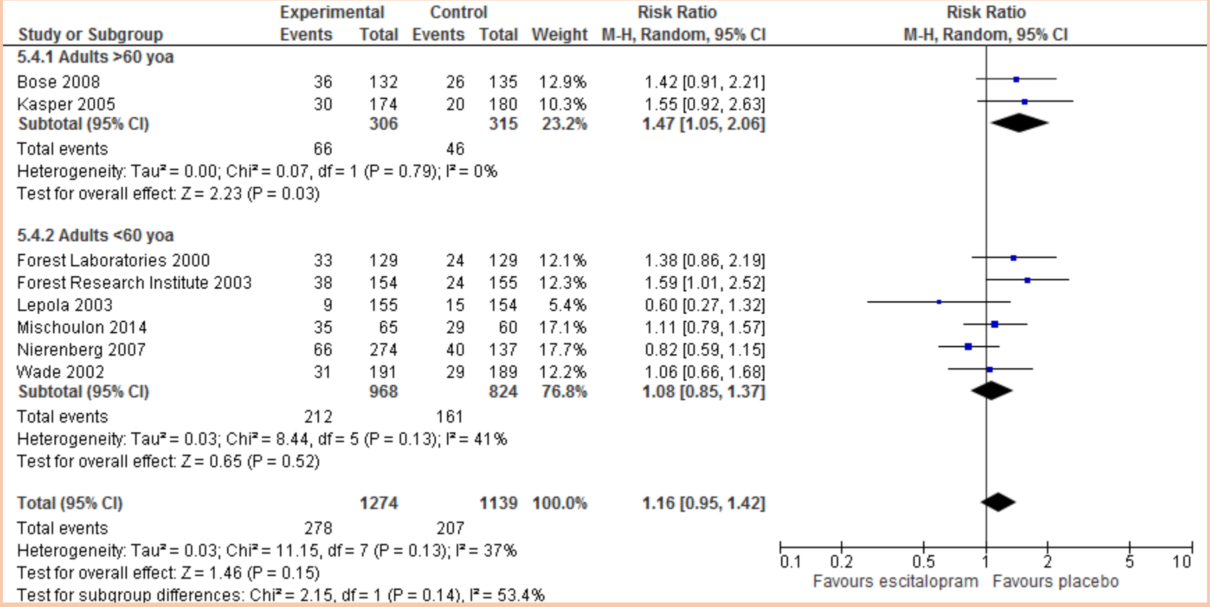
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Adults >60 yoa						
Bose 2008	44	96	39	109	15.7%	1.28 [0.92, 1.79]
Kasper 2005	69	144	76	160	29.7%	1.01 [0.80, 1.28]
Subtotal (95% CI)		**240**		**269**	**45.4%**	**1.10 [0.88, 1.38]**
Total events	113		115			
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.33, df = 1 (P = 0.25); I^2 = 25%						
Test for overall effect: Z = 0.85 (P = 0.40)						
5.2.2 Adults <60 yoa						
Lepola 2003	78	146	63	139	29.4%	1.18 [0.93, 1.49]
Mischoulon 2014	18	30	10	31	5.2%	1.86 [1.03, 3.35]
Nierenberg 2007	90	208	38	97	20.0%	1.10 [0.82, 1.48]
Subtotal (95% CI)		**384**		**267**	**54.6%**	**1.21 [0.99, 1.49]**
Total events	186		111			
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.47, df = 2 (P = 0.29); I^2 = 19%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Total (95% CI)		**624**		**536**	**100.0%**	**1.15 [1.01, 1.32]**
Total events	299		226			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.28, df = 4 (P = 0.37); I^2 = 7%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 = 0%						

Response at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 Adults >60 yoa						
Bose 2008	59	96	51	109	11.7%	1.31 [1.02, 1.70]
Kasper 2005	78	144	85	160	17.4%	1.02 [0.83, 1.26]
Subtotal (95% CI)		**240**		**269**	**29.1%**	**1.14 [0.89, 1.47]**
Total events	137		136			
Heterogeneity: Tau² = 0.02; Chi² = 2.26, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 1.07 (P = 0.28)						
5.3.2 Adults <60 yoa						
Forest Laboratories 2000	57	96	51	105	11.5%	1.22 [0.95, 1.58]
Lepola 2003	95	146	68	139	17.8%	1.33 [1.08, 1.64]
Mischoulon 2014	22	30	18	31	5.6%	1.26 [0.87, 1.83]
Nierenberg 2007	124	208	51	97	15.8%	1.13 [0.91, 1.41]
Wade 2002	103	160	79	160	20.1%	1.30 [1.07, 1.58]
Subtotal (95% CI)		**640**		**532**	**70.9%**	**1.25 [1.13, 1.39]**
Total events	401		267			
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 4.27 (P < 0.0001)						
Total (95% CI)		**880**		**801**	**100.0%**	**1.22 [1.11, 1.33]**
Total events	538		403			
Heterogeneity: Tau² = 0.00; Chi² = 4.72, df = 6 (P = 0.58); I² = 0%						
Test for overall effect: Z = 4.39 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%						

Discontinuation any reason

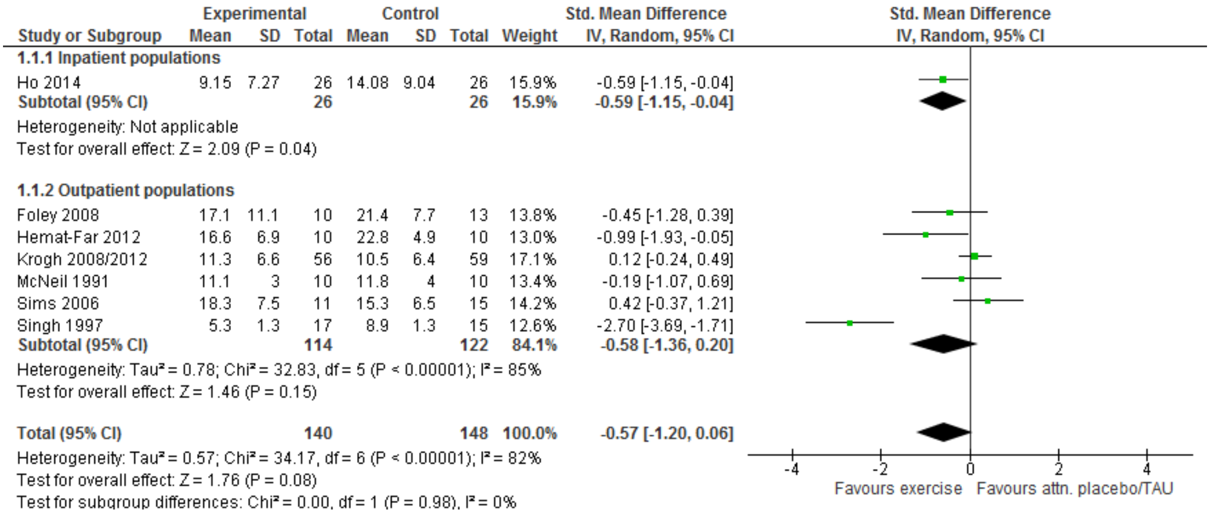


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 Adults >60 yoa						
Bose 2008	36	132	26	135	12.9%	1.42 [0.91, 2.21]
Kasper 2005	30	174	20	180	10.3%	1.55 [0.92, 2.63]
Subtotal (95% CI)		**306**		**315**	**23.2%**	**1.47 [1.05, 2.06]**
Total events	66		46			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
5.4.2 Adults <60 yoa						
Forest Laboratories 2000	33	129	24	129	12.1%	1.38 [0.86, 2.19]
Forest Research Institute 2003	38	154	24	155	12.3%	1.59 [1.01, 2.52]
Lepola 2003	9	155	15	154	5.4%	0.60 [0.27, 1.32]
Mischoulon 2014	35	65	29	60	17.1%	1.11 [0.79, 1.57]
Nierenberg 2007	66	274	40	137	17.7%	0.82 [0.59, 1.15]
Wade 2002	31	191	29	189	12.2%	1.06 [0.66, 1.68]
Subtotal (95% CI)		**968**		**824**	**76.8%**	**1.08 [0.85, 1.37]**
Total events	212		161			
Heterogeneity: Tau² = 0.03; Chi² = 8.44, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**1274**		**1139**	**100.0%**	**1.16 [0.95, 1.42]**
Total events	278		207			
Heterogeneity: Tau² = 0.03; Chi² = 11.15, df = 7 (P = 0.13); I² = 37%						
Test for overall effect: Z = 1.46 (P = 0.15)						
Test for subgroup differences: Chi² = 2.15, df = 1 (P = 0.14), I² = 53.4%						

Inpatients

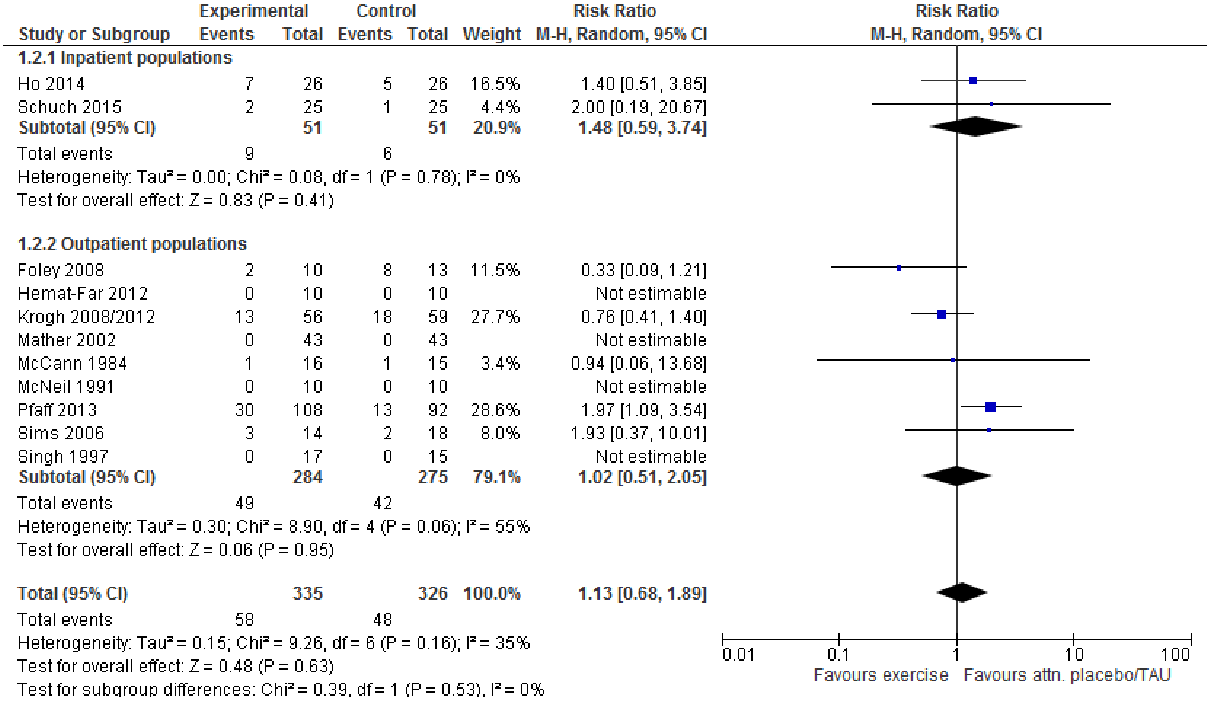
Exercise versus attention placebo/TAU

Depression symptomatology at endpoint



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Inpatient populations								
Ho 2014	9.15	7.27	26	14.08	9.04	26	15.9%	-0.59 [-1.15, -0.04]
Subtotal (95% CI)			**26**			**26**	**15.9%**	**-0.59 [-1.15, -0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.09 (P = 0.04)								
1.1.2 Outpatient populations								
Foley 2008	17.1	11.1	10	21.4	7.7	13	13.8%	-0.45 [-1.28, 0.39]
Hemat-Far 2012	16.6	6.9	10	22.8	4.9	10	13.0%	-0.99 [-1.93, -0.05]
Krogh 2008/2012	11.3	6.6	56	10.5	6.4	59	17.1%	0.12 [-0.24, 0.49]
McNeil 1991	11.1	3	10	11.8	4	10	13.4%	-0.19 [-1.07, 0.69]
Sims 2006	18.3	7.5	11	15.3	6.5	15	14.2%	0.42 [-0.37, 1.21]
Singh 1997	5.3	1.3	17	8.9	1.3	15	12.6%	-2.70 [-3.69, -1.71]
Subtotal (95% CI)			**114**			**122**	**84.1%**	**-0.58 [-1.36, 0.20]**
Heterogeneity: Tau² = 0.78; Chi² = 32.83, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 1.46 (P = 0.15)								
Total (95% CI)			**140**			**148**	**100.0%**	**-0.57 [-1.20, 0.06]**
Heterogeneity: Tau² = 0.57; Chi² = 34.17, df = 6 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 1.76 (P = 0.08)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%								

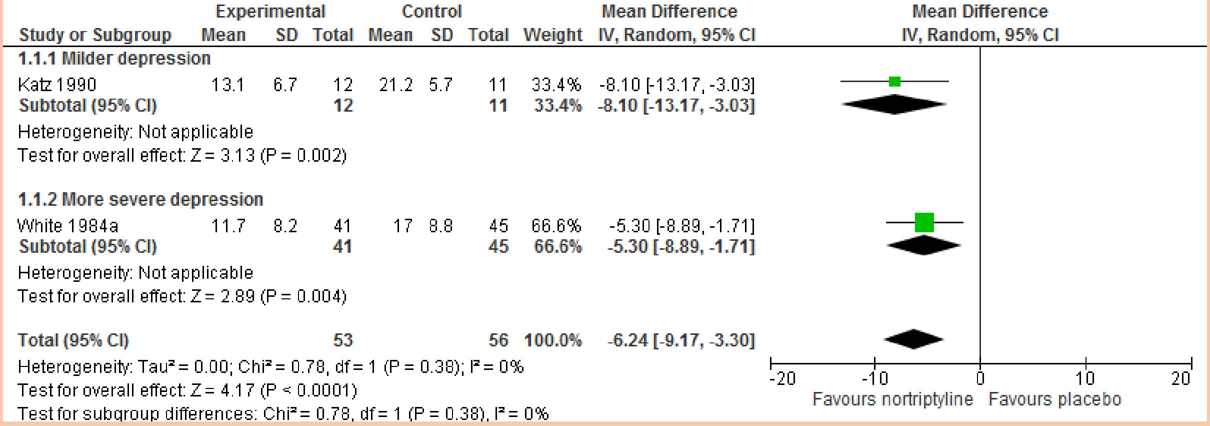
Discontinuation any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Inpatient populations						
Ho 2014	7	26	5	26	16.5%	1.40 [0.51, 3.85]
Schuch 2015	2	25	1	25	4.4%	2.00 [0.19, 20.67]
Subtotal (95% CI)		**51**		**51**	**20.9%**	**1.48 [0.59, 3.74]**
Total events	9		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.2.2 Outpatient populations						
Foley 2008	2	10	8	13	11.5%	0.33 [0.09, 1.21]
Hemat-Far 2012	0	10	0	10		Not estimable
Krogh 2008/2012	13	56	18	59	27.7%	0.76 [0.41, 1.40]
Mather 2002	0	43	0	43		Not estimable
McCann 1984	1	16	1	15	3.4%	0.94 [0.06, 13.68]
McNeil 1991	0	10	0	10		Not estimable
Pfaff 2013	30	108	13	92	28.6%	1.97 [1.09, 3.54]
Sims 2006	3	14	2	18	8.0%	1.93 [0.37, 10.01]
Singh 1997	0	17	0	15		Not estimable
Subtotal (95% CI)		**284**		**275**	**79.1%**	**1.02 [0.51, 2.05]**
Total events	49		42			
Heterogeneity: Tau² = 0.30; Chi² = 8.90, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**335**		**326**	**100.0%**	**1.13 [0.68, 1.89]**
Total events	58		48			
Heterogeneity: Tau² = 0.15; Chi² = 9.26, df = 6 (P = 0.16); I² = 35%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						

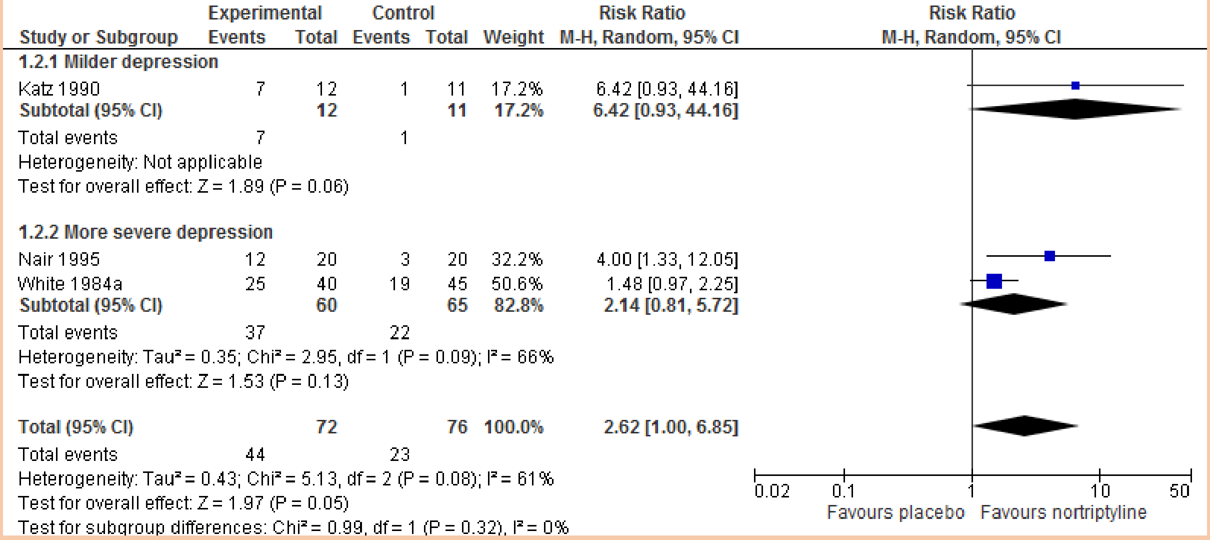
Nortriptyline in older adults

Depressive symptoms at endpoint (HAMD)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Milder depression								
Katz 1990	13.1	6.7	12	21.2	5.7	11	33.4%	-8.10 [-13.17, -3.03]
Subtotal (95% CI)			**12**			**11**	**33.4%**	**-8.10 [-13.17, -3.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.13 (P = 0.002)								
1.1.2 More severe depression								
White 1984a	11.7	8.2	41	17	8.8	45	66.6%	-5.30 [-8.89, -1.71]
Subtotal (95% CI)			**41**			**45**	**66.6%**	**-5.30 [-8.89, -1.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.89 (P = 0.004)								
Total (95% CI)			**53**			**56**	**100.0%**	**-6.24 [-9.17, -3.30]**
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%								
Test for overall effect: Z = 4.17 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%								

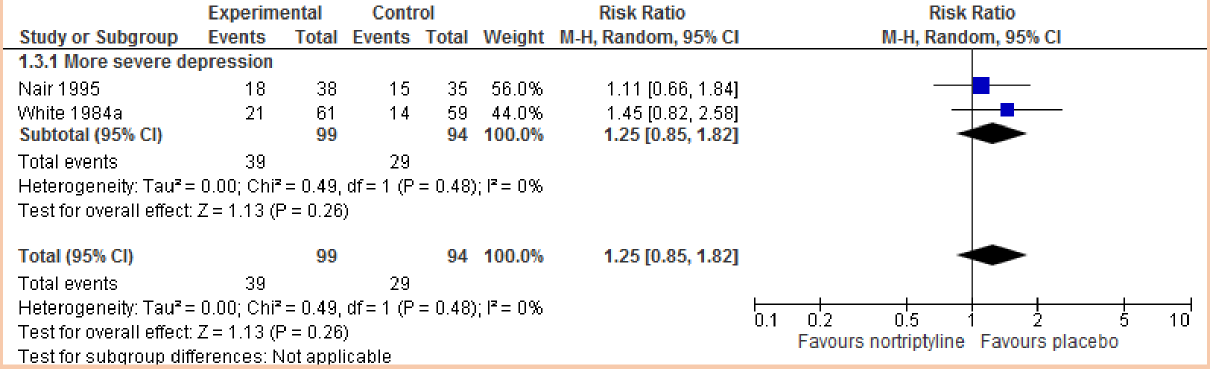
Remission (CGI/HAMD) at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Milder depression						
Katz 1990	7	12	1	11	17.2%	6.42 [0.93, 44.16]
Subtotal (95% CI)		**12**		**11**	**17.2%**	**6.42 [0.93, 44.16]**
Total events	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
1.2.2 More severe depression						
Nair 1995	12	20	3	20	32.2%	4.00 [1.33, 12.05]
White 1984a	25	40	19	45	50.6%	1.48 [0.97, 2.25]
Subtotal (95% CI)		**60**		**65**	**82.8%**	**2.14 [0.81, 5.72]**
Total events	37		22			
Heterogeneity: Tau^2 = 0.35; Chi^2 = 2.95, df = 1 (P = 0.09); I^2 = 66%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)		**72**		**76**	**100.0%**	**2.62 [1.00, 6.85]**
Total events	44		23			
Heterogeneity: Tau^2 = 0.43; Chi^2 = 5.13, df = 2 (P = 0.08); I^2 = 61%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi^2 = 0.99, df = 1 (P = 0.32), I^2 = 0%						

Risk Ratio
M-H, Random, 95% CI
0.02
0.1
1
10
50
Favours placebo
Favours nortriptyline

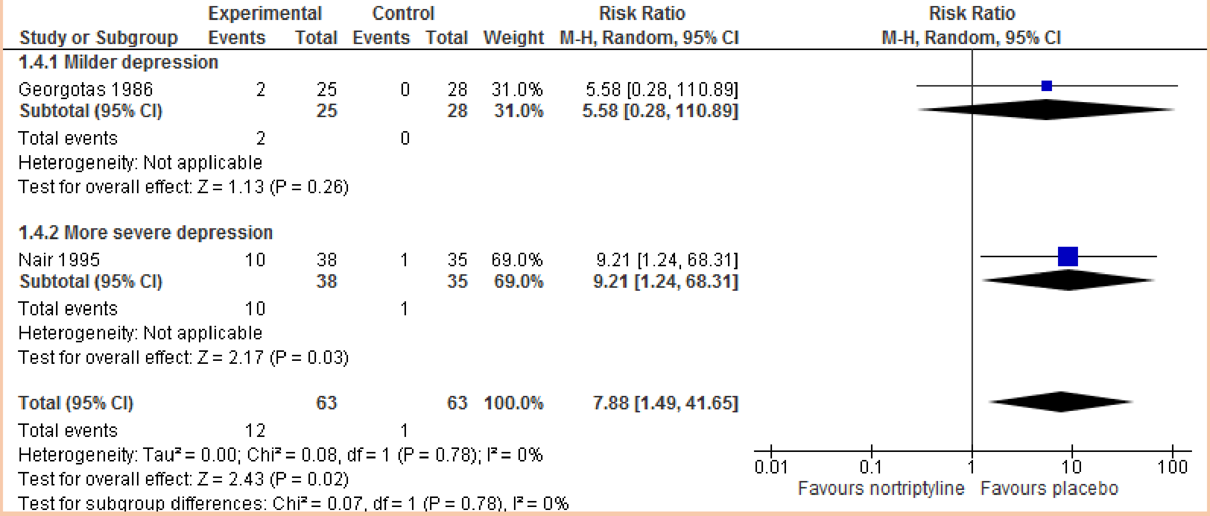
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 More severe depression						
Nair 1995	18	38	15	35	56.0%	1.11 [0.66, 1.84]
White 1984a	21	61	14	59	44.0%	1.45 [0.82, 2.58]
Subtotal (95% CI)		**99**		**94**	**100.0%**	**1.25 [0.85, 1.82]**
Total events	39		29			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.49, df = 1 (P = 0.48); I^2 = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**99**		**94**	**100.0%**	**1.25 [0.85, 1.82]**
Total events	39		29			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.49, df = 1 (P = 0.48); I^2 = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours nortriptyline
Favours placebo

Discontinuation due to side effects



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Milder depression						
Georgotas 1986	2	25	0	28	31.0%	5.58 [0.28, 110.89]
Subtotal (95% CI)		**25**		**28**	**31.0%**	**5.58 [0.28, 110.89]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.4.2 More severe depression						
Nair 1995	10	38	1	35	69.0%	9.21 [1.24, 68.31]
Subtotal (95% CI)		**38**		**35**	**69.0%**	**9.21 [1.24, 68.31]**
Total events	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						
Total (95% CI)		**63**		**63**	**100.0%**	**7.88 [1.49, 41.65]**
Total events	12		1			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.08, df = 1 (P = 0.78); I^2 = 0%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.78), I^2 = 0%						

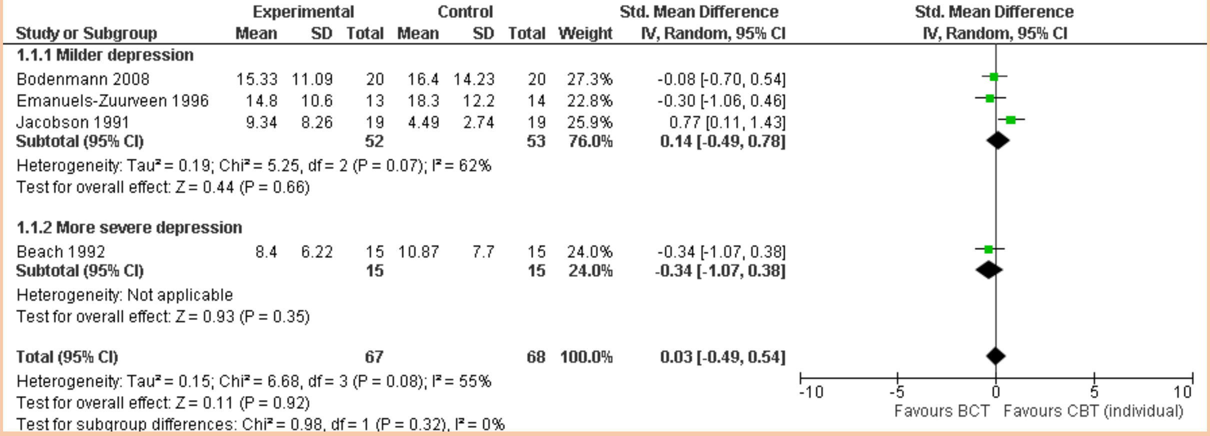
Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours nortriptyline
Favours placebo

Pairwise comparisons for interventions excluded from the NMA

Behavioural couples therapy

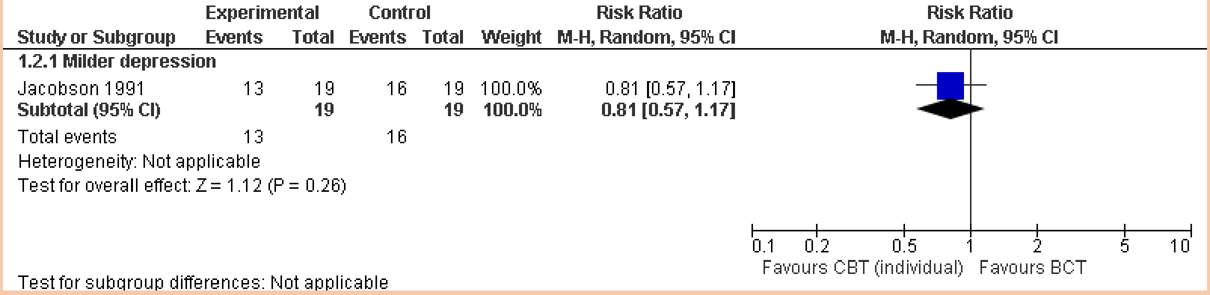
Behavioural couples therapy versus CBT

Depression symptomatology at endpoint: milder depression and more severe depression



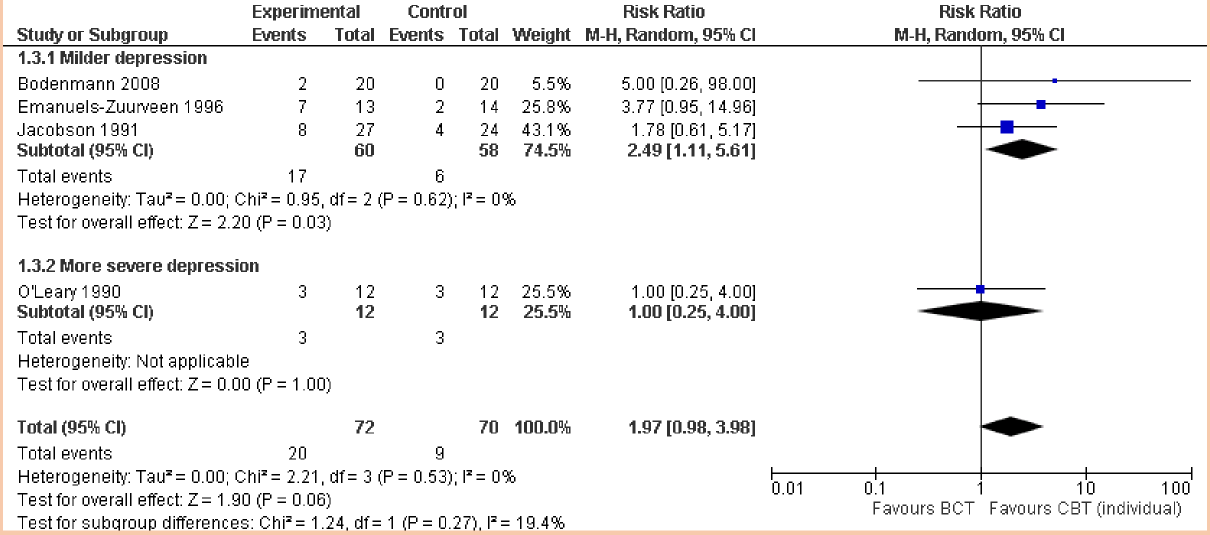
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Milder depression								
Bodenmann 2008	15.33	11.09	20	16.4	14.23	20	27.3%	-0.08 [-0.70, 0.54]
Emanuels-Zuurveen 1996	14.8	10.6	13	18.3	12.2	14	22.8%	-0.30 [-1.06, 0.46]
Jacobson 1991	9.34	8.26	19	4.49	2.74	19	25.9%	0.77 [0.11, 1.43]
Subtotal (95% CI)			**52**			**53**	**76.0%**	**0.14 [-0.49, 0.78]**
Heterogeneity: Tau² = 0.19; Chi² = 5.25, df = 2 (P = 0.07); I² = 62%								
Test for overall effect: Z = 0.44 (P = 0.66)								
1.1.2 More severe depression								
Beach 1992	8.4	6.22	15	10.87	7.7	15	24.0%	-0.34 [-1.07, 0.38]
Subtotal (95% CI)			**15**			**15**	**24.0%**	**-0.34 [-1.07, 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
Total (95% CI)			**67**			**68**	**100.0%**	**0.03 [-0.49, 0.54]**
Heterogeneity: Tau² = 0.15; Chi² = 6.68, df = 3 (P = 0.08); I² = 55%								
Test for overall effect: Z = 0.11 (P = 0.92)								
Test for subgroup differences: Chi² = 0.98, df = 1 (P = 0.32), I² = 0%								

Remission: milder depression



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Milder depression						
Jacobson 1991	13	19	16	19	100.0%	0.81 [0.57, 1.17]
Subtotal (95% CI)		**19**		**19**	**100.0%**	**0.81 [0.57, 1.17]**
Total events	13		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Not applicable						

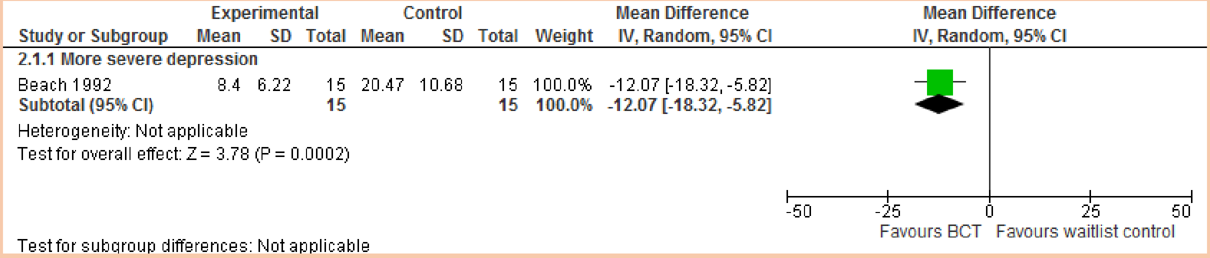
Treatment discontinuation: milder depression and more severe depression



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Milder depression						
Bodenmann 2008	2	20	0	20	5.5%	5.00 [0.26, 98.00]
Emanuels-Zuurveen 1996	7	13	2	14	25.8%	3.77 [0.95, 14.96]
Jacobson 1991	8	27	4	24	43.1%	1.78 [0.61, 5.17]
Subtotal (95% CI)		**60**		**58**	**74.5%**	**2.49 [1.11, 5.61]**
Total events	17		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
1.3.2 More severe depression						
O'Leary 1990	3	12	3	12	25.5%	1.00 [0.25, 4.00]
Subtotal (95% CI)		**12**		**12**	**25.5%**	**1.00 [0.25, 4.00]**
Total events	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**72**		**70**	**100.0%**	**1.97 [0.98, 3.98]**
Total events	20		9			
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.4%						

Behavioural couples therapy versus waitlist control

Depression symptoms at endpoint

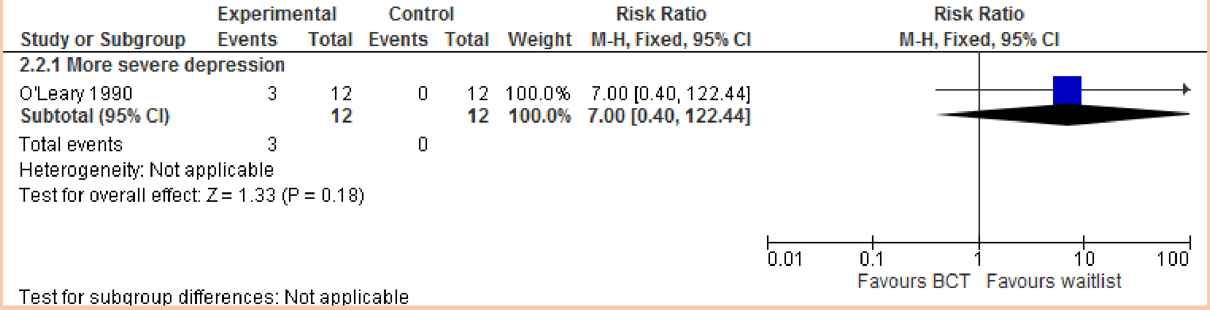


Study or Subgroup	Experimental			Control			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI
2.1.1 More severe depression								
Beach 1992	8.4	6.22	15	20.47	10.68	15	100.0%	-12.07 [-18.32, -5.82]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**-12.07 [-18.32, -5.82]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.78 (P = 0.0002)

Test for subgroup differences: Not applicable

Treatment discontinuation



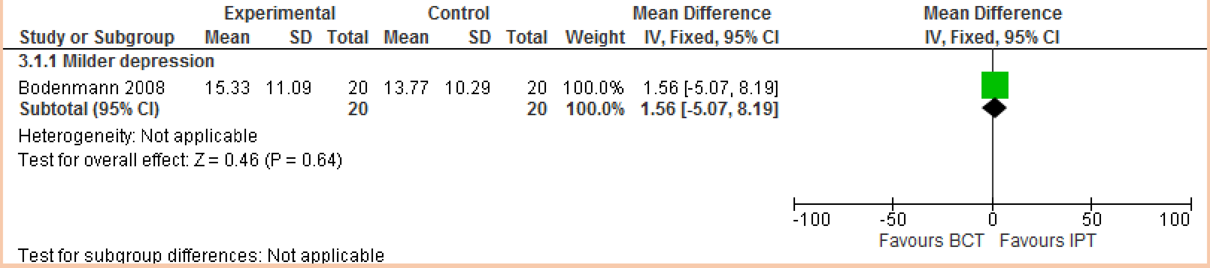
Study or Subgroup	Experimental		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI
2.2.1 More severe depression						
O'Leary 1990	3	12	0	12	100.0%	7.00 [0.40, 122.44]
Subtotal (95% CI)		**12**		**12**	**100.0%**	**7.00 [0.40, 122.44]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable

Behavioural couples therapy versus interpersonal psychotherapy (IPT)

Depression symptoms at endpoint

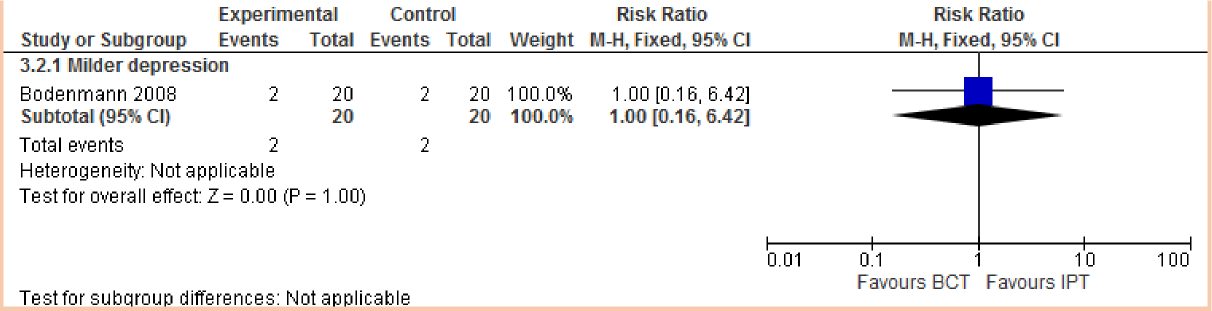


Study or Subgroup	Experimental			Control			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
3.1.1 Milder depression								
Bodenmann 2008	15.33	11.09	20	13.77	10.29	20	100.0%	1.56 [-5.07, 8.19]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**1.56 [-5.07, 8.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)

Test for subgroup differences: Not applicable

Treatment discontinuation



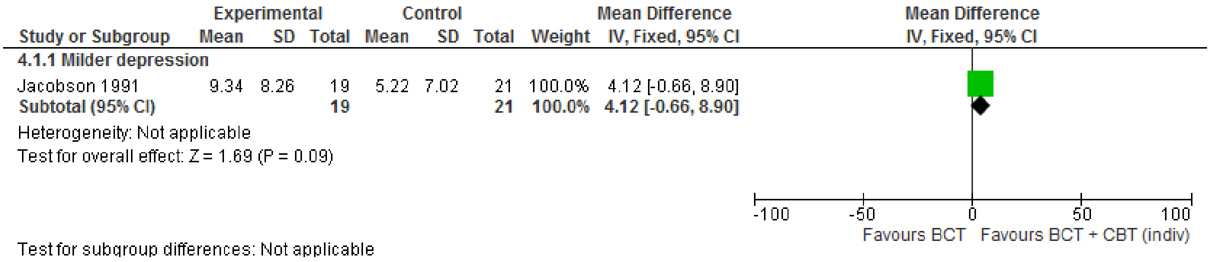
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Milder depression						
Bodenmann 2008	2	20	2	20	100.0%	1.00 [0.16, 6.42]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.16, 6.42]**
Total events	2		2			

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

Test for subgroup differences: Not applicable

Behavioural couples therapy (BCT) versus combined BCT and CBT (individual CBT for the depressed wife)

Depression symptoms at endpoint

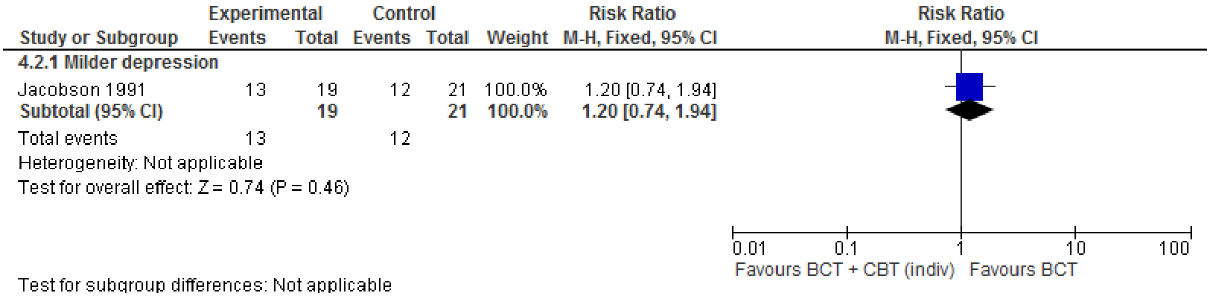


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 Milder depression								
Jacobson 1991	9.34	8.26	19	5.22	7.02	21	100.0%	4.12 [-0.66, 8.90]
Subtotal (95% CI)			**19**			**21**	**100.0%**	**4.12 [-0.66, 8.90]**

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

Test for subgroup differences: Not applicable

Remission

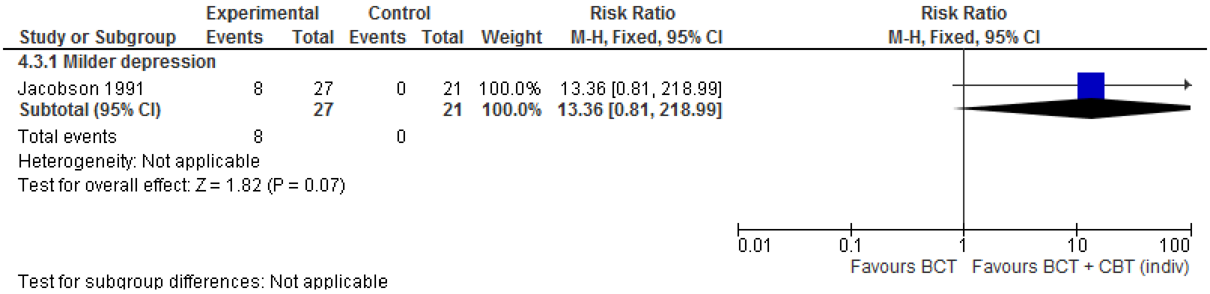


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Milder depression						
Jacobson 1991	13	19	12	21	100.0%	1.20 [0.74, 1.94]
Subtotal (95% CI)		**19**		**21**	**100.0%**	**1.20 [0.74, 1.94]**
Total events	13		12			

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

Test for subgroup differences: Not applicable

Treatment discontinuation



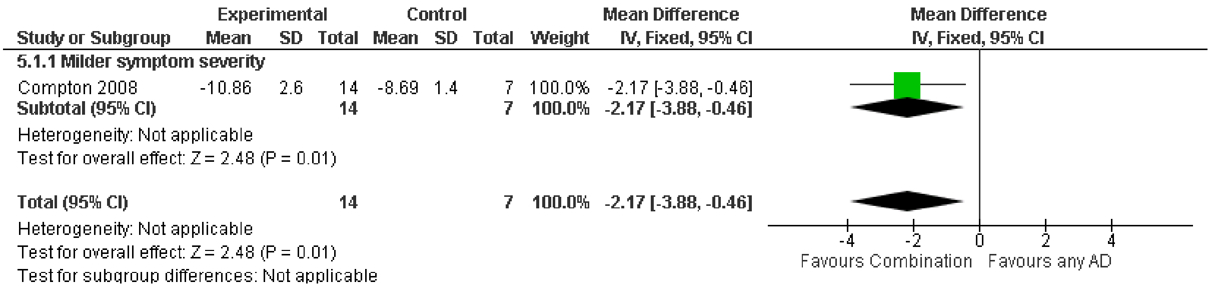
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Milder depression						
Jacobson 1991	8	27	0	21	100.0%	13.36 [0.81, 218.99]
Subtotal (95% CI)		**27**		**21**	**100.0%**	**13.36 [0.81, 218.99]**
Total events	8		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)

Test for subgroup differences: Not applicable

Behavioural couples therapy + any antidepressant versus any antidepressant

Depression symptomatology: milder depression severity



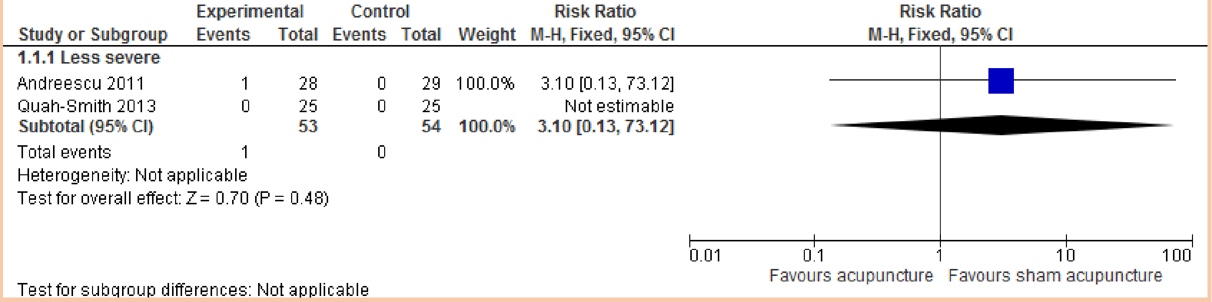
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
5.1.1 Milder symptom severity								
Compton 2008	-10.86	2.6	14	-8.69	1.4	7	100.0%	-2.17 [-3.88, -0.46]
Subtotal (95% CI)			**14**			**7**	**100.0%**	**-2.17 [-3.88, -0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.48 (P = 0.01)								
Total (95% CI)			**14**			**7**	**100.0%**	**-2.17 [-3.88, -0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.48 (P = 0.01)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-4
-2
0
2
4
Favours Combination
Favours any AD

Acupuncture

Acupuncture versus sham acupuncture

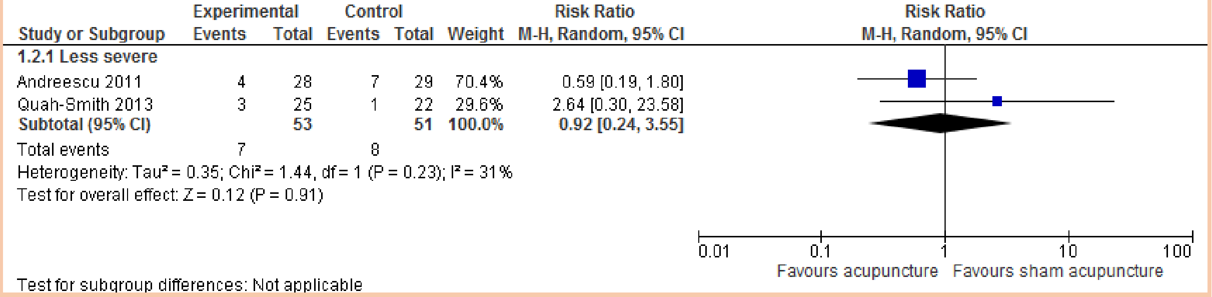
Discontinuation due to side effects



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Less severe						
Andreescu 2011	1	28	0	29	100.0%	3.10 [0.13, 73.12]
Quah-Smith 2013	0	25	0	25		Not estimable
Subtotal (95% CI)		**53**		**54**	**100.0%**	**3.10 [0.13, 73.12]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours acupuncture
Favours sham acupuncture

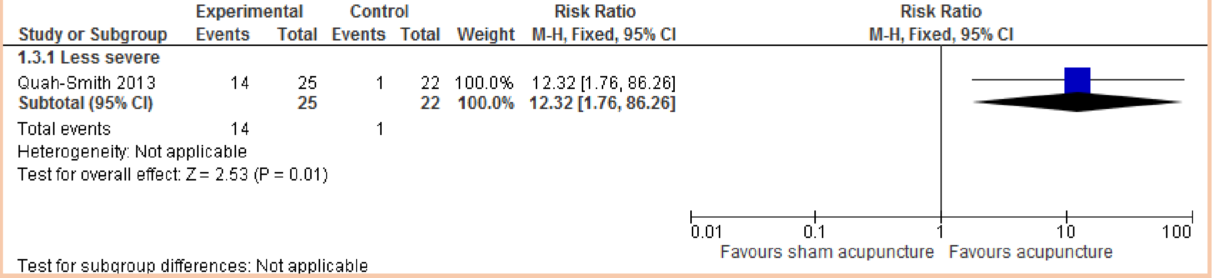
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Less severe						
Andreescu 2011	4	28	7	29	70.4%	0.59 [0.19, 1.80]
Quah-Smith 2013	3	25	1	22	29.6%	2.64 [0.30, 23.58]
Subtotal (95% CI)		**53**		**51**	**100.0%**	**0.92 [0.24, 3.55]**
Total events	7		8			
Heterogeneity: Tau² = 0.35; Chi² = 1.44, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Not applicable						

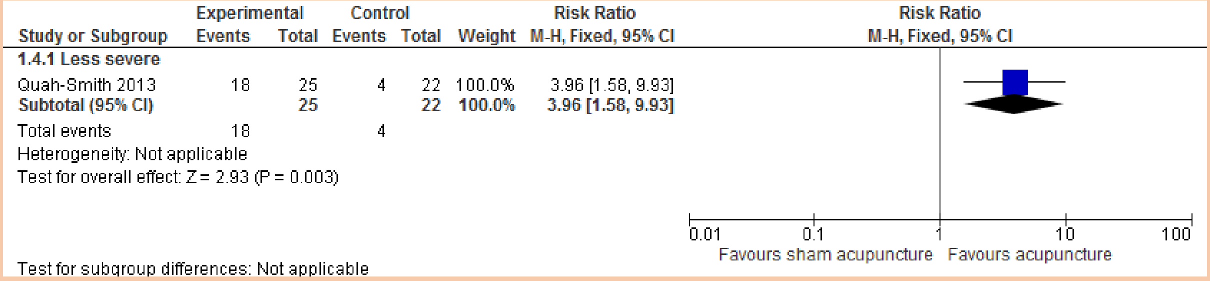
Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acupuncture
Favours sham acupuncture

Remission (HAMD endpoint score of 7 or below)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Less severe						
Quah-Smith 2013	14	25	1	22	100.0%	12.32 [1.76, 86.26]
Subtotal (95% CI)		**25**		**22**	**100.0%**	**12.32 [1.76, 86.26]**
Total events	14		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.53 (P = 0.01)						
Test for subgroup differences: Not applicable						

Response (reduction of at least 50% from the baseline score on HAMD)

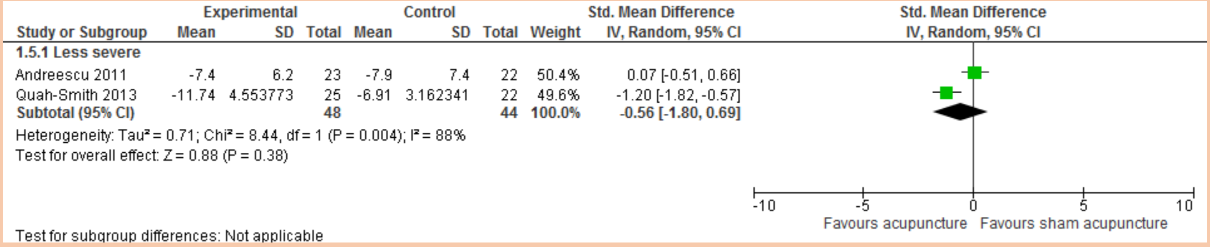


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Less severe						
Quah-Smith 2013	18	25	4	22	100.0%	3.96 [1.58, 9.93]
Subtotal (95% CI)		**25**		**22**	**100.0%**	**3.96 [1.58, 9.93]**
Total events	18		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.93 (P = 0.003)

Test for subgroup differences: Not applicable

Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Less severe								
Andreescu 2011	-7.4	6.2	23	-7.9	7.4	22	50.4%	0.07 [-0.51, 0.66]
Quah-Smith 2013	-11.74	4.553773	25	-6.91	3.162341	22	49.6%	-1.20 [-1.82, -0.57]
Subtotal (95% CI)			**48**			**44**	**100.0%**	**-0.56 [-1.80, 0.69]**

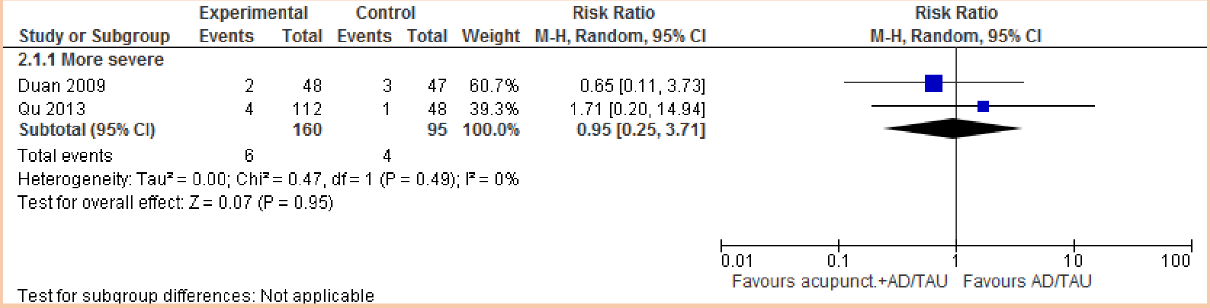
Heterogeneity: Tau² = 0.71; Chi² = 8.44, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours acupuncture
Favours sham acupuncture

Acupuncture + AD/TAU versus TAU

Discontinuation due to side effects



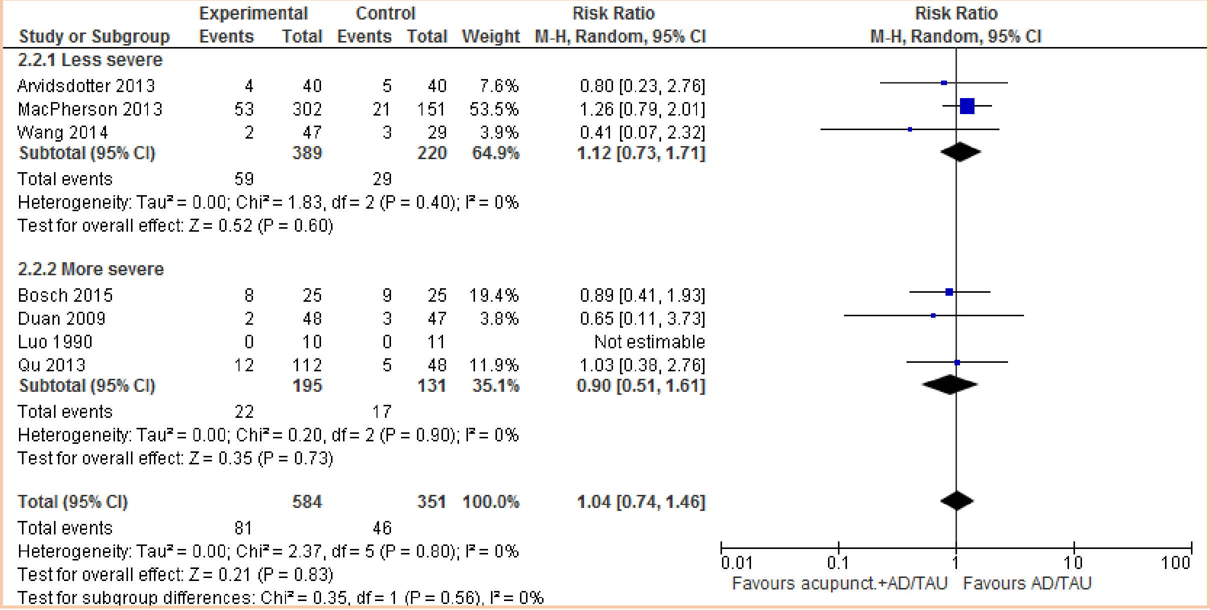
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 More severe						
Duan 2009	2	48	3	47	60.7%	0.65 [0.11, 3.73]
Qu 2013	4	112	1	48	39.3%	1.71 [0.20, 14.94]
Subtotal (95% CI)		**160**		**95**	**100.0%**	**0.95 [0.25, 3.71]**
Total events	6		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acupunct.+AD/TAU
Favours AD/TAU

Discontinuation for any reason

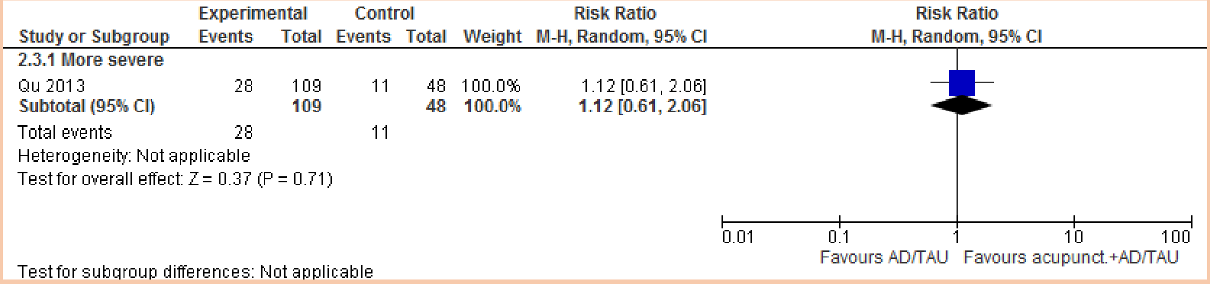


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Less severe						
Arvidsdotter 2013	4	40	5	40	7.6%	0.80 [0.23, 2.76]
MacPherson 2013	53	302	21	151	53.5%	1.26 [0.79, 2.01]
Wang 2014	2	47	3	29	3.9%	0.41 [0.07, 2.32]
Subtotal (95% CI)		**389**		**220**	**64.9%**	**1.12 [0.73, 1.71]**
Total events	59		29			
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.60)						
2.2.2 More severe						
Bosch 2015	8	25	9	25	19.4%	0.89 [0.41, 1.93]
Duan 2009	2	48	3	47	3.8%	0.65 [0.11, 3.73]
Luo 1990	0	10	0	11		Not estimable
Qu 2013	12	112	5	48	11.9%	1.03 [0.38, 2.76]
Subtotal (95% CI)		**195**		**131**	**35.1%**	**0.90 [0.51, 1.61]**
Total events	22		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**584**		**351**	**100.0%**	**1.04 [0.74, 1.46]**
Total events	81		46			

Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 5 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acupunct.+AD/TAU
Favours AD/TAU

Remission (HAMD endpoint score of 7 or below)

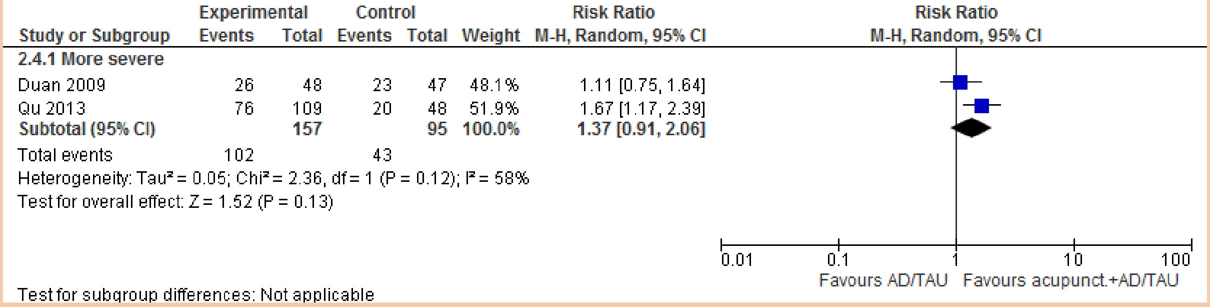


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 More severe						
Qu 2013	28	109	11	48	100.0%	1.12 [0.61, 2.06]
Subtotal (95% CI)		**109**		**48**	**100.0%**	**1.12 [0.61, 2.06]**
Total events	28		11			

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

Test for subgroup differences: Not applicable

Response (reduction of at least 50% from baseline score on HAMD)

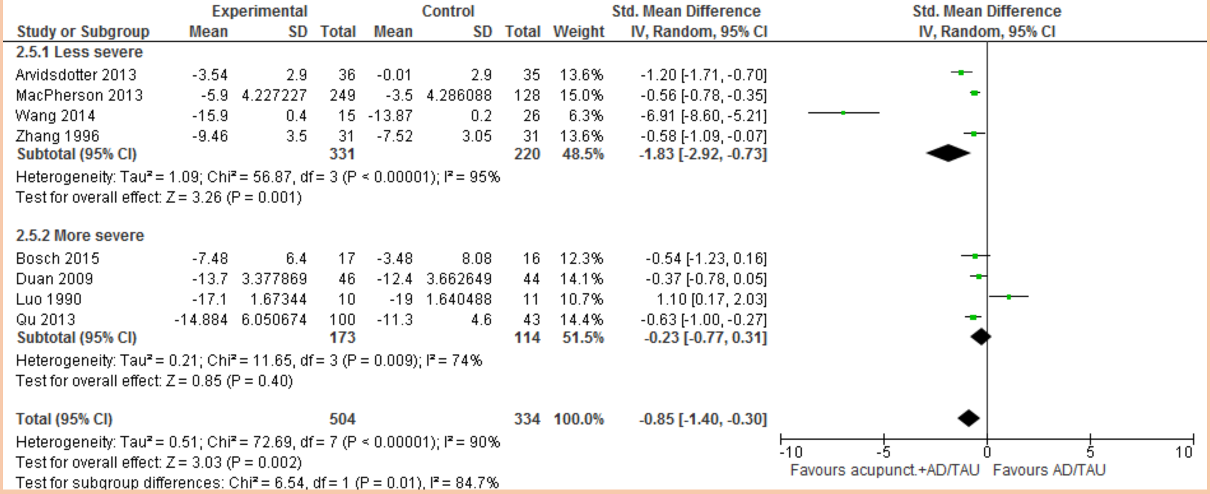


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 More severe						
Duan 2009	26	48	23	47	48.1%	1.11 [0.75, 1.64]
Qu 2013	76	109	20	48	51.9%	1.67 [1.17, 2.39]
Subtotal (95% CI)		**157**		**95**	**100.0%**	**1.37 [0.91, 2.06]**
Total events	102		43			

Heterogeneity: Tau² = 0.05; Chi² = 2.36, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

Depression symptomatology (HAMD/PHQ-9/BDI-II change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 Less severe								
Arvidsdotter 2013	-3.54	2.9	36	-0.01	2.9	35	13.6%	-1.20 [-1.71, -0.70]
MacPherson 2013	-5.9	4.227227	249	-3.5	4.286088	128	15.0%	-0.56 [-0.78, -0.35]
Wang 2014	-15.9	0.4	15	-13.87	0.2	26	6.3%	-6.91 [-8.60, -5.21]
Zhang 1996	-9.46	3.5	31	-7.52	3.05	31	13.6%	-0.58 [-1.09, -0.07]
Subtotal (95% CI)			**331**			**220**	**48.5%**	**-1.83 [-2.92, -0.73]**

Heterogeneity: Tau² = 1.09; Chi² = 56.87, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.26 (P = 0.001)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.2 More severe								
Bosch 2015	-7.48	6.4	17	-3.48	8.08	16	12.3%	-0.54 [-1.23, 0.16]
Duan 2009	-13.7	3.377869	46	-12.4	3.662649	44	14.1%	-0.37 [-0.78, 0.05]
Luo 1990	-17.1	1.67344	10	-19	1.640488	11	10.7%	1.10 [0.17, 2.03]
Qu 2013	-14.884	6.050674	100	-11.3	4.6	43	14.4%	-0.63 [-1.00, -0.27]
Subtotal (95% CI)			**173**			**114**	**51.5%**	**-0.23 [-0.77, 0.31]**

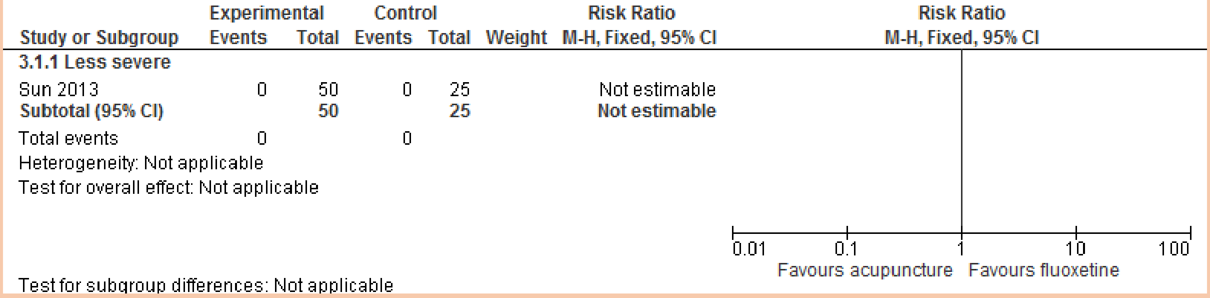
Heterogeneity: Tau² = 0.21; Chi² = 11.65, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 0.85 (P = 0.40)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total (95% CI)			**504**			**334**	**100.0%**	**-0.85 [-1.40, -0.30]**

Heterogeneity: Tau² = 0.51; Chi² = 72.69, df = 7 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.03 (P = 0.002)
Test for subgroup differences: Chi² = 6.54, df = 1 (P = 0.01), I² = 84.7%

Acupuncture versus SSRI

Discontinuation due to side effects

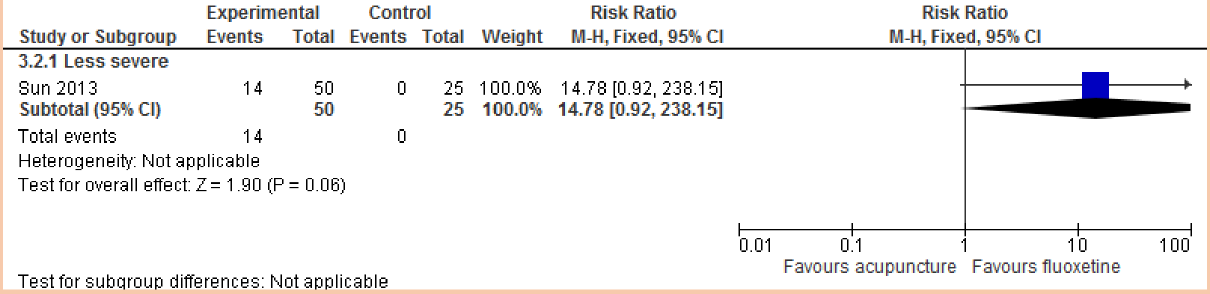


	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
3.1.1 Less severe						
Sun 2013	0	50	0	25		Not estimable
Subtotal (95% CI)		**50**		**25**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Test for subgroup differences: Not applicable

Discontinuation for any reason

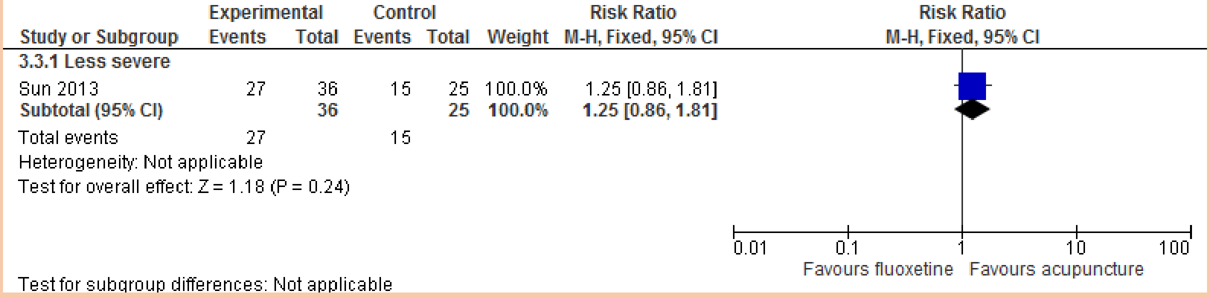


	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
3.2.1 Less severe						
Sun 2013	14	50	0	25	100.0%	14.78 [0.92, 238.15]
Subtotal (95% CI)		**50**		**25**	**100.0%**	**14.78 [0.92, 238.15]**
Total events	14		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)

Test for subgroup differences: Not applicable

Response (reduction of at least 50% from the baseline score on HAMD)

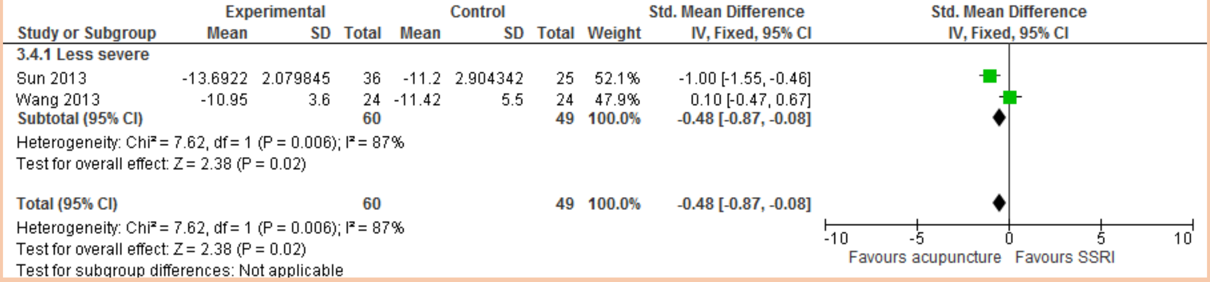


	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
3.3.1 Less severe						
Sun 2013	27	36	15	25	100.0%	1.25 [0.86, 1.81]
Subtotal (95% CI)		**36**		**25**	**100.0%**	**1.25 [0.86, 1.81]**
Total events	27		15			

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

Test for subgroup differences: Not applicable

Depression symptomatology (HAMD/MADRS change score)



	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
3.4.1 Less severe								
Sun 2013	-13.6922	2.079845	36	-11.2	2.904342	25	52.1%	-1.00 [-1.55, -0.46]
Wang 2013	-10.95	3.6	24	-11.42	5.5	24	47.9%	0.10 [-0.47, 0.67]
Subtotal (95% CI)			**60**			**49**	**100.0%**	**-0.48 [-0.87, -0.08]**

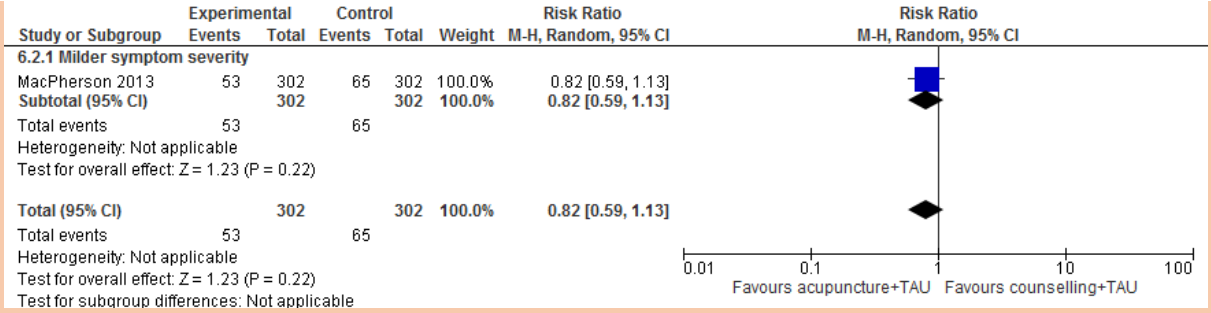
Heterogeneity: Chi² = 7.62, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 2.38 (P = 0.02)

Total (95% CI)			**60**			**49**	**100.0%**	**-0.48 [-0.87, -0.08]**

Heterogeneity: Chi² = 7.62, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 2.38 (P = 0.02)
Test for subgroup differences: Not applicable

Acupuncture + TAU versus counselling + TAU

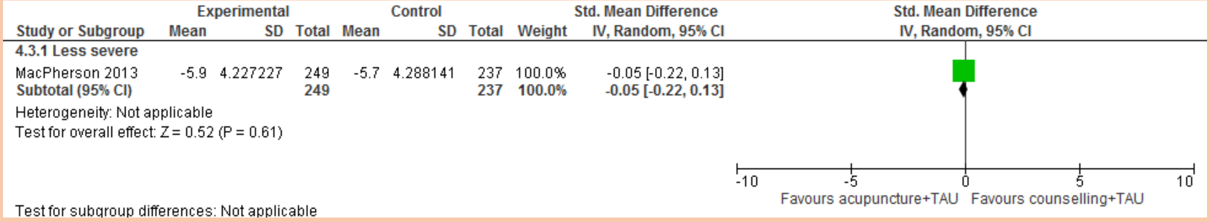
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Milder symptom severity						
MacPherson 2013	53	302	65	302	100.0%	0.82 [0.59, 1.13]
Subtotal (95% CI)		**302**		**302**	**100.0%**	**0.82 [0.59, 1.13]**
Total events	53		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
Total (95% CI)		**302**		**302**	**100.0%**	**0.82 [0.59, 1.13]**
Total events	53		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours acupuncture+TAU
Favours counselling+TAU

Depression symptomatology (PHQ-9 change score)

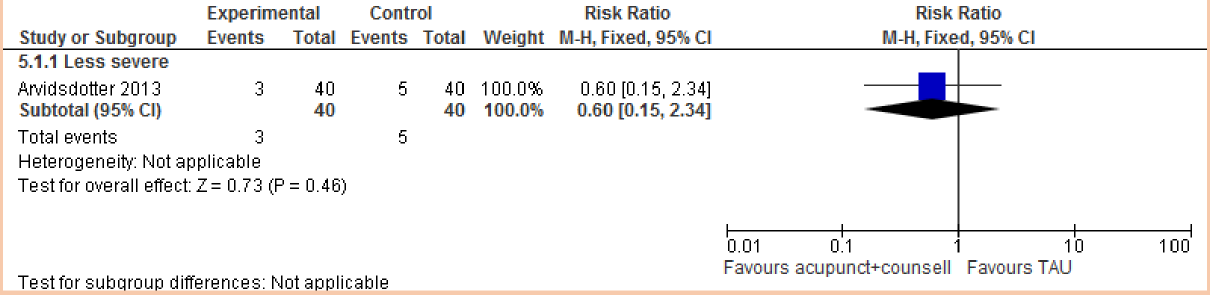


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.3.1 Less severe								
MacPherson 2013	-5.9	4.227227	249	-5.7	4.288141	237	100.0%	-0.05 [-0.22, 0.13]
Subtotal (95% CI)			**249**			**237**	**100.0%**	**-0.05 [-0.22, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.61)								
Test for subgroup differences: Not applicable								

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours acupuncture+TAU
Favours counselling+TAU

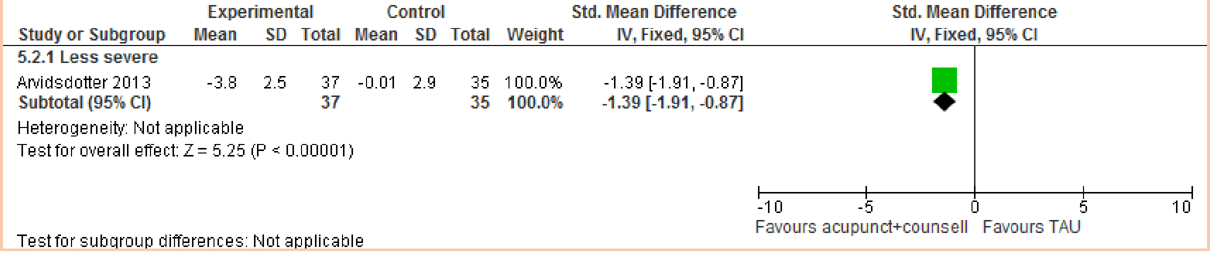
Acupuncture + counselling versus TAU

Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Less severe						
Arvidsdotter 2013	3	40	5	40	100.0%	0.60 [0.15, 2.34]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.60 [0.15, 2.34]**
Total events	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
Test for subgroup differences: Not applicable						

Depression symptomatology (HADS-D change score)



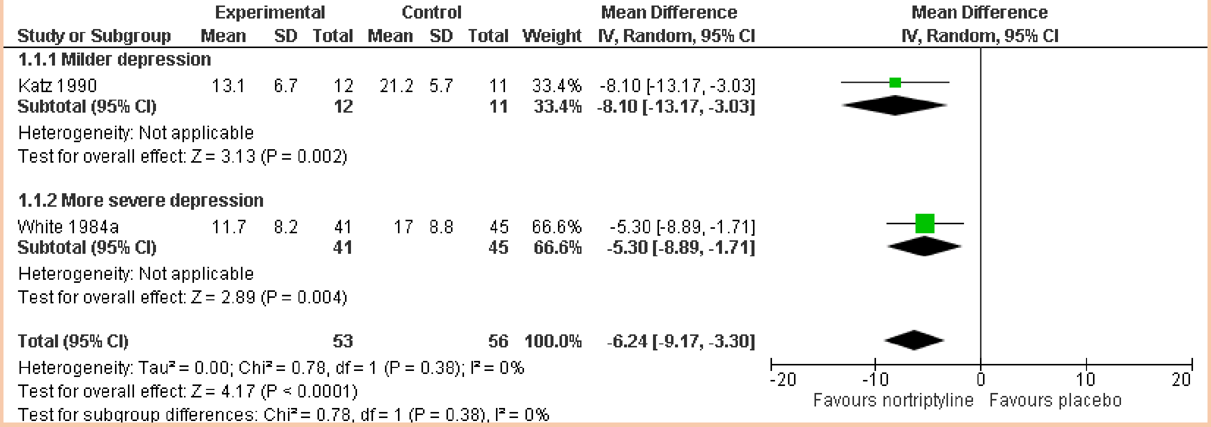
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
5.2.1 Less severe								
Arvidsdotter 2013	-3.8	2.5	37	-0.01	2.9	35	100.0%	-1.39 [-1.91, -0.87]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**-1.39 [-1.91, -0.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.25 (P < 0.00001)								
Test for subgroup differences: Not applicable								

Std. Mean Difference
IV, Fixed, 95% CI
-10
-5
0
5
10
Favours acupunct+counsell
Favours TAU

Nortriptyline

Nortriptyline versus placebo

Depression symptomatology at endpoint: milder and more severe depression

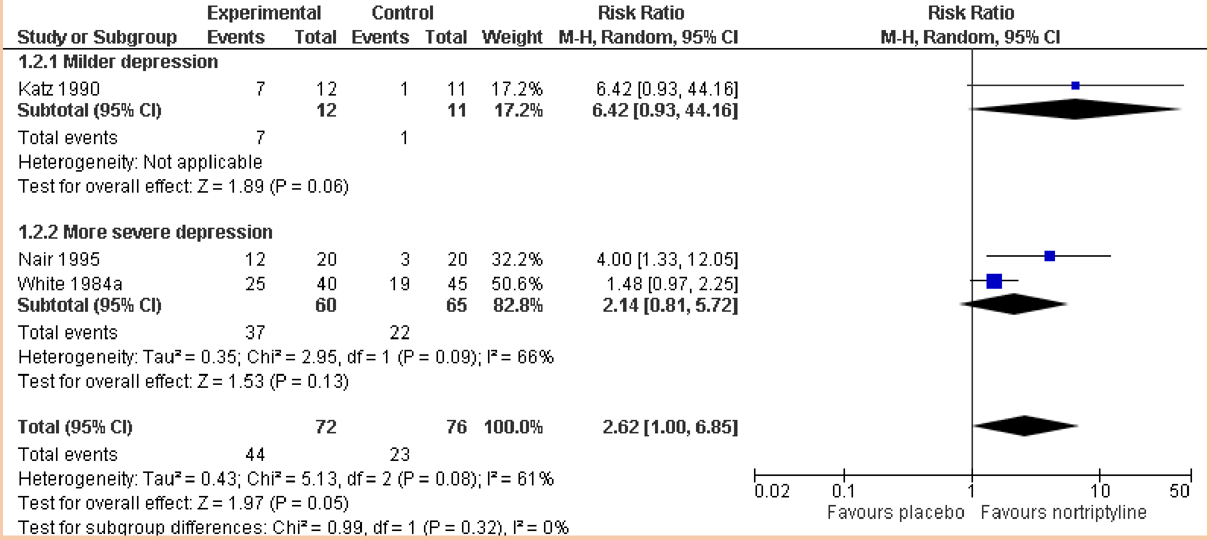


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Milder depression								
Katz 1990	13.1	6.7	12	21.2	5.7	11	33.4%	-8.10 [-13.17, -3.03]
Subtotal (95% CI)			**12**			**11**	**33.4%**	**-8.10 [-13.17, -3.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.13 (P = 0.002)								
1.1.2 More severe depression								
White 1984a	11.7	8.2	41	17	8.8	45	66.6%	-5.30 [-8.89, -1.71]
Subtotal (95% CI)			**41**			**45**	**66.6%**	**-5.30 [-8.89, -1.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.89 (P = 0.004)								
Total (95% CI)			**53**			**56**	**100.0%**	**-6.24 [-9.17, -3.30]**

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 4.17 (P < 0.0001)
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%

Mean Difference
IV, Random, 95% CI
-20
-10
0
10
20
Favours nortriptyline
Favours placebo

Remission at endpoint: milder and more severe depression

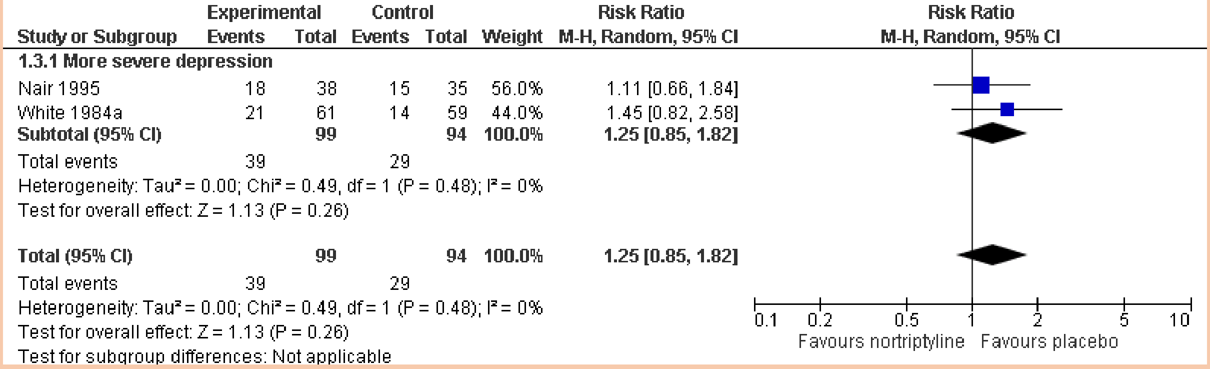


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Milder depression						
Katz 1990	7	12	1	11	17.2%	6.42 [0.93, 44.16]
Subtotal (95% CI)		**12**		**11**	**17.2%**	**6.42 [0.93, 44.16]**
Total events	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
1.2.2 More severe depression						
Nair 1995	12	20	3	20	32.2%	4.00 [1.33, 12.05]
White 1984a	25	40	19	45	50.6%	1.48 [0.97, 2.25]
Subtotal (95% CI)		**60**		**65**	**82.8%**	**2.14 [0.81, 5.72]**
Total events	37		22			
Heterogeneity: Tau² = 0.35; Chi² = 2.95, df = 1 (P = 0.09); I² = 66%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)		**72**		**76**	**100.0%**	**2.62 [1.00, 6.85]**
Total events	44		23			

Heterogeneity: Tau² = 0.43; Chi² = 5.13, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%

Risk Ratio
M-H, Random, 95% CI
0.02
0.1
1
10
50
Favours placebo
Favours nortriptyline

Treatment discontinuation: more severe depression

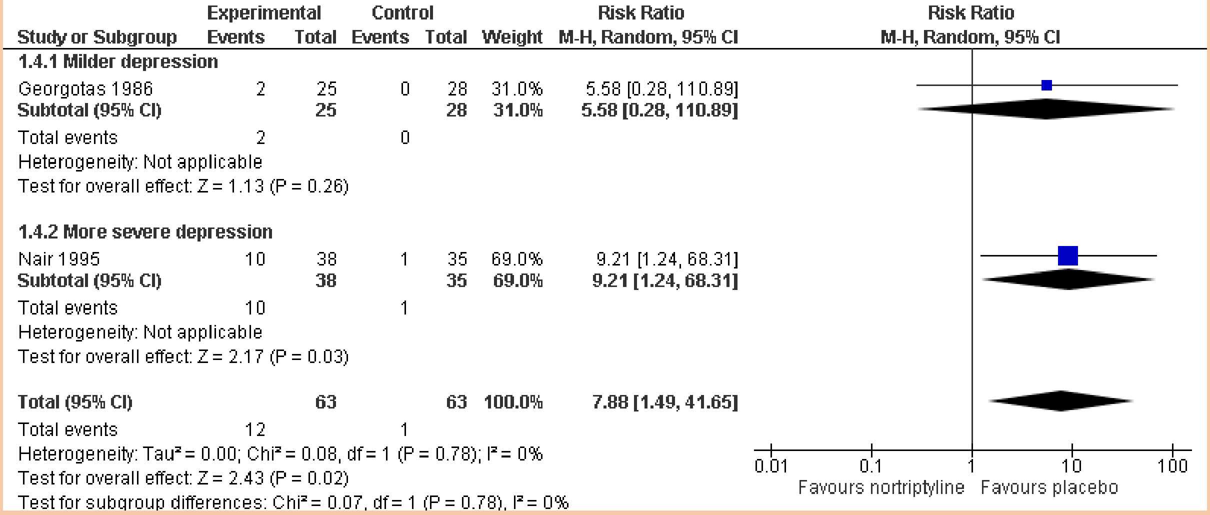


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 More severe depression						
Nair 1995	18	38	15	35	56.0%	1.11 [0.66, 1.84]
White 1984a	21	61	14	59	44.0%	1.45 [0.82, 2.58]
Subtotal (95% CI)		**99**		**94**	**100.0%**	**1.25 [0.85, 1.82]**
Total events	39		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**99**		**94**	**100.0%**	**1.25 [0.85, 1.82]**
Total events	39		29			

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours nortriptyline
Favours placebo

Treatment discontinuation due to side effect: milder and more severe depression

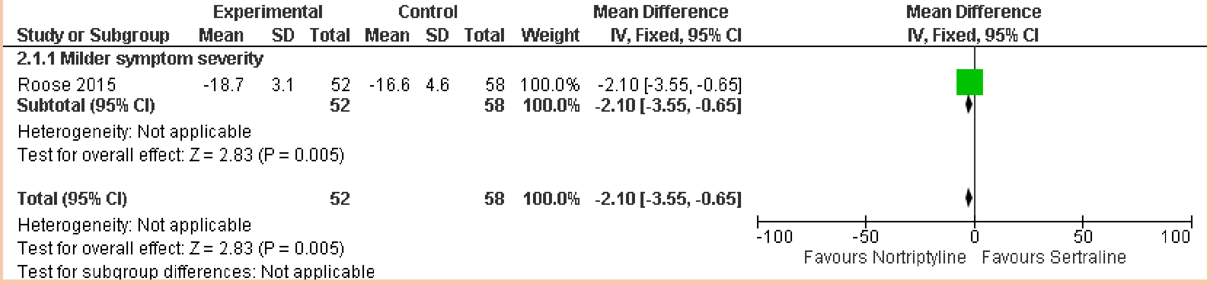


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Milder depression						
Georgotas 1986	2	25	0	28	31.0%	5.58 [0.28, 110.89]
Subtotal (95% CI)		**25**		**28**	**31.0%**	**5.58 [0.28, 110.89]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.4.2 More severe depression						
Nair 1995	10	38	1	35	69.0%	9.21 [1.24, 68.31]
Subtotal (95% CI)		**38**		**35**	**69.0%**	**9.21 [1.24, 68.31]**
Total events	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						
Total (95% CI)		**63**		**63**	**100.0%**	**7.88 [1.49, 41.65]**
Total events	12		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.78), I² = 0%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours nortriptyline
Favours placebo

Nortriptyline versus sertraline

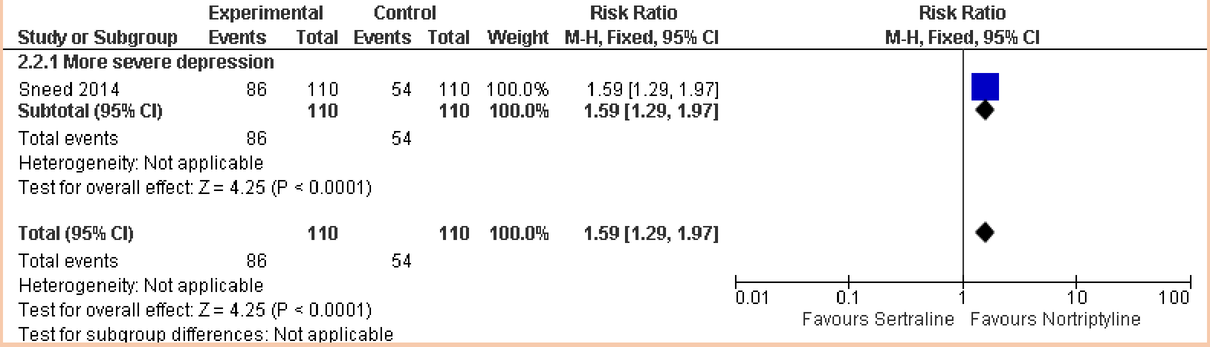
Depression symptomatology



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Milder symptom severity								
Roose 2015	-18.7	3.1	52	-16.6	4.6	58	100.0%	-2.10 [-3.55, -0.65]
Subtotal (95% CI)			**52**			**58**	**100.0%**	**-2.10 [-3.55, -0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.83 (P = 0.005)								
Total (95% CI)			**52**			**58**	**100.0%**	**-2.10 [-3.55, -0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.83 (P = 0.005)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-100
-50
0
50
100
Favours Nortriptyline
Favours Sertraline

Response



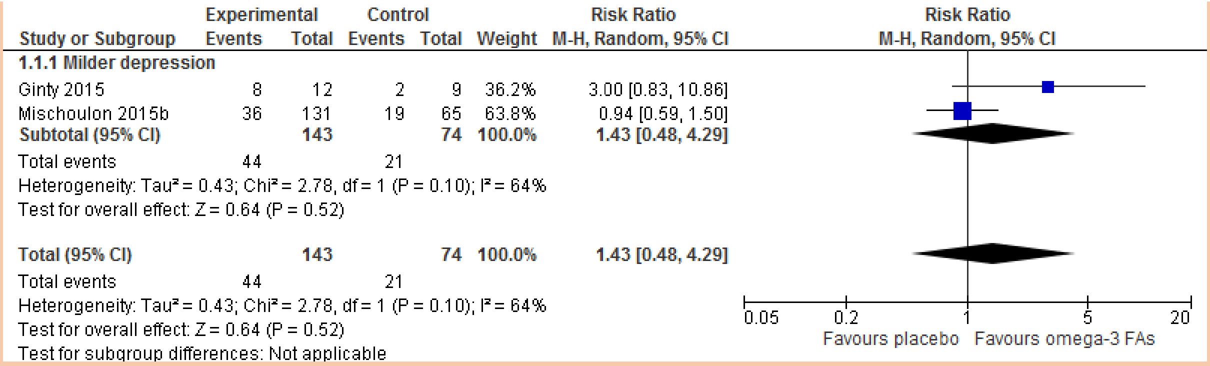
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 More severe depression						
Sneed 2014	86	110	54	110	100.0%	1.59 [1.29, 1.97]
Subtotal (95% CI)		**110**		**110**	**100.0%**	**1.59 [1.29, 1.97]**
Total events	86		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
Total (95% CI)		**110**		**110**	**100.0%**	**1.59 [1.29, 1.97]**
Total events	86		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours Sertraline
Favours Nortriptyline

Omega-3 fatty acids

Omega-3 fatty acids versus placebo

Remission (BDI<=10 or HAMD-17 <=7)



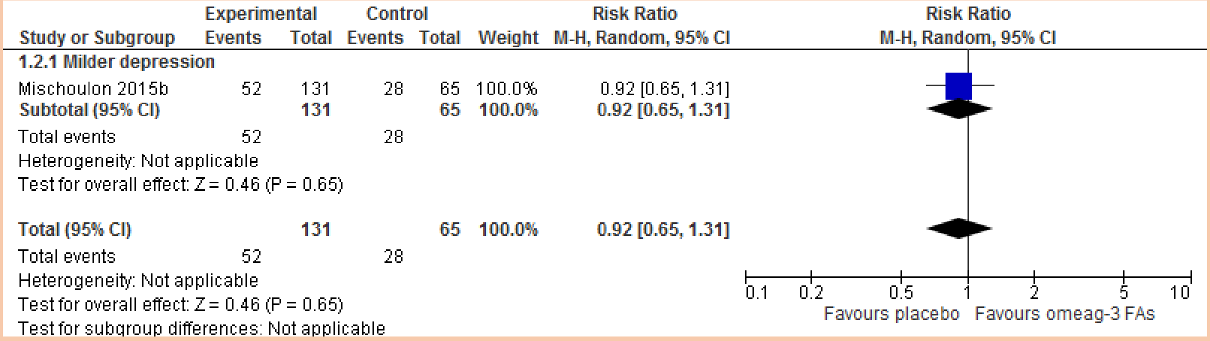
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Milder depression						
Ginty 2015	8	12	2	9	36.2%	3.00 [0.83, 10.86]
Mischoulon 2015b	36	131	19	65	63.8%	0.94 [0.59, 1.50]
Subtotal (95% CI)		**143**		**74**	**100.0%**	**1.43 [0.48, 4.29]**
Total events	44		21			
Total (95% CI)		**143**		**74**	**100.0%**	**1.43 [0.48, 4.29]**
Total events	44		21			

Heterogeneity: Tau² = 0.43; Chi² = 2.78, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 0.64 (P = 0.52)

Heterogeneity: Tau² = 0.43; Chi² = 2.78, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.05
0.2
1
5
20
Favours placebo
Favours omega-3 FAs

Response (HAMD reduced by >=50%)



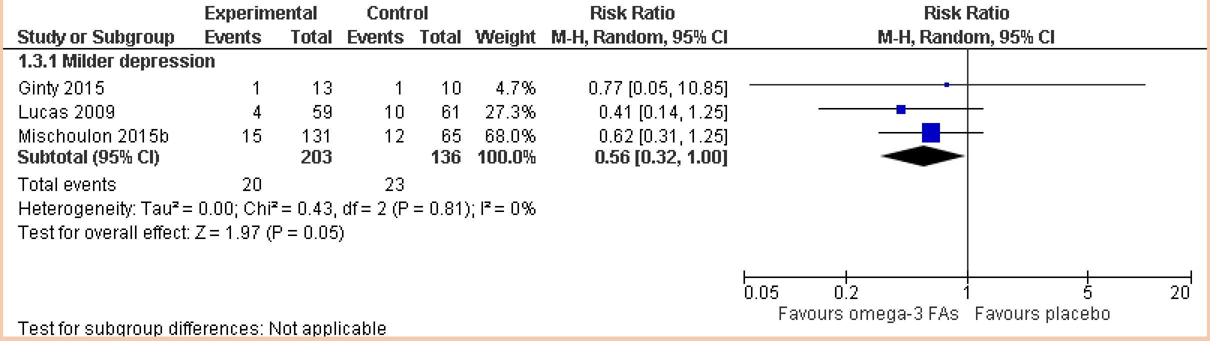
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Milder depression						
Mischoulon 2015b	52	131	28	65	100.0%	0.92 [0.65, 1.31]
Subtotal (95% CI)		**131**		**65**	**100.0%**	**0.92 [0.65, 1.31]**
Total events	52		28			
Total (95% CI)		**131**		**65**	**100.0%**	**0.92 [0.65, 1.31]**
Total events	52		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours placebo
Favours omeag-3 FAs

Treatment discontinuation



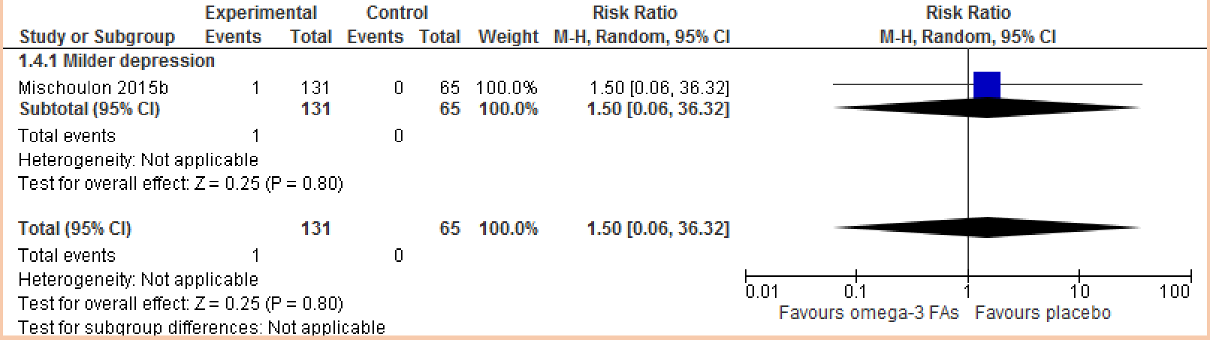
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Milder depression						
Ginty 2015	1	13	1	10	4.7%	0.77 [0.05, 10.85]
Lucas 2009	4	59	10	61	27.3%	0.41 [0.14, 1.25]
Mischoulon 2015b	15	131	12	65	68.0%	0.62 [0.31, 1.25]
Subtotal (95% CI)		**203**		**136**	**100.0%**	**0.56 [0.32, 1.00]**
Total events	20		23			

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.05
0.2
1
5
20
Favours omega-3 FAs
Favours placebo

Discontinuation due to side effects



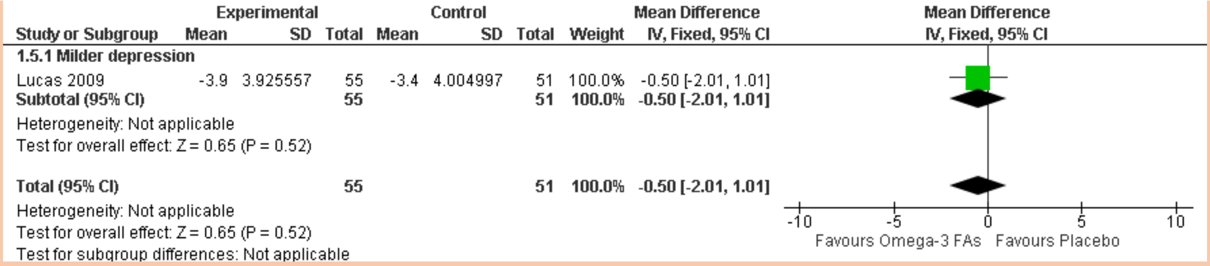
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Milder depression						
Mischoulon 2015b	1	131	0	65	100.0%	1.50 [0.06, 36.32]
Subtotal (95% CI)		**131**		**65**	**100.0%**	**1.50 [0.06, 36.32]**
Total events	1		0			
Total (95% CI)		**131**		**65**	**100.0%**	**1.50 [0.06, 36.32]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours omega-3 FAs
Favours placebo

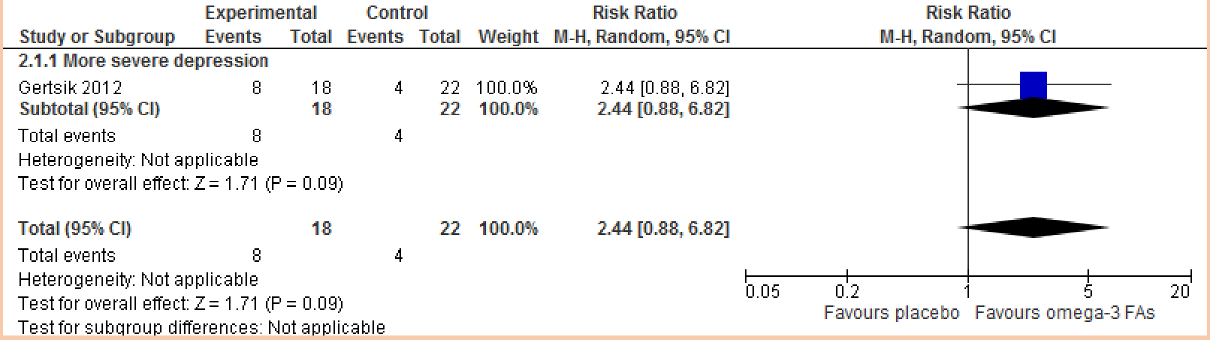
Depression symptomatology



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Milder depression								
Lucas 2009	-3.9	3.925557	55	-3.4	4.004997	51	100.0%	-0.50 [-2.01, 1.01]
Subtotal (95% CI)			**55**			**51**	**100.0%**	**-0.50 [-2.01, 1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.52)								
Total (95% CI)			**55**			**51**	**100.0%**	**-0.50 [-2.01, 1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.52)								
Test for subgroup differences: Not applicable								

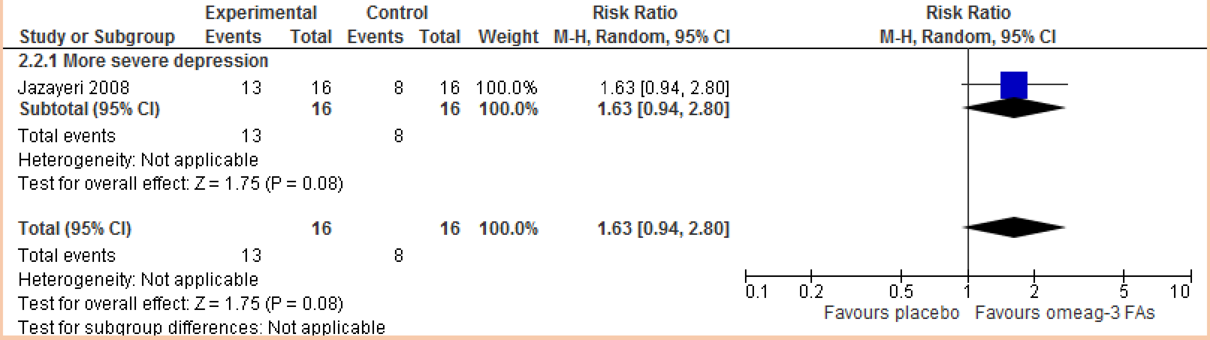
Omega-3 fatty acids + SSRI/antidepressant versus placebo + SSRI/antidepressant

Remission (BDI<=10 or HAMD<=7 at endpoint)



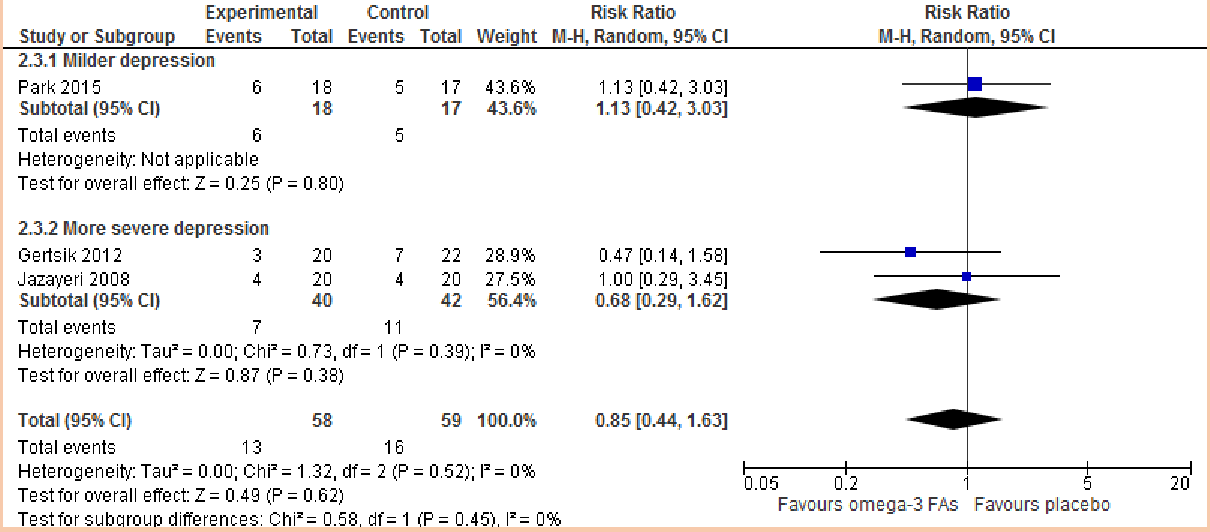
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 More severe depression						
Gertsik 2012	8	18	4	22	100.0%	2.44 [0.88, 6.82]
Subtotal (95% CI)		**18**		**22**	**100.0%**	**2.44 [0.88, 6.82]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
Total (95% CI)		**18**		**22**	**100.0%**	**2.44 [0.88, 6.82]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
Test for subgroup differences: Not applicable						

Response (HAMD reduced by >50% at endpoint)



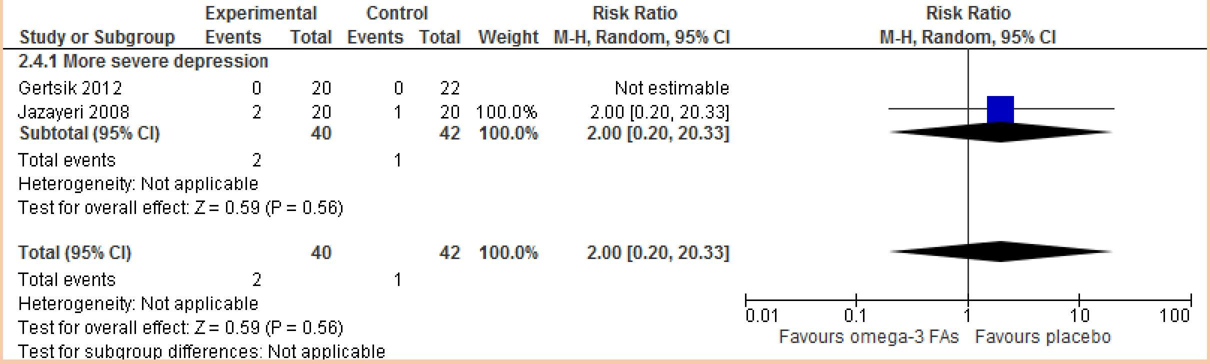
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 More severe depression						
Jazayeri 2008	13	16	8	16	100.0%	1.63 [0.94, 2.80]
Subtotal (95% CI)		**16**		**16**	**100.0%**	**1.63 [0.94, 2.80]**
Total events	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**16**		**16**	**100.0%**	**1.63 [0.94, 2.80]**
Total events	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Not applicable						

Treatment discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Milder depression						
Park 2015	6	18	5	17	43.6%	1.13 [0.42, 3.03]
Subtotal (95% CI)		**18**		**17**	**43.6%**	**1.13 [0.42, 3.03]**
Total events	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
2.3.2 More severe depression						
Gertsik 2012	3	20	7	22	28.9%	0.47 [0.14, 1.58]
Jazayeri 2008	4	20	4	20	27.5%	1.00 [0.29, 3.45]
Subtotal (95% CI)		**40**		**42**	**56.4%**	**0.68 [0.29, 1.62]**
Total events	7		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Total (95% CI)		**58**		**59**	**100.0%**	**0.85 [0.44, 1.63]**
Total events	13		16			
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.45), I² = 0%						

Discontinuation due to side effects

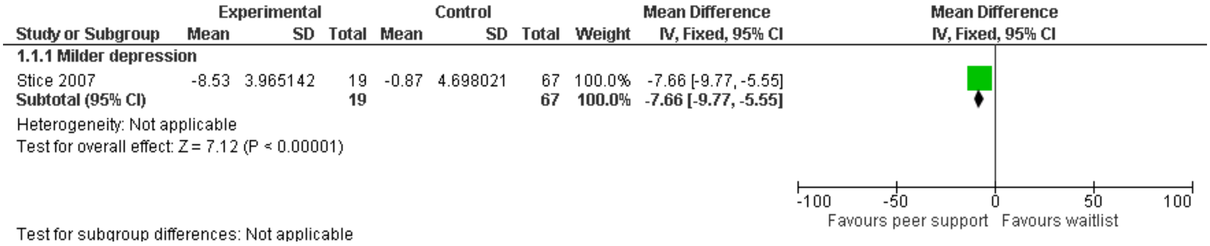


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 More severe depression						
Gertsik 2012	0	20	0	22		Not estimable
Jazayeri 2008	2	20	1	20	100.0%	2.00 [0.20, 20.33]
Subtotal (95% CI)		**40**		**42**	**100.0%**	**2.00 [0.20, 20.33]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Total (95% CI)		**40**		**42**	**100.0%**	**2.00 [0.20, 20.33]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Not applicable						

Psychosocial interventions (peer support)

Peer support versus waitlist

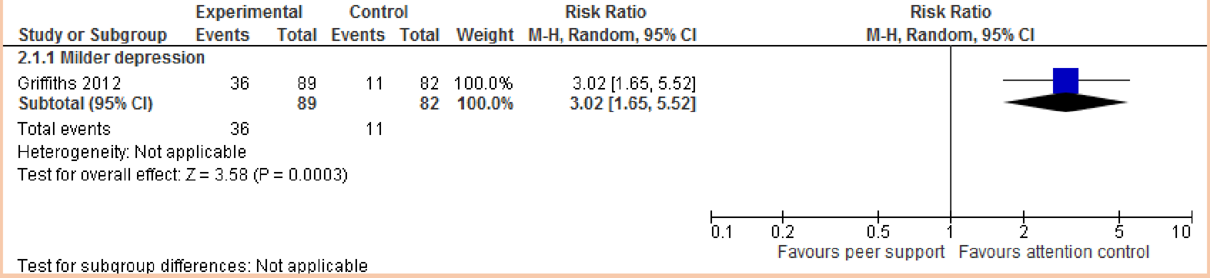
Depression symptomatology at endpoint (BDI)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Milder depression								
Stice 2007	-8.53	3.965142	19	-0.87	4.698021	67	100.0%	-7.66 [-9.77, -5.55]
Subtotal (95% CI)			**19**			**67**	**100.0%**	**-7.66 [-9.77, -5.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.12 (P < 0.00001)								
Test for subgroup differences: Not applicable								

Peer support (online support group) versus attention-placebo control

Treatment discontinuation rates



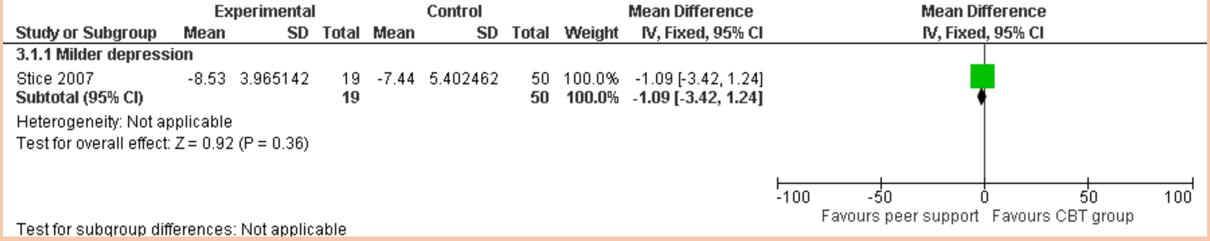
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Milder depression						
Griffiths 2012	36	89	11	82	100.0%	3.02 [1.65, 5.52]
Subtotal (95% CI)		**89**		**82**	**100.0%**	**3.02 [1.65, 5.52]**
Total events	36		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.58 (P = 0.0003)

Test for subgroup differences: Not applicable

Peer support group versus CBT group

Depression symptomatology at endpoint (BDI)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
3.1.1 Milder depression								
Stice 2007	-8.53	3.965142	19	-7.44	5.402462	50	100.0%	-1.09 [-3.42, 1.24]
Subtotal (95% CI)			**19**			**50**	**100.0%**	**-1.09 [-3.42, 1.24]**

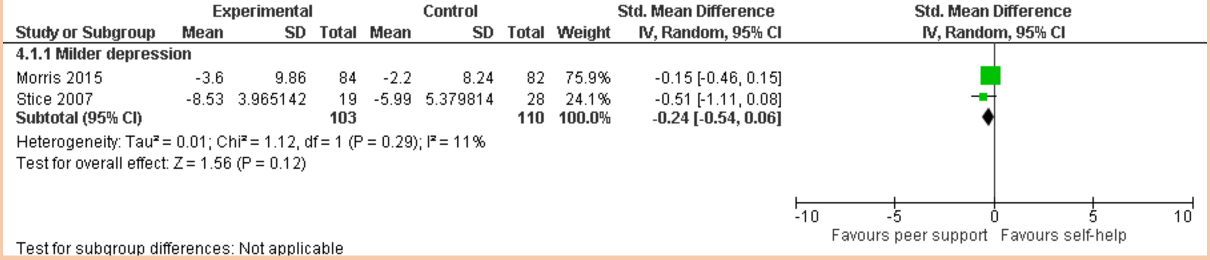
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

Mean Difference
IV, Fixed, 95% CI
-100
-50
0
50
100
Favours peer support
Favours CBT group

Peer support group versus self-help (without support)

Depression symptomatology at endpoint (BDI)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Milder depression								
Morris 2015	-3.6	9.86	84	-2.2	8.24	82	75.9%	-0.15 [-0.46, 0.15]
Stice 2007	-8.53	3.965142	19	-5.99	5.379814	28	24.1%	-0.51 [-1.11, 0.08]
Subtotal (95% CI)			**103**			**110**	**100.0%**	**-0.24 [-0.54, 0.06]**

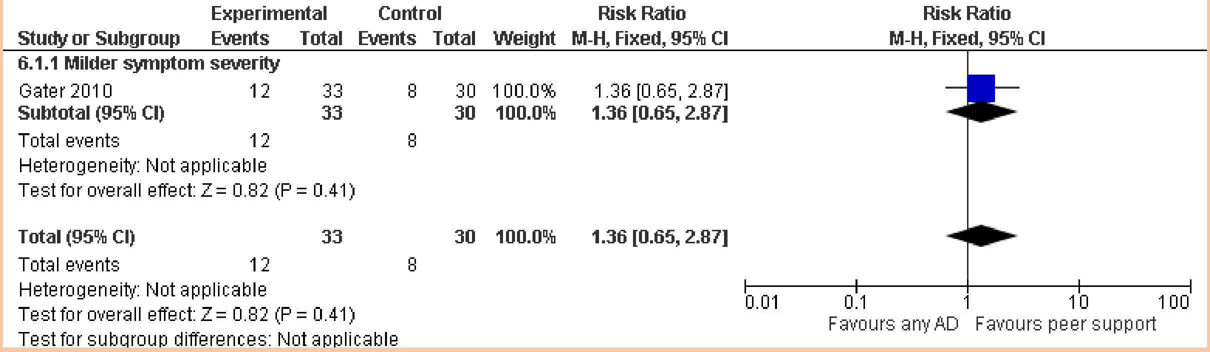
Heterogeneity: Tau² = 0.01; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours peer support
Favours self-help

Peer support + any antidepressant versus any antidepressant

Remission



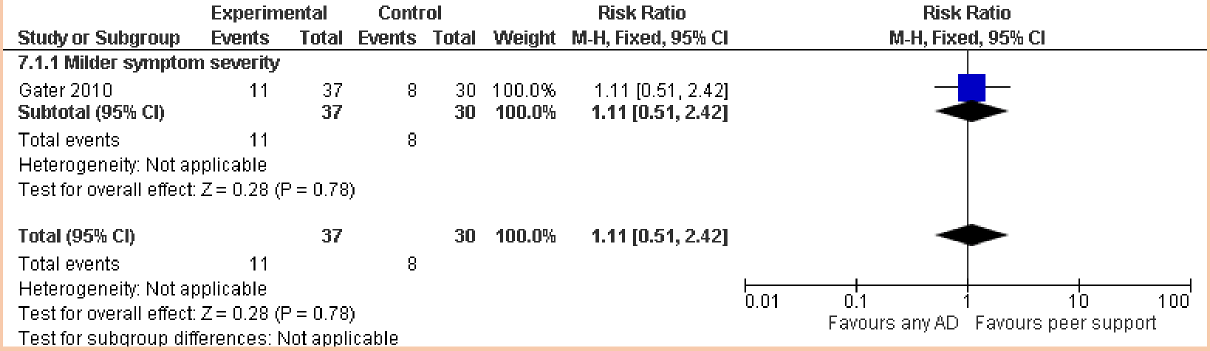
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Milder symptom severity						
Gater 2010	12	33	8	30	100.0%	1.36 [0.65, 2.87]
Subtotal (95% CI)		**33**		**30**	**100.0%**	**1.36 [0.65, 2.87]**
Total events	12		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**33**		**30**	**100.0%**	**1.36 [0.65, 2.87]**
Total events	12		8			

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

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours any AD
Favours peer support

Social intervention + any antidepressant versus any antidepressant

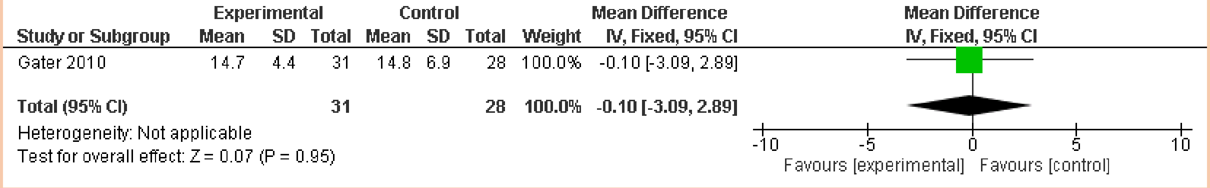
Remission



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Milder symptom severity						
Gater 2010	11	37	8	30	100.0%	1.11 [0.51, 2.42]
Subtotal (95% CI)		**37**		**30**	**100.0%**	**1.11 [0.51, 2.42]**
Total events	11		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**37**		**30**	**100.0%**	**1.11 [0.51, 2.42]**
Total events	11		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours any AD
Favours peer support

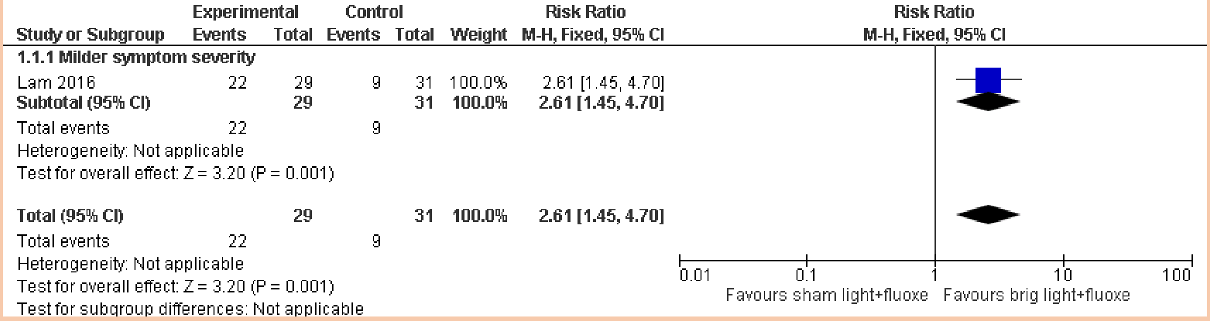
Depression symptomatology



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Gater 2010	14.7	4.4	31	14.8	6.9	28	100.0%	-0.10 [-3.09, 2.89]
Total (95% CI)			**31**			**28**	**100.0%**	**-0.10 [-3.09, 2.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.95)								

Bright light therapy

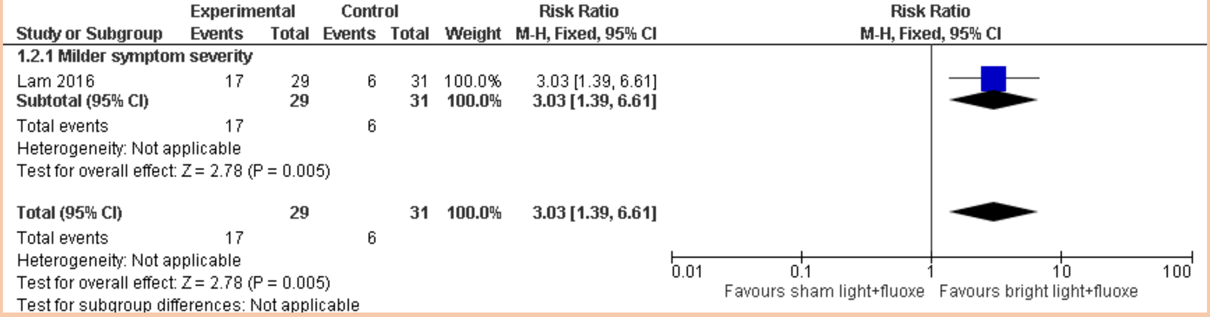
Response



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Milder symptom severity						
Lam 2016	22	29	9	31	100.0%	2.61 [1.45, 4.70]
Subtotal (95% CI)		**29**		**31**	**100.0%**	**2.61 [1.45, 4.70]**
Total events	22		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)		**29**		**31**	**100.0%**	**2.61 [1.45, 4.70]**
Total events	22		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.20 (P = 0.001)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours sham light+fluoxe
Favours brig light+fluoxe

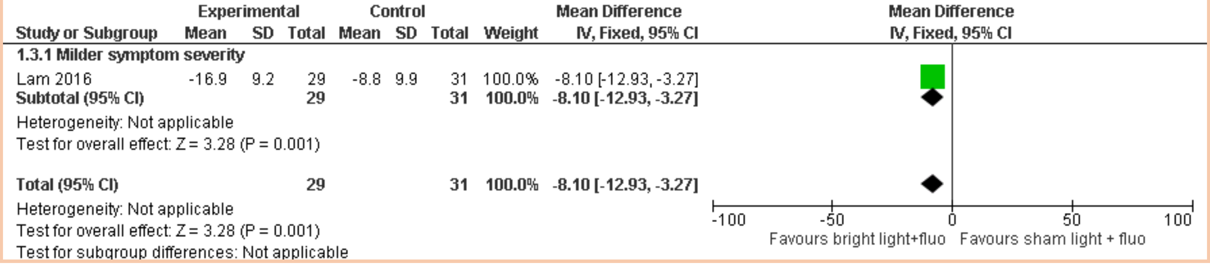
Remission



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Milder symptom severity						
Lam 2016	17	29	6	31	100.0%	3.03 [1.39, 6.61]
Subtotal (95% CI)		**29**		**31**	**100.0%**	**3.03 [1.39, 6.61]**
Total events	17		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
Total (95% CI)		**29**		**31**	**100.0%**	**3.03 [1.39, 6.61]**
Total events	17		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours sham light+fluoxe
Favours bright light+fluoxe

Depression symptomatology

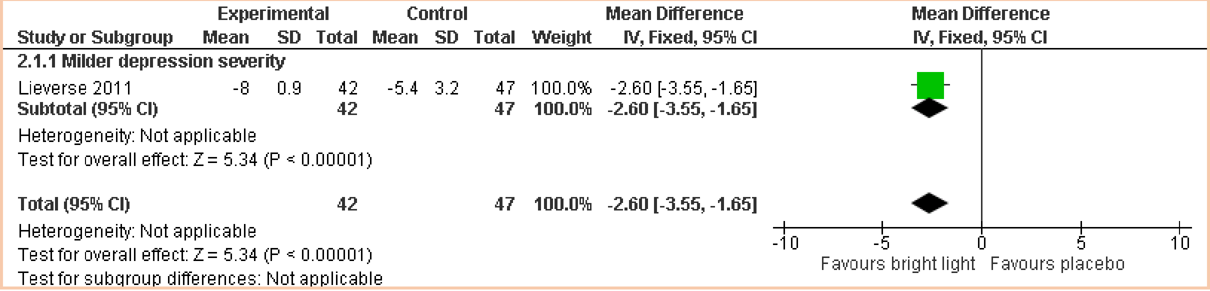


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Milder symptom severity								
Lam 2016	-16.9	9.2	29	-8.8	9.9	31	100.0%	-8.10 [-12.93, -3.27]
Subtotal (95% CI)			**29**			**31**	**100.0%**	**-8.10 [-12.93, -3.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.28 (P = 0.001)								
Total (95% CI)			**29**			**31**	**100.0%**	**-8.10 [-12.93, -3.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.28 (P = 0.001)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-100
-50
0
50
100
Favours bright light+fluo
Favours sham light + fluo

Bright light therapy versus placebo

Depression symptomatology

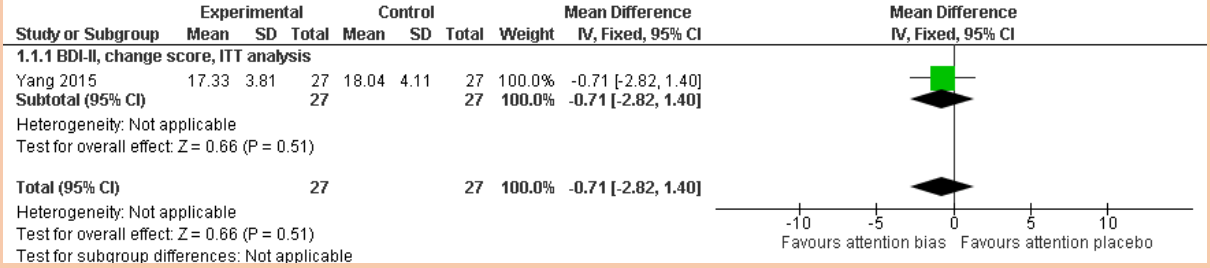


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Milder depression severity								
Lieverse 2011	-8	0.9	42	-5.4	3.2	47	100.0%	-2.60 [-3.55, -1.65]
Subtotal (95% CI)			**42**			**47**	**100.0%**	**-2.60 [-3.55, -1.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.34 (P < 0.00001)								
Total (95% CI)			**42**			**47**	**100.0%**	**-2.60 [-3.55, -1.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.34 (P < 0.00001)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-10
-5
0
5
10
Favours bright light
Favours placebo

Attention modification bias

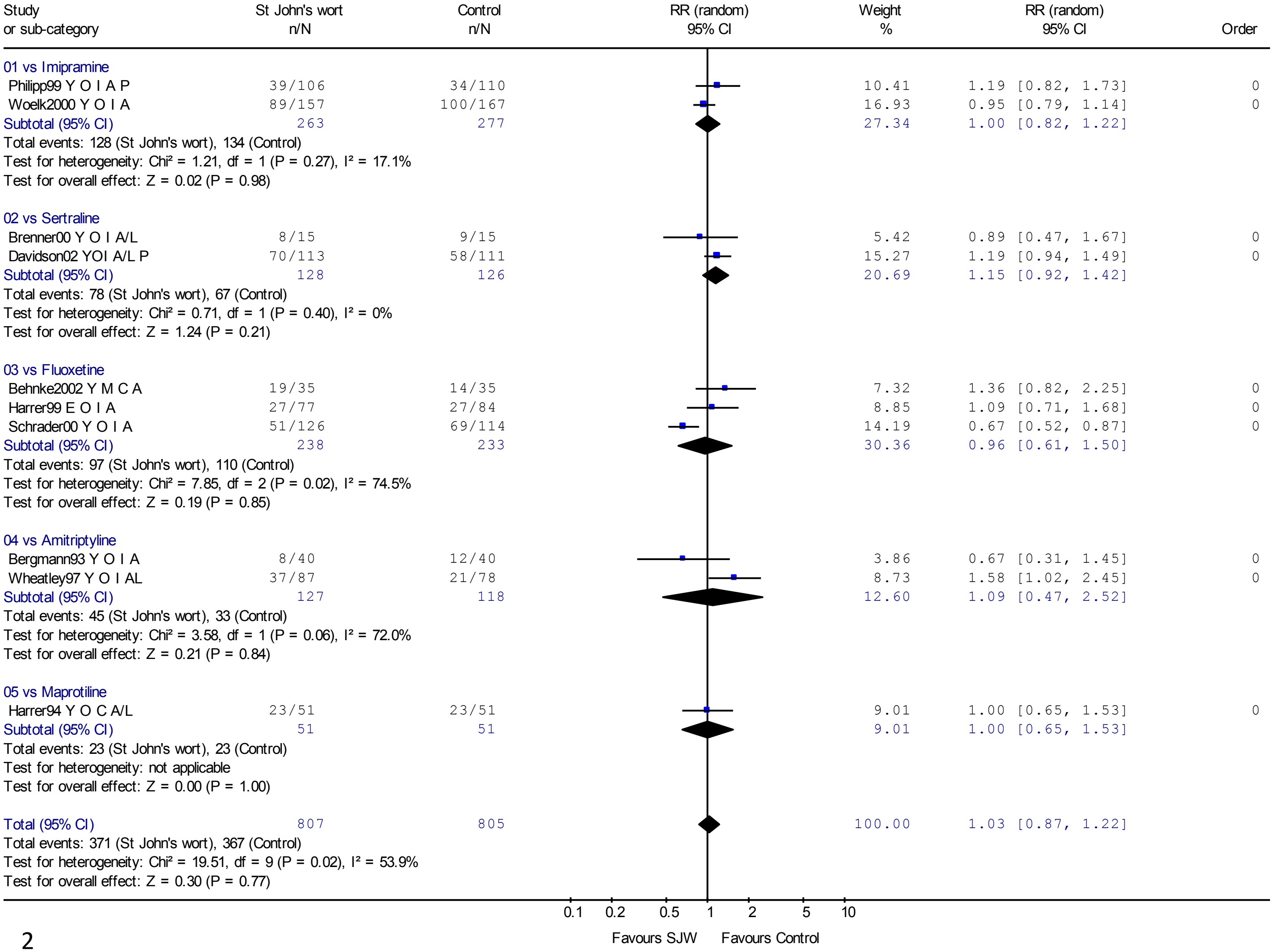
Depression symptomatology



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 BDI-II, change score, ITT analysis								
Yang 2015	17.33	3.81	27	18.04	4.11	27	100.0%	-0.71 [-2.82, 1.40]
Subtotal (95% CI)			**27**			**27**	**100.0%**	**-0.71 [-2.82, 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Total (95% CI)			**27**			**27**	**100.0%**	**-0.71 [-2.82, 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Test for subgroup differences: Not applicable								

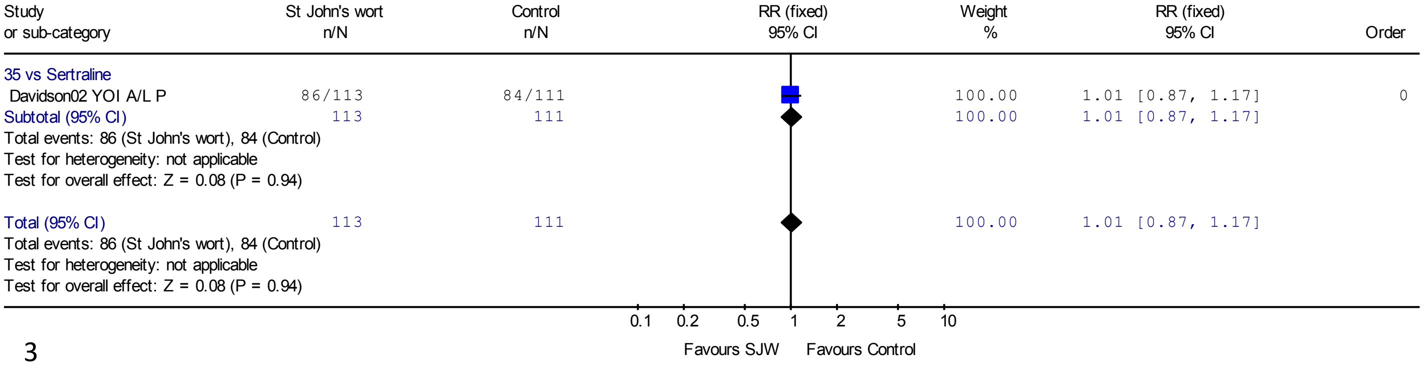
Mean Difference
IV, Fixed, 95% CI
-10
-5
0
5
10
Favours attention bias
Favours attention placebo

St John's wort



Review: Pharmacology: St John's wort
Comparison: 01 Efficacy against ADs
Outcome: 01 Number of people not achieving at least 50% reduction in depression score

Study or sub-category	St John's wort n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
01 vs Imipramine						
Philipp99 Y O I A P	39/106	34/110		10.41	1.19 [0.82, 1.73]	0
Woelk2000 Y O I A	89/157	100/167		16.93	0.95 [0.79, 1.14]	0
Subtotal (95% CI)	263	277		27.34	1.00 [0.82, 1.22]	
Total events: 128 (St John's wort), 134 (Control)						
Test for heterogeneity: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.1%						
Test for overall effect: Z = 0.02 (P = 0.98)						
02 vs Sertraline						
Brenner00 Y O I A/L	8/15	9/15		5.42	0.89 [0.47, 1.67]	0
Davidson02 YOI A/L P	70/113	58/111		15.27	1.19 [0.94, 1.49]	0
Subtotal (95% CI)	128	126		20.69	1.15 [0.92, 1.42]	
Total events: 78 (St John's wort), 67 (Control)						
Test for heterogeneity: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
03 vs Fluoxetine						
Behnke2002 Y M C A	19/35	14/35		7.32	1.36 [0.82, 2.25]	0
Harrer99 E O I A	27/77	27/84		8.85	1.09 [0.71, 1.68]	0
Schrader00 Y O I A	51/126	69/114		14.19	0.67 [0.52, 0.87]	0
Subtotal (95% CI)	238	233		30.36	0.96 [0.61, 1.50]	
Total events: 97 (St John's wort), 110 (Control)						
Test for heterogeneity: Chi² = 7.85, df = 2 (P = 0.02), I² = 74.5%						
Test for overall effect: Z = 0.19 (P = 0.85)						
04 vs Amitriptyline						
Bergmann93 Y O I A	8/40	12/40		3.86	0.67 [0.31, 1.45]	0
Wheatley97 Y O I AL	37/87	21/78		8.73	1.58 [1.02, 2.45]	0
Subtotal (95% CI)	127	118		12.60	1.09 [0.47, 2.52]	
Total events: 45 (St John's wort), 33 (Control)						
Test for heterogeneity: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.0%						
Test for overall effect: Z = 0.21 (P = 0.84)						
05 vs Maprotiline						
Harrer94 Y O C A/L	23/51	23/51		9.01	1.00 [0.65, 1.53]	0
Subtotal (95% CI)	51	51		9.01	1.00 [0.65, 1.53]	
Total events: 23 (St John's wort), 23 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)	807	805		100.00	1.03 [0.87, 1.22]	
Total events: 371 (St John's wort), 367 (Control)						
Test for heterogeneity: Chi² = 19.51, df = 9 (P = 0.02), I² = 53.9%						
Test for overall effect: Z = 0.30 (P = 0.77)						

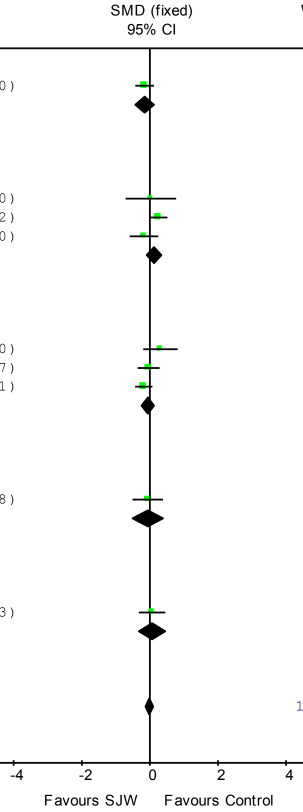


Review: Pharmacology: St John's wort
Comparison: 01 Efficacy against ADs
Outcome: 02 Number of people not achieving remission

Study or sub-category	St John's wort n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
35 vs Sertraline						
Davidson02 YOI A/L P	86/113	84/111		100.00	1.01 [0.87, 1.17]	0
Subtotal (95% CI)	113	111		100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)	113	111		100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						

Review: Pharmacology: St John's wort
Comparison: 01 Efficacy against ADs
Outcome: 03 Mean endpoint scores

Study or sub-category	St John's wort N	St John's wort Mean (SD)	Control N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 vs Imipramine							
Philipp99 Y O I A P	100	-15.40(8.10)	105	-14.20(7.30)	17.58	-0.16 [-0.43, 0.12]	0
Subtotal (95% CI)	100		105		17.58	-0.16 [-0.43, 0.12]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
02 vs Sertraline							
Brenner00 Y O I A/L	13	12.70(6.70)	15	12.50(5.60)	2.40	0.03 [-0.71, 0.77]	0
Davidson02 YOI A/L P	113	-8.68(7.23)	109	-10.53(7.52)	18.95	0.25 [-0.01, 0.51]	0
vanGurp02 Y O I AL	44	-9.50(7.10)	43	-8.20(7.50)	7.46	-0.18 [-0.60, 0.24]	0
Subtotal (95% CI)	170		167		28.81	0.12 [-0.09, 0.34]	
Test for heterogeneity: Chi² = 2.89, df = 2 (P = 0.24), I² = 30.8%							
Test for overall effect: Z = 1.11 (P = 0.27)							
03 vs Fluoxetine							
Behnke2002 Y M C A	29	-10.00(5.80)	32	-12.00(6.80)	5.17	0.31 [-0.19, 0.82]	0
Harrer99 E O I A	70	7.91(5.04)	79	8.11(5.67)	12.78	-0.04 [-0.36, 0.28]	0
Schrader00 Y O I A	125	-8.11(4.85)	113	-7.25(4.61)	20.35	-0.18 [-0.44, 0.07]	0
Subtotal (95% CI)	224		224		38.30	-0.07 [-0.25, 0.12]	
Test for heterogeneity: Chi² = 2.95, df = 2 (P = 0.23), I² = 32.2%							
Test for overall effect: Z = 0.70 (P = 0.48)							
04 vs Amitriptyline							
Bergmann93 Y O I A	38	6.34(4.19)	38	6.65(5.98)	6.54	-0.06 [-0.51, 0.39]	0
Subtotal (95% CI)	38		38		6.54	-0.06 [-0.51, 0.39]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.80)							
05 vs Maprotiline							
Harrer94 Y O C A/L	51	12.78(10.19)	51	12.20(7.83)	8.78	0.06 [-0.32, 0.45]	0
Subtotal (95% CI)	51		51		8.78	0.06 [-0.32, 0.45]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							
Total (95% CI)	583		585		100.00	-0.02 [-0.13, 0.10]	
Test for heterogeneity: Chi² = 8.89, df = 8 (P = 0.35), I² = 10.0%							
Test for overall effect: Z = 0.27 (P = 0.78)							



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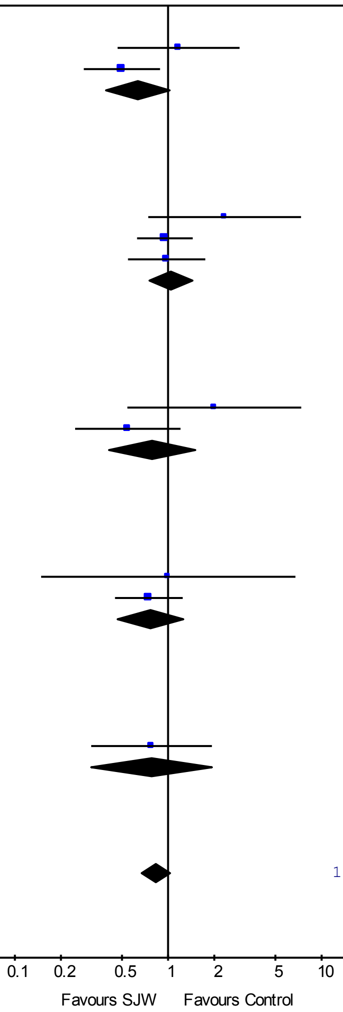
Review: Pharmacology: St John's wort
Comparison: 02 Tolerability against ADs
Outcome: 01 Leaving the study early

Study or sub-category	St John's wort n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine						
Philipp99 Y O I A P	9/106	8/110		5.46	1.17 [0.47, 2.91]	0
Woelk2000 Y O I A	15/157	32/167		21.55	0.50 [0.28, 0.88]	0
Subtotal (95% CI)	263	277		27.00	0.63 [0.39, 1.02]	
Total events: 24 (St John's wort), 40 (Control)						
Test for heterogeneity: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.1%						
Test for overall effect: Z = 1.87 (P = 0.06)						
02 vs Sertraline						
Brenner00 Y O I A/L	7/15	3/15		2.08	2.33 [0.74, 7.35]	0
Davidson02 YOI A/L P	31/113	32/111		22.43	0.95 [0.63, 1.45]	0
vanGurp02 Y O I AL	15/44	15/43		10.54	0.98 [0.55, 1.74]	0
Subtotal (95% CI)	172	169		35.06	1.04 [0.75, 1.44]	
Total events: 53 (St John's wort), 50 (Control)						
Test for heterogeneity: Chi² = 2.12, df = 2 (P = 0.35), I² = 5.8%						
Test for overall effect: Z = 0.25 (P = 0.81)						
03 vs Fluoxetine						
Behnke2002 Y M C A	6/35	3/35		2.08	2.00 [0.54, 7.37]	0
Harrer99 E O I A	8/77	16/84		10.63	0.55 [0.25, 1.20]	0
Subtotal (95% CI)	112	119		12.72	0.78 [0.41, 1.50]	
Total events: 14 (St John's wort), 19 (Control)						
Test for heterogeneity: Chi² = 2.79, df = 1 (P = 0.09), I² = 64.2%						
Test for overall effect: Z = 0.74 (P = 0.46)						
04 vs Amitriptyline						
Bergmann93 Y O I A	2/40	2/40		1.39	1.00 [0.15, 6.76]	0
Wheatley97 Y O I AL	20/87	24/78		17.58	0.75 [0.45, 1.24]	0
Subtotal (95% CI)	127	118		18.97	0.77 [0.47, 1.25]	
Total events: 22 (St John's wort), 26 (Control)						
Test for heterogeneity: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
05 vs Maprotiline						
Harrer94 Y O C A/L	7/51	9/51		6.25	0.78 [0.31, 1.93]	0
Subtotal (95% CI)	51	51		6.25	0.78 [0.31, 1.93]	
Total events: 7 (St John's wort), 9 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)	725	734		100.00	0.83 [0.67, 1.03]	
Total events: 120 (St John's wort), 144 (Control)						
Test for heterogeneity: Chi² = 10.45, df = 9 (P = 0.32), I² = 13.9%						
Test for overall effect: Z = 1.70 (P = 0.09)						



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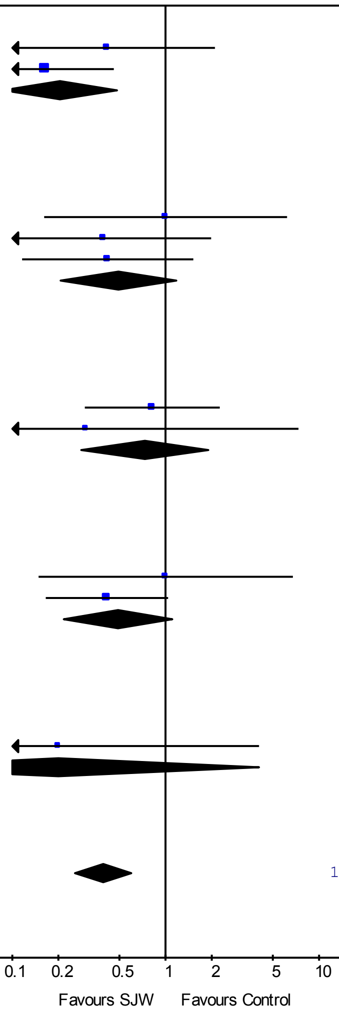
Review: Pharmacology: St John's wort
Comparison: 02 Tolerability against ADs
Outcome: 02 Leaving the study early due to side effects



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	2/106	5/110	6.85	0.42 [0.08, 2.09]	0
Woelk2000 Y O I A	4/157	26/167	35.16	0.16 [0.06, 0.46]	0
Subtotal (95% CI)	263	277	42.01	0.20 [0.09, 0.48]	
Total events: 6 (St John's wort), 31 (Control)					
Test for heterogeneity: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%					
Test for overall effect: Z = 3.63 (P = 0.0003)					
02 vs Sertraline					
Brenner00 Y O I A/L	2/15	2/15	2.79	1.00 [0.16, 6.20]	0
Davidson02 YOI A/L P	2/113	5/111	7.04	0.39 [0.08, 1.98]	0
vanGurp02 Y O I AL	3/44	7/43	9.88	0.42 [0.12, 1.51]	0
Subtotal (95% CI)	172	169	19.71	0.49 [0.21, 1.17]	
Total events: 7 (St John's wort), 14 (Control)					
Test for heterogeneity: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%					
Test for overall effect: Z = 1.60 (P = 0.11)					
03 vs Fluoxetine					
Harrer99 E O I A	6/77	8/84	10.68	0.82 [0.30, 2.25]	0
Schrader00 Y O I A	0/126	1/114	2.20	0.30 [0.01, 7.34]	0
Subtotal (95% CI)	203	198	12.87	0.73 [0.28, 1.90]	
Total events: 6 (St John's wort), 9 (Control)					
Test for heterogeneity: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%					
Test for overall effect: Z = 0.65 (P = 0.52)					
04 vs Amitriptyline					
Bergmann93 Y O I A	2/40	2/40	2.79	1.00 [0.15, 6.76]	0
Wheatley97 Y O I AL	6/87	13/78	19.13	0.41 [0.17, 1.04]	0
Subtotal (95% CI)	127	118	21.92	0.49 [0.22, 1.10]	
Total events: 8 (St John's wort), 15 (Control)					
Test for heterogeneity: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%					
Test for overall effect: Z = 1.72 (P = 0.08)					
05 vs Maprotiline					
Harrer94 Y O C A/L	0/51	2/51	3.49	0.20 [0.01, 4.07]	0
Subtotal (95% CI)	51	51	3.49	0.20 [0.01, 4.07]	
Total events: 0 (St John's wort), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
Total (95% CI)	816	813	100.00	0.39 [0.26, 0.60]	
Total events: 27 (St John's wort), 71 (Control)					
Test for heterogeneity: Chi² = 6.98, df = 9 (P = 0.64), I² = 0%					
Test for overall effect: Z = 4.35 (P < 0.0001)					

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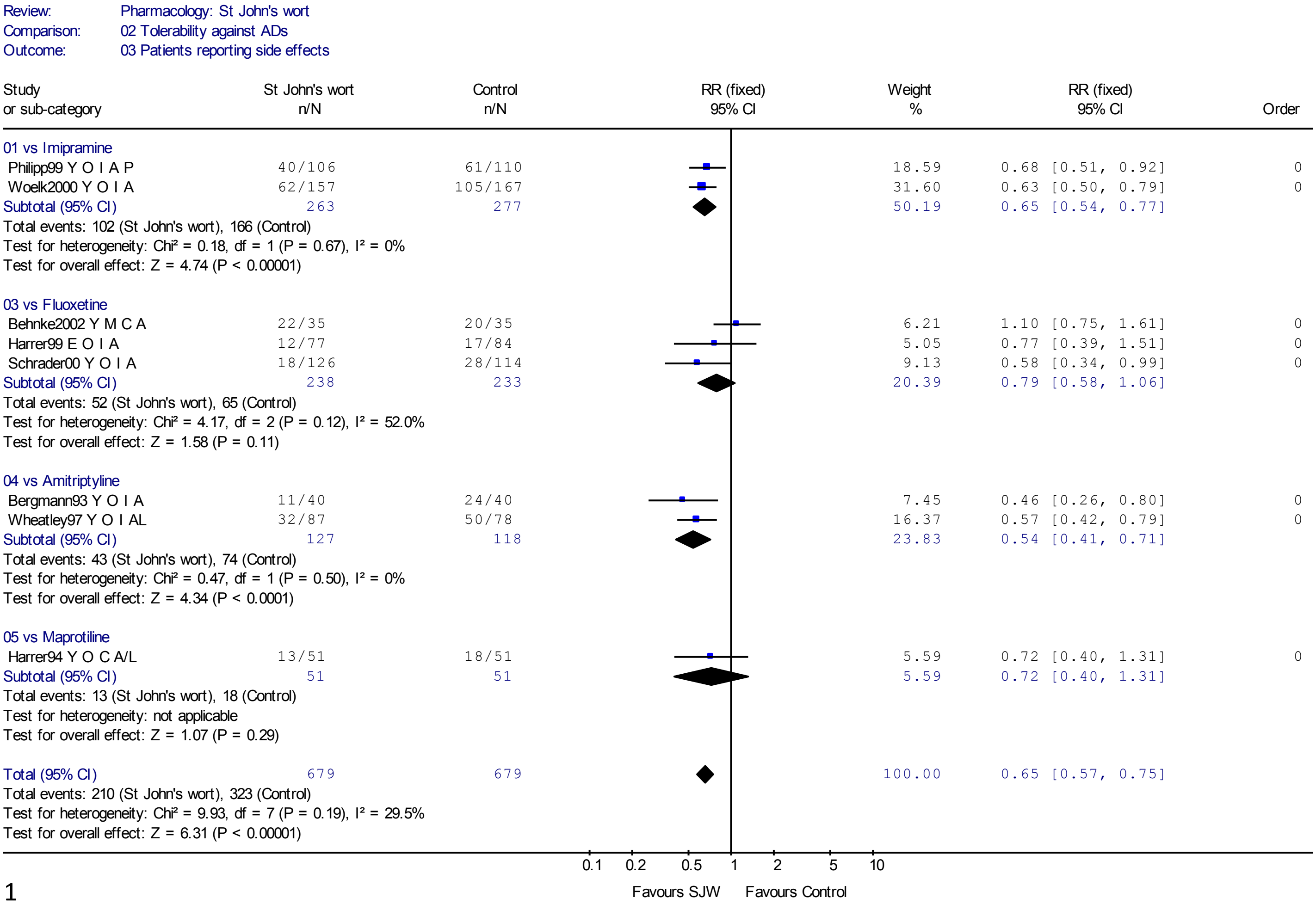

Review: Pharmacology: St John's wort
Comparison: 02 Tolerability against ADs
Outcome: 03 Patients reporting side effects

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	40/106	61/110	18.59	0.68 [0.51, 0.92]	0
Woelk2000 Y O I A	62/157	105/167	31.60	0.63 [0.50, 0.79]	0
Subtotal (95% CI)	263	277	50.19	0.65 [0.54, 0.77]	
03 vs Fluoxetine					
Behnke2002 Y M C A	22/35	20/35	6.21	1.10 [0.75, 1.61]	0
Harrer99 E O I A	12/77	17/84	5.05	0.77 [0.39, 1.51]	0
Schrader00 Y O I A	18/126	28/114	9.13	0.58 [0.34, 0.99]	0
Subtotal (95% CI)	238	233	20.39	0.79 [0.58, 1.06]	
04 vs Amitriptyline					
Bergmann93 Y O I A	11/40	24/40	7.45	0.46 [0.26, 0.80]	0
Wheatley97 Y O I AL	32/87	50/78	16.37	0.57 [0.42, 0.79]	0
Subtotal (95% CI)	127	118	23.83	0.54 [0.41, 0.71]	
05 vs Maprotiline					
Harrer94 Y O C A/L	13/51	18/51	5.59	0.72 [0.40, 1.31]	0
Subtotal (95% CI)	51	51	5.59	0.72 [0.40, 1.31]	
Total (95% CI)	679	679	100.00	0.65 [0.57, 0.75]	

01 vs Imipramine: Total events: 102 (St John's wort), 166 (Control)
Test for heterogeneity: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%
Test for overall effect: Z = 4.74 (P < 0.00001)

03 vs Fluoxetine: Total events: 52 (St John's wort), 65 (Control)
Test for heterogeneity: Chi² = 4.17, df = 2 (P = 0.12), I² = 52.0%
Test for overall effect: Z = 1.58 (P = 0.11)

04 vs Amitriptyline: Total events: 43 (St John's wort), 74 (Control)
Test for heterogeneity: Chi² = 0.47, df = 1 (P = 0.50), I² = 0%
Test for overall effect: Z = 4.34 (P < 0.0001)

05 vs Maprotiline: Total events: 13 (St John's wort), 18 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.07 (P = 0.29)

Total (95% CI): Total events: 210 (St John's wort), 323 (Control)
Test for heterogeneity: Chi² = 9.93, df = 7 (P = 0.19), I² = 29.5%
Test for overall effect: Z = 6.31 (P < 0.00001)

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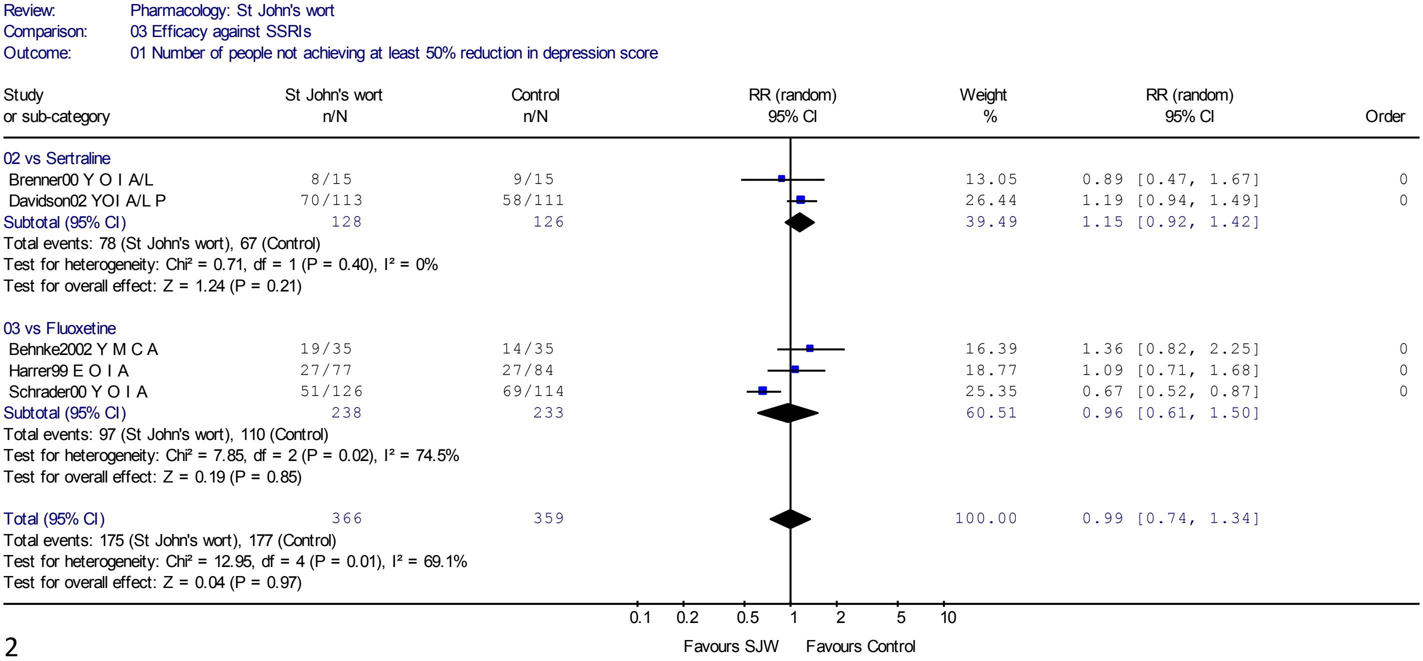


Review: Pharmacology: St John's wort
Comparison: 03 Efficacy against SSRIs
Outcome: 01 Number of people not achieving at least 50% reduction in depression score

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (random) 95% CI	Order
02 vs Sertraline					
Brenner00 Y O I A/L	8/15	9/15	13.05	0.89 [0.47, 1.67]	0
Davidson02 YOI A/L P	70/113	58/111	26.44	1.19 [0.94, 1.49]	0
Subtotal (95% CI)	128	126	39.49	1.15 [0.92, 1.42]	
03 vs Fluoxetine					
Behnke2002 Y M C A	19/35	14/35	16.39	1.36 [0.82, 2.25]	0
Harrer99 E O I A	27/77	27/84	18.77	1.09 [0.71, 1.68]	0
Schrader00 Y O I A	51/126	69/114	25.35	0.67 [0.52, 0.87]	0
Subtotal (95% CI)	238	233	60.51	0.96 [0.61, 1.50]	
Total (95% CI)	366	359	100.00	0.99 [0.74, 1.34]	

02 vs Sertraline: Total events: 78 (St John's wort), 67 (Control)
Test for heterogeneity: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)

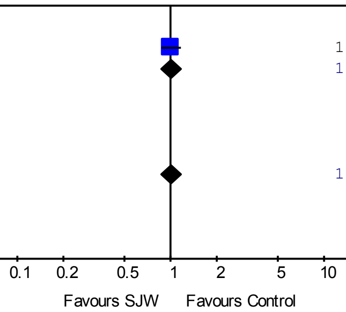
03 vs Fluoxetine: Total events: 97 (St John's wort), 110 (Control)
Test for heterogeneity: Chi² = 7.85, df = 2 (P = 0.02), I² = 74.5%
Test for overall effect: Z = 0.19 (P = 0.85)

Total (95% CI): Total events: 175 (St John's wort), 177 (Control)
Test for heterogeneity: Chi² = 12.95, df = 4 (P = 0.01), I² = 69.1%
Test for overall effect: Z = 0.04 (P = 0.97)

2

Review: Pharmacology: St John's wort
Comparison: 03 Efficacy against SSRIs
Outcome: 02 Number of people not achieving remission

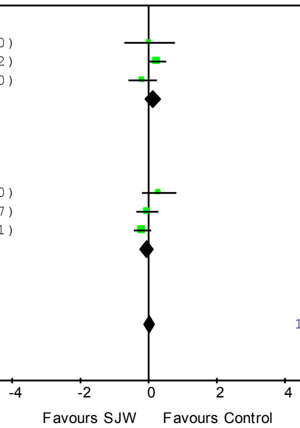
Study or sub-category	St John's wort n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline						
Davidson02 YOI A/L P	86/113	84/111		100.00	1.01 [0.87, 1.17]	0
Subtotal (95% CI)	113	111		100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)	113	111		100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						



1

Review: Pharmacology: St John's wort
Comparison: 03 Efficacy against SSRIs
Outcome: 03 Mean endpoint scores

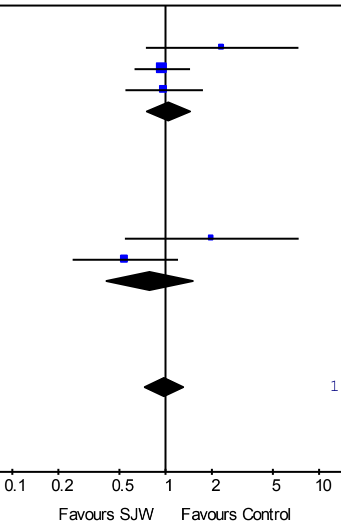
Study	St John's wort		Control		SMD (fixed)	Weight	SMD (fixed)	
or sub-category	N	Mean (SD)	N	Mean (SD)	95% CI	%	95% CI	Order
02 vs Sertraline								
Brenner00 Y O I A/L	13	12.70(6.70)	15	12.50(5.60)		3.57	0.03 [-0.71, 0.77]	0
Davidson02 YOI A/L P	113	-8.68(7.23)	109	-10.53(7.52)		28.24	0.25 [-0.01, 0.51]	0
vanGurp02 Y O I AL	44	-9.50(7.10)	43	-8.20(7.50)		11.11	-0.18 [-0.60, 0.24]	0
Subtotal (95% CI)	170		167			42.93	0.12 [-0.09, 0.34]	
Test for heterogeneity: Chi² = 2.89, df = 2 (P = 0.24), I² = 30.8%								
Test for overall effect: Z = 1.11 (P = 0.27)								
03 vs Fluoxetine								
Behnke2002 Y M C A	29	-10.00(5.80)	32	-12.00(6.80)		7.71	0.31 [-0.19, 0.82]	0
Harrer99 E O I A	70	7.91(5.04)	79	8.11(5.67)		19.04	-0.04 [-0.36, 0.28]	0
Schrader00 Y O I A	125	-8.11(4.85)	113	-7.25(4.61)		30.33	-0.18 [-0.44, 0.07]	0
Subtotal (95% CI)	224		224			57.07	-0.07 [-0.25, 0.12]	
Test for heterogeneity: Chi² = 2.95, df = 2 (P = 0.23), I² = 32.2%								
Test for overall effect: Z = 0.70 (P = 0.48)								
Total (95% CI)	394		391			100.00	0.01 [-0.13, 0.15]	
Test for heterogeneity: Chi² = 7.52, df = 5 (P = 0.18), I² = 33.5%								
Test for overall effect: Z = 0.20 (P = 0.84)								



2

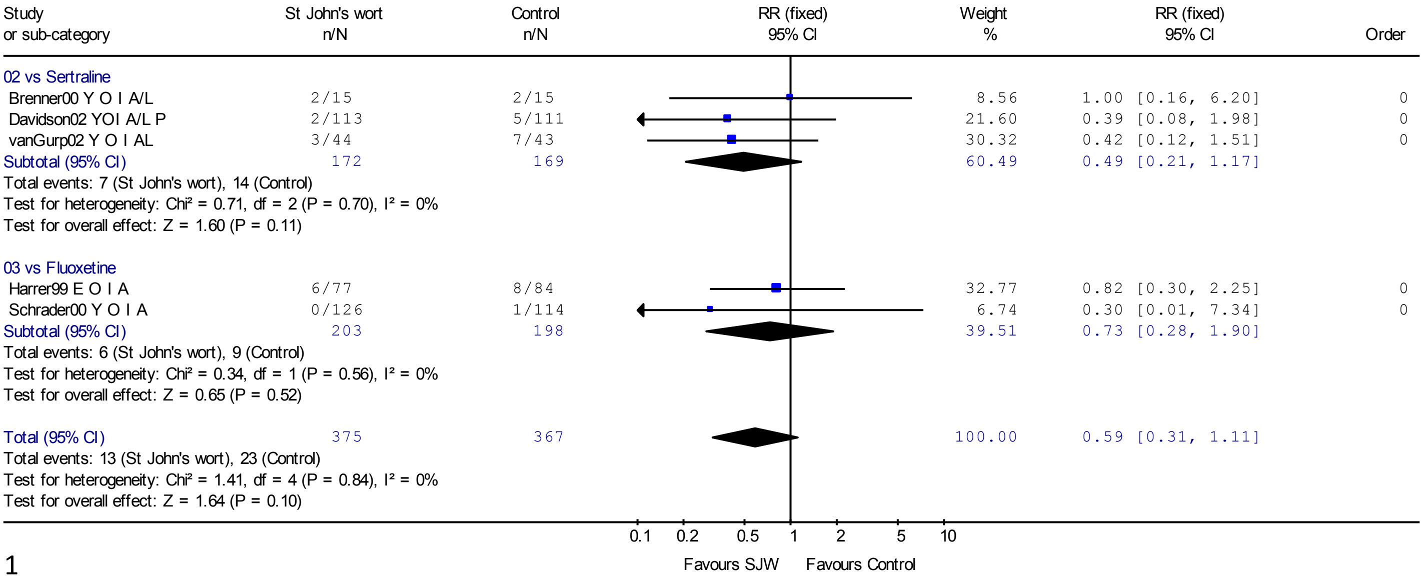
Review: Pharmacology: St John's wort
Comparison: 04 Tolerability against SSRIs
Outcome: 01 Leaving the study early

Study or sub-category	St John's wort n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline						
Brenner00 Y O I A/L	7/15	3/15		4.36	2.33 [0.74, 7.35]	0
Davidson02 YOI A/L P	31/113	32/111		46.95	0.95 [0.63, 1.45]	0
vanGurp02 Y O I AL	15/44	15/43		22.06	0.98 [0.55, 1.74]	0
Subtotal (95% CI)	172	169		73.38	1.04 [0.75, 1.44]	
Total events: 53 (St John's wort), 50 (Control)						
Test for heterogeneity: Chi² = 2.12, df = 2 (P = 0.35), I² = 5.8%						
Test for overall effect: Z = 0.25 (P = 0.81)						
03 vs Fluoxetine						
Behnke2002 Y M C A	6/35	3/35		4.36	2.00 [0.54, 7.37]	0
Harrer99 E O I A	8/77	16/84		22.26	0.55 [0.25, 1.20]	0
Subtotal (95% CI)	112	119		26.62	0.78 [0.41, 1.50]	
Total events: 14 (St John's wort), 19 (Control)						
Test for heterogeneity: Chi² = 2.79, df = 1 (P = 0.09), I² = 64.2%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)	284	288		100.00	0.97 [0.73, 1.30]	
Total events: 67 (St John's wort), 69 (Control)						
Test for heterogeneity: Chi² = 5.47, df = 4 (P = 0.24), I² = 26.9%						
Test for overall effect: Z = 0.19 (P = 0.85)						



3

Review: Pharmacology: St John's wort
Comparison: 04 Tolerability against SSRIs
Outcome: 02 Leaving the study early due to side effects



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Brenner00 Y O I A/L	2/15	2/15	8.56	1.00 [0.16, 6.20]	0
Davidson02 YOI A/L P	2/113	5/111	21.60	0.39 [0.08, 1.98]	0
vanGurp02 Y O I AL	3/44	7/43	30.32	0.42 [0.12, 1.51]	0
Subtotal (95% CI)	172	169	60.49	0.49 [0.21, 1.17]	

Total events: 7 (St John's wort), 14 (Control)
Test for heterogeneity: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
03 vs Fluoxetine					
Harrer99 E O I A	6/77	8/84	32.77	0.82 [0.30, 2.25]	0
Schrader00 Y O I A	0/126	1/114	6.74	0.30 [0.01, 7.34]	0
Subtotal (95% CI)	203	198	39.51	0.73 [0.28, 1.90]	

Total events: 6 (St John's wort), 9 (Control)
Test for heterogeneity: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
Total (95% CI)	375	367	100.00	0.59 [0.31, 1.11]	

Total events: 13 (St John's wort), 23 (Control)
Test for heterogeneity: Chi² = 1.41, df = 4 (P = 0.84), I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)

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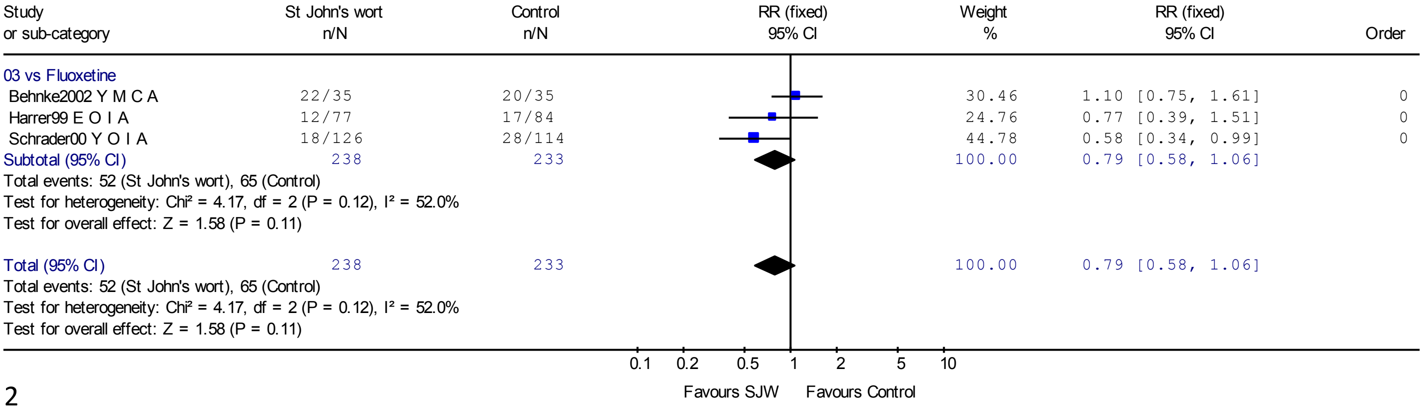
Review: Pharmacology: St John's wort
Comparison: 04 Tolerability against SSRIs
Outcome: 03 Patients reporting side effects



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
03 vs Fluoxetine					
Behnke2002 Y M C A	22/35	20/35	30.46	1.10 [0.75, 1.61]	0
Harrer99 E O I A	12/77	17/84	24.76	0.77 [0.39, 1.51]	0
Schrader00 Y O I A	18/126	28/114	44.78	0.58 [0.34, 0.99]	0
Subtotal (95% CI)	238	233	100.00	0.79 [0.58, 1.06]	

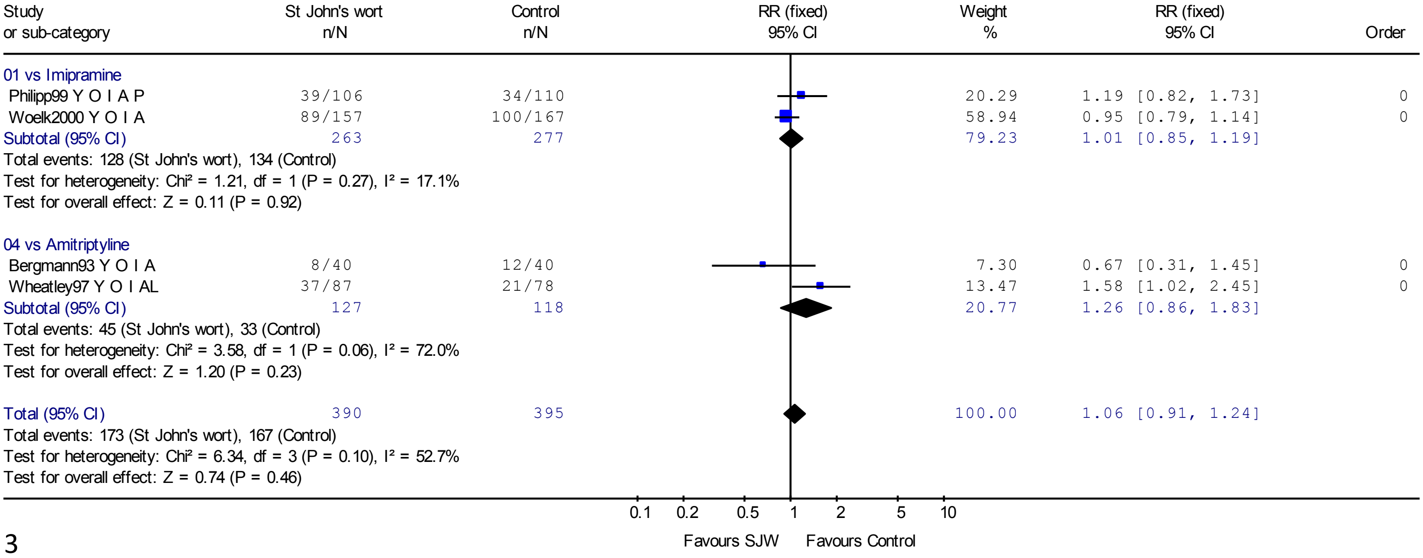
Total events: 52 (St John's wort), 65 (Control)
Test for heterogeneity: Chi² = 4.17, df = 2 (P = 0.12), I² = 52.0%
Test for overall effect: Z = 1.58 (P = 0.11)

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
Total (95% CI)	238	233	100.00	0.79 [0.58, 1.06]	

Total events: 52 (St John's wort), 65 (Control)
Test for heterogeneity: Chi² = 4.17, df = 2 (P = 0.12), I² = 52.0%
Test for overall effect: Z = 1.58 (P = 0.11)

2

Review: Pharmacology: St John's wort
Comparison: 05 Efficacy against TCAs
Outcome: 01 Number of people not achieving at least 50% reduction in depression score



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	39/106	34/110	20.29	1.19 [0.82, 1.73]	0
Woelk2000 Y O I A	89/157	100/167	58.94	0.95 [0.79, 1.14]	0
Subtotal (95% CI)	263	277	79.23	1.01 [0.85, 1.19]	

Total events: 128 (St John's wort), 134 (Control)
Test for heterogeneity: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.1%
Test for overall effect: Z = 0.11 (P = 0.92)

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
04 vs Amitriptyline					
Bergmann93 Y O I A	8/40	12/40	7.30	0.67 [0.31, 1.45]	0
Wheatley97 Y O I AL	37/87	21/78	13.47	1.58 [1.02, 2.45]	0
Subtotal (95% CI)	127	118	20.77	1.26 [0.86, 1.83]	

Total events: 45 (St John's wort), 33 (Control)
Test for heterogeneity: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.0%
Test for overall effect: Z = 1.20 (P = 0.23)

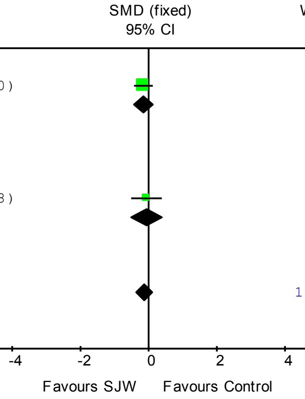
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
Total (95% CI)	390	395	100.00	1.06 [0.91, 1.24]	

Total events: 173 (St John's wort), 167 (Control)
Test for heterogeneity: Chi² = 6.34, df = 3 (P = 0.10), I² = 52.7%
Test for overall effect: Z = 0.74 (P = 0.46)

3

Review: Pharmacology: St John's wort
Comparison: 05 Efficacy against TCAs
Outcome: 03 Mean endpoint scores

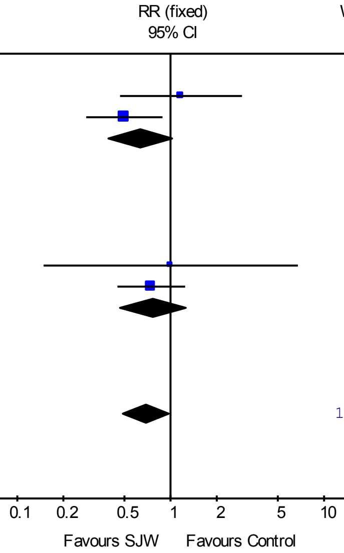
Study or sub-category	St John's wort N	St John's wort Mean (SD)	Control N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 vs Imipramine							
Philipp99 Y O I A P	100	-15.40(8.10)	105	-14.20(7.30)	72.89	-0.16 [-0.43, 0.12]	0
Subtotal (95% CI)	100		105		72.89	-0.16 [-0.43, 0.12]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
04 vs Amitriptyline							
Bergmann93 Y O I A	38	6.34(4.19)	38	6.65(5.98)	27.11	-0.06 [-0.51, 0.39]	0
Subtotal (95% CI)	38		38		27.11	-0.06 [-0.51, 0.39]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.80)							
Total (95% CI)	138		143		100.00	-0.13 [-0.36, 0.10]	
Test for heterogeneity: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%							
Test for overall effect: Z = 1.08 (P = 0.28)							



1

Review: Pharmacology: St John's wort
Comparison: 06 Tolerability against TCAs
Outcome: 01 Leaving the study early

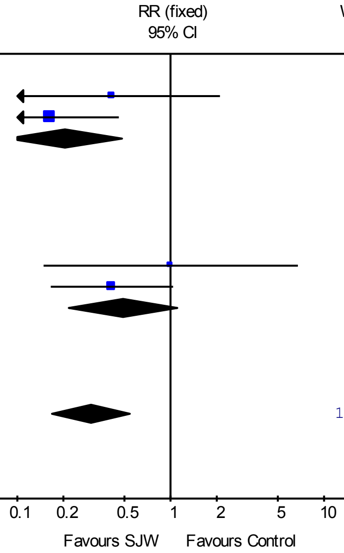
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	9/106	8/110	11.87	1.17 [0.47, 2.91]	0
Woelk2000 Y O I A	15/157	32/167	46.87	0.50 [0.28, 0.88]	0
Subtotal (95% CI)	263	277	58.73	0.63 [0.39, 1.02]	
Total events: 24 (St John's wort), 40 (Control)					
Test for heterogeneity: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.1%					
Test for overall effect: Z = 1.87 (P = 0.06)					
04 vs Amitriptyline					
Bergmann93 Y O I A	2/40	2/40	3.02	1.00 [0.15, 6.76]	0
Wheatley97 Y O I AL	20/87	24/78	38.25	0.75 [0.45, 1.24]	0
Subtotal (95% CI)	127	118	41.27	0.77 [0.47, 1.25]	
Total events: 22 (St John's wort), 26 (Control)					
Test for heterogeneity: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	390	395	100.00	0.69 [0.49, 0.97]	
Total events: 46 (St John's wort), 66 (Control)					
Test for heterogeneity: Chi² = 2.74, df = 3 (P = 0.43), I² = 0%					
Test for overall effect: Z = 2.13 (P = 0.03)					



2

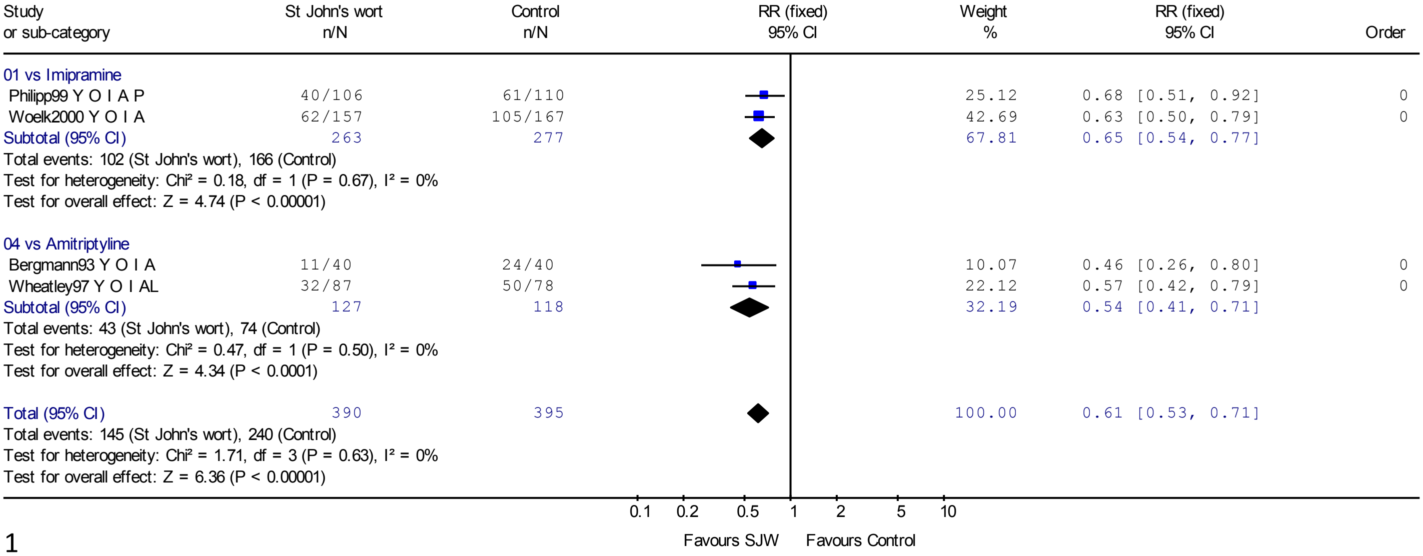
Review: Pharmacology: St John's wort
Comparison: 06 Tolerability against TCAs
Outcome: 02 Leaving the study early due to side effects

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	2/106	5/110	10.71	0.42 [0.08, 2.09]	0
Woelk2000 Y O I A	4/157	26/167	55.00	0.16 [0.06, 0.46]	0
Subtotal (95% CI)	263	277	65.71	0.20 [0.09, 0.48]	
Total events: 6 (St John's wort), 31 (Control)					
Test for heterogeneity: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%					
Test for overall effect: Z = 3.63 (P = 0.0003)					
04 vs Amitriptyline					
Bergmann93 Y O I A	2/40	2/40	4.37	1.00 [0.15, 6.76]	0
Wheatley97 Y O I AL	6/87	13/78	29.92	0.41 [0.17, 1.04]	0
Subtotal (95% CI)	127	118	34.29	0.49 [0.22, 1.10]	
Total events: 8 (St John's wort), 15 (Control)					
Test for heterogeneity: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%					
Test for overall effect: Z = 1.72 (P = 0.08)					
Total (95% CI)	390	395	100.00	0.30 [0.17, 0.54]	
Total events: 14 (St John's wort), 46 (Control)					
Test for heterogeneity: Chi² = 3.47, df = 3 (P = 0.32), I² = 13.5%					
Test for overall effect: Z = 4.02 (P < 0.0001)					



3

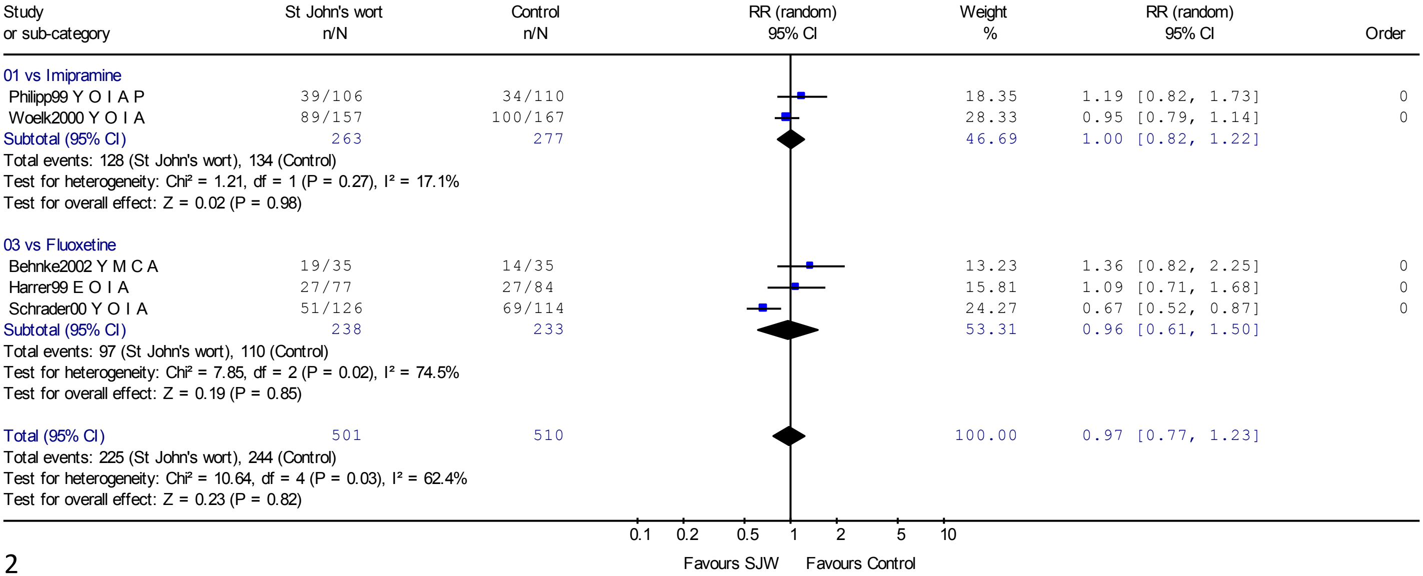
Review: Pharmacology: St John's wort
Comparison: 06 Tolerability against TCAs
Outcome: 03 Patients reporting side effects



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	40/106	61/110	25.12	0.68 [0.51, 0.92]	0
Woelk2000 Y O I A	62/157	105/167	42.69	0.63 [0.50, 0.79]	0
Subtotal (95% CI)	263	277	67.81	0.65 [0.54, 0.77]	
Total events: 102 (St John's wort), 166 (Control)					
Test for heterogeneity: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%					
Test for overall effect: Z = 4.74 (P < 0.00001)					
04 vs Amitriptyline					
Bergmann93 Y O I A	11/40	24/40	10.07	0.46 [0.26, 0.80]	0
Wheatley97 Y O I AL	32/87	50/78	22.12	0.57 [0.42, 0.79]	0
Subtotal (95% CI)	127	118	32.19	0.54 [0.41, 0.71]	
Total events: 43 (St John's wort), 74 (Control)					
Test for heterogeneity: Chi² = 0.47, df = 1 (P = 0.50), I² = 0%					
Test for overall effect: Z = 4.34 (P < 0.0001)					
Total (95% CI)	390	395	100.00	0.61 [0.53, 0.71]	
Total events: 145 (St John's wort), 240 (Control)					
Test for heterogeneity: Chi² = 1.71, df = 3 (P = 0.63), I² = 0%					
Test for overall effect: Z = 6.36 (P < 0.00001)					

1

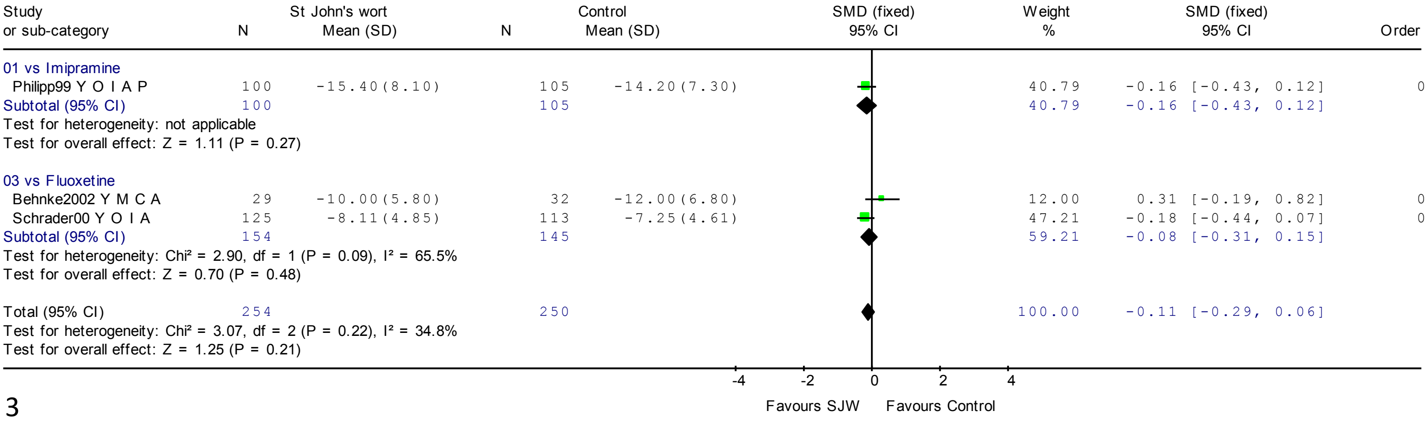
Review: Pharmacology: St John's wort
Comparison: 07 Efficacy against therapeutic doses of ADs
Outcome: 01 Number of people not achieving at least 50% reduction in depression score



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (random) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	39/106	34/110	18.35	1.19 [0.82, 1.73]	0
Woelk2000 Y O I A	89/157	100/167	28.33	0.95 [0.79, 1.14]	0
Subtotal (95% CI)	263	277	46.69	1.00 [0.82, 1.22]	
Total events: 128 (St John's wort), 134 (Control)					
Test for heterogeneity: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.1%					
Test for overall effect: Z = 0.02 (P = 0.98)					
03 vs Fluoxetine					
Behnke2002 Y M C A	19/35	14/35	13.23	1.36 [0.82, 2.25]	0
Harrer99 E O I A	27/77	27/84	15.81	1.09 [0.71, 1.68]	0
Schrader00 Y O I A	51/126	69/114	24.27	0.67 [0.52, 0.87]	0
Subtotal (95% CI)	238	233	53.31	0.96 [0.61, 1.50]	
Total events: 97 (St John's wort), 110 (Control)					
Test for heterogeneity: Chi² = 7.85, df = 2 (P = 0.02), I² = 74.5%					
Test for overall effect: Z = 0.19 (P = 0.85)					
Total (95% CI)	501	510	100.00	0.97 [0.77, 1.23]	
Total events: 225 (St John's wort), 244 (Control)					
Test for heterogeneity: Chi² = 10.64, df = 4 (P = 0.03), I² = 62.4%					
Test for overall effect: Z = 0.23 (P = 0.82)					

2

Review: Pharmacology: St John's wort
Comparison: 07 Efficacy against therapeutic doses of ADs
Outcome: 03 Mean endpoint scores

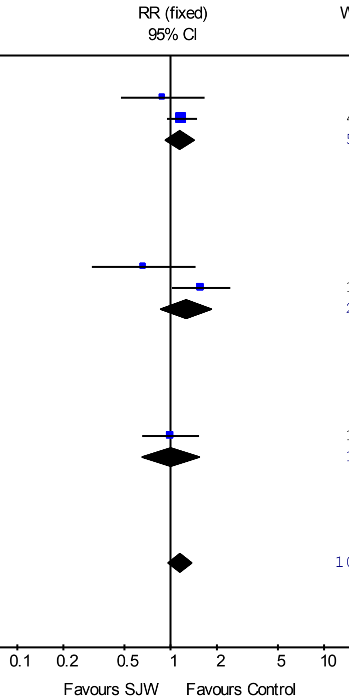


Study or sub-category	St John's wort N	St John's wort Mean (SD)	Control N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 vs Imipramine							
Philipp99 Y O I A P	100	-15.40(8.10)	105	-14.20(7.30)	40.79	-0.16 [-0.43, 0.12]	0
Subtotal (95% CI)	100		105		40.79	-0.16 [-0.43, 0.12]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
03 vs Fluoxetine							
Behnke2002 Y M C A	29	-10.00(5.80)	32	-12.00(6.80)	12.00	0.31 [-0.19, 0.82]	0
Schrader00 Y O I A	125	-8.11(4.85)	113	-7.25(4.61)	47.21	-0.18 [-0.44, 0.07]	0
Subtotal (95% CI)	154		145		59.21	-0.08 [-0.31, 0.15]	
Test for heterogeneity: Chi² = 2.90, df = 1 (P = 0.09), I² = 65.5%							
Test for overall effect: Z = 0.70 (P = 0.48)							
Total (95% CI)	254		250		100.00	-0.11 [-0.29, 0.06]	
Test for heterogeneity: Chi² = 3.07, df = 2 (P = 0.22), I² = 34.8%							
Test for overall effect: Z = 1.25 (P = 0.21)							

3

Review: Pharmacology: St John's wort
Comparison: 08 Efficacy against low doses of ADs
Outcome: 01 Number of people not achieving at least 50% reduction in depression score

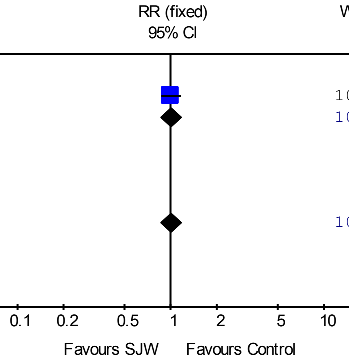
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Brenner00 Y O I A/L	8/15	9/15	7.22	0.89 [0.47, 1.67]	0
Davidson02 YOI A/L P	70/113	58/111	46.94	1.19 [0.94, 1.49]	0
Subtotal (95% CI)	128	126	54.16	1.15 [0.92, 1.42]	
Total events: 78 (St John's wort), 67 (Control)					
Test for heterogeneity: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%					
Test for overall effect: Z = 1.24 (P = 0.21)					
04 vs Amitriptyline					
Bergmann93 Y O I A	8/40	12/40	9.63	0.67 [0.31, 1.45]	0
Wheatley97 Y O I AL	37/87	21/78	17.76	1.58 [1.02, 2.45]	0
Subtotal (95% CI)	127	118	27.39	1.26 [0.86, 1.83]	
Total events: 45 (St John's wort), 33 (Control)					
Test for heterogeneity: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
05 vs Maprotiline					
Harrer94 Y O C A/L	23/51	23/51	18.45	1.00 [0.65, 1.53]	0
Subtotal (95% CI)	51	51	18.45	1.00 [0.65, 1.53]	
Total events: 23 (St John's wort), 23 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					
Total (95% CI)	306	295	100.00	1.15 [0.97, 1.37]	
Total events: 146 (St John's wort), 123 (Control)					
Test for heterogeneity: Chi² = 5.00, df = 4 (P = 0.29), I² = 20.0%					
Test for overall effect: Z = 1.57 (P = 0.12)					



1

Review: Pharmacology: St John's wort
Comparison: 08 Efficacy against low doses of ADs
Outcome: 02 Number of people not achieving remission

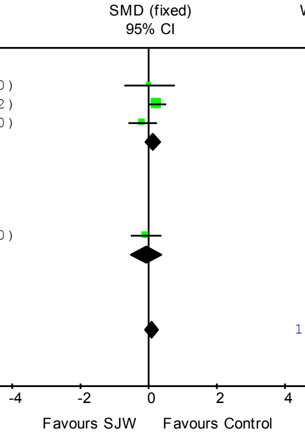
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Davidson02 YOI A/L P	86/113	84/111	100.00	1.01 [0.87, 1.17]	0
Subtotal (95% CI)	113	111	100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
Total (95% CI)	113	111	100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					



2

Review: Pharmacology: St John's wort
Comparison: 08 Efficacy against low doses of ADs
Outcome: 03 Mean endpoint scores

Study or sub-category	St John's wort N	St John's wort Mean (SD)	Control N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
02 vs Sertraline							
Brenner00 Y O I A/L	13	12.70(6.70)	15	12.50(5.60)	6.78	0.03 [-0.71, 0.77]	0
Davidson02 YOI A/L P	113	-8.68(7.23)	109	-10.53(7.52)	53.62	0.25 [-0.01, 0.51]	0
vanGurp02 Y O I AL	44	-9.50(7.10)	43	-8.20(7.50)	21.10	-0.18 [-0.60, 0.24]	0
Subtotal (95% CI)	170		167		81.51	0.12 [-0.09, 0.34]	
Test for heterogeneity: Chi² = 2.89, df = 2 (P = 0.24), I² = 30.8%							
Test for overall effect: Z = 1.11 (P = 0.27)							
04 vs Amitriptyline							
Bergmann93 Y O I A	38	6.30(4.20)	38	6.70(6.00)	18.49	-0.08 [-0.53, 0.37]	0
Subtotal (95% CI)	38		38		18.49	-0.08 [-0.53, 0.37]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.33 (P = 0.74)							
Total (95% CI)	208		205		100.00	0.08 [-0.11, 0.28]	
Test for heterogeneity: Chi² = 3.49, df = 3 (P = 0.32), I² = 14.2%							
Test for overall effect: Z = 0.86 (P = 0.39)							



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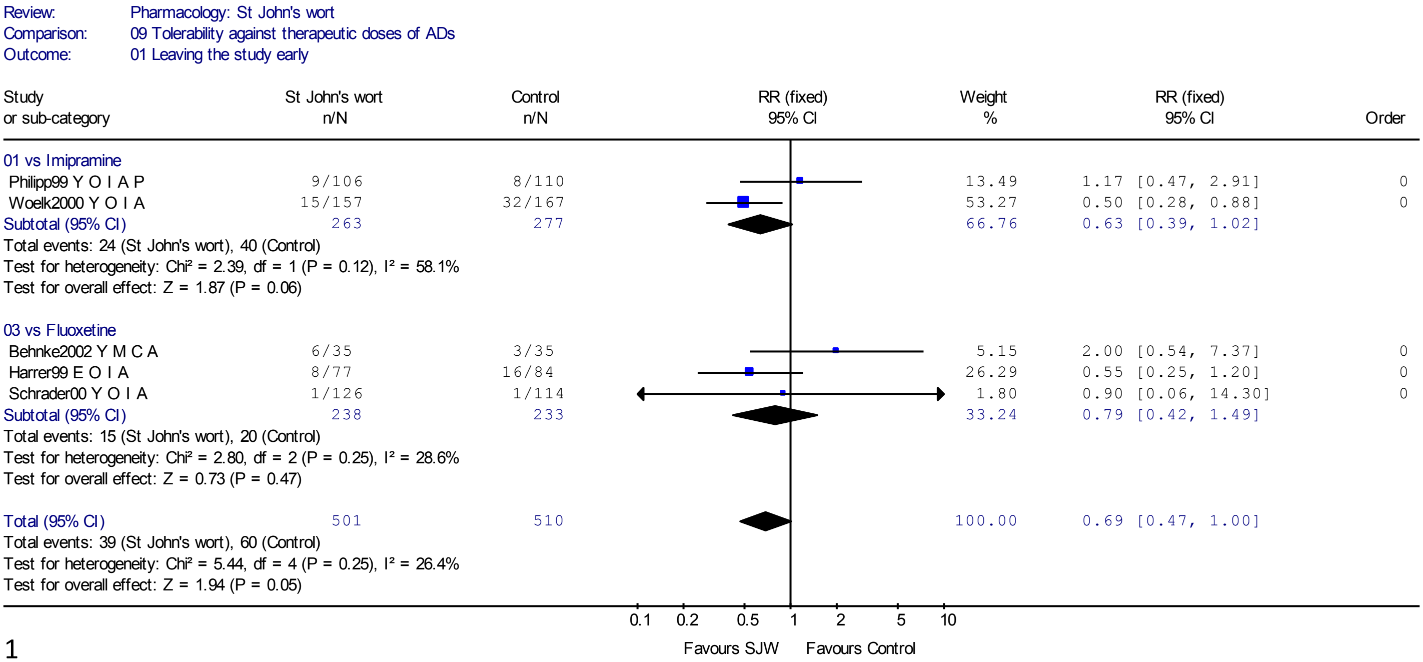
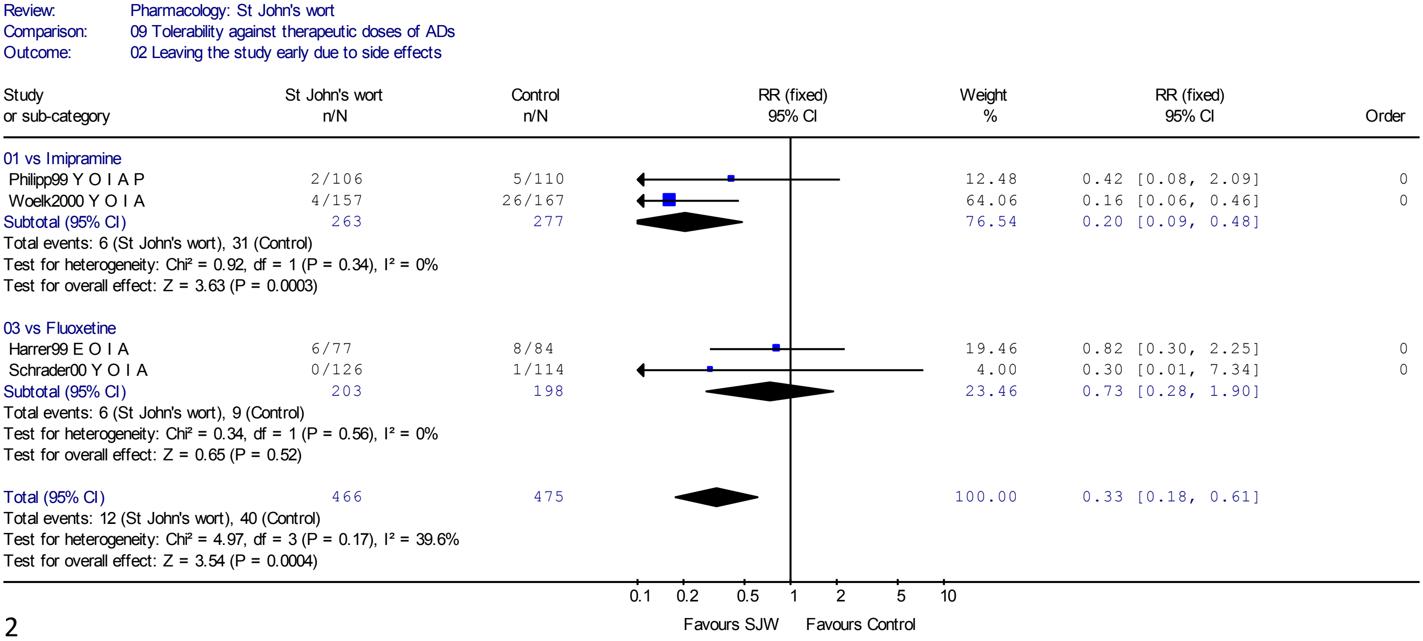


Review: Pharmacology: St John's wort
Comparison: 09 Tolerability against therapeutic doses of ADs
Outcome: 01 Leaving the study early

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	9/106	8/110	13.49	1.17 [0.47, 2.91]	0
Woelk2000 Y O I A	15/157	32/167	53.27	0.50 [0.28, 0.88]	0
Subtotal (95% CI)	263	277	66.76	0.63 [0.39, 1.02]	
Total events: 24 (St John's wort), 40 (Control)					
Test for heterogeneity: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.1%					
Test for overall effect: Z = 1.87 (P = 0.06)					
03 vs Fluoxetine					
Behnke2002 Y M C A	6/35	3/35	5.15	2.00 [0.54, 7.37]	0
Harrer99 E O I A	8/77	16/84	26.29	0.55 [0.25, 1.20]	0
Schrader00 Y O I A	1/126	1/114	1.80	0.90 [0.06, 14.30]	0
Subtotal (95% CI)	238	233	33.24	0.79 [0.42, 1.49]	
Total events: 15 (St John's wort), 20 (Control)					
Test for heterogeneity: Chi² = 2.80, df = 2 (P = 0.25), I² = 28.6%					
Test for overall effect: Z = 0.73 (P = 0.47)					
Total (95% CI)	501	510	100.00	0.69 [0.47, 1.00]	
Total events: 39 (St John's wort), 60 (Control)					
Test for heterogeneity: Chi² = 5.44, df = 4 (P = 0.25), I² = 26.4%					
Test for overall effect: Z = 1.94 (P = 0.05)					

1



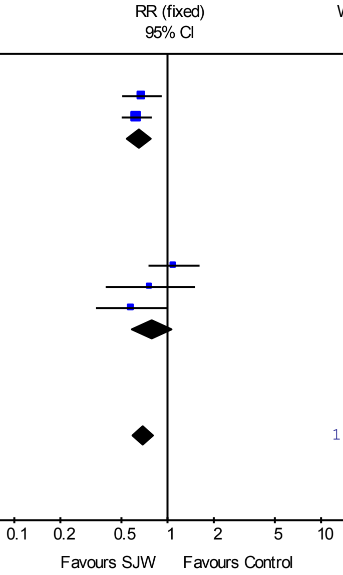
Review: Pharmacology: St John's wort
Comparison: 09 Tolerability against therapeutic doses of ADs
Outcome: 02 Leaving the study early due to side effects

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	2/106	5/110	12.48	0.42 [0.08, 2.09]	0
Woelk2000 Y O I A	4/157	26/167	64.06	0.16 [0.06, 0.46]	0
Subtotal (95% CI)	263	277	76.54	0.20 [0.09, 0.48]	
Total events: 6 (St John's wort), 31 (Control)					
Test for heterogeneity: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%					
Test for overall effect: Z = 3.63 (P = 0.0003)					
03 vs Fluoxetine					
Harrer99 E O I A	6/77	8/84	19.46	0.82 [0.30, 2.25]	0
Schrader00 Y O I A	0/126	1/114	4.00	0.30 [0.01, 7.34]	0
Subtotal (95% CI)	203	198	23.46	0.73 [0.28, 1.90]	
Total events: 6 (St John's wort), 9 (Control)					
Test for heterogeneity: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%					
Test for overall effect: Z = 0.65 (P = 0.52)					
Total (95% CI)	466	475	100.00	0.33 [0.18, 0.61]	
Total events: 12 (St John's wort), 40 (Control)					
Test for heterogeneity: Chi² = 4.97, df = 3 (P = 0.17), I² = 39.6%					
Test for overall effect: Z = 3.54 (P = 0.0004)					

2

Review: Pharmacology: St John's wort
Comparison: 09 Tolerability against therapeutic doses of ADs
Outcome: 03 Patients reporting side effects

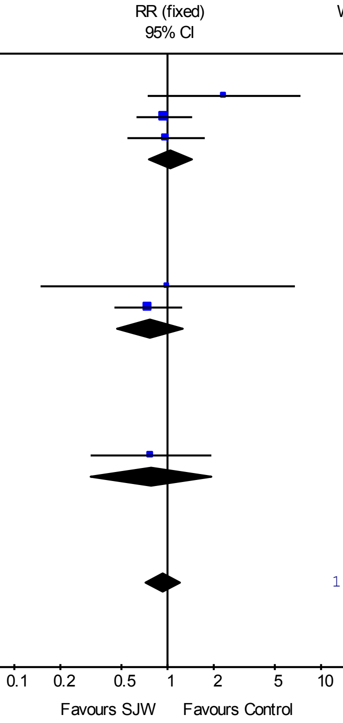
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	40/106	61/110	26.34	0.68 [0.51, 0.92]	0
Woelk2000 Y O I A	62/157	105/167	44.77	0.63 [0.50, 0.79]	0
Subtotal (95% CI)	263	277	71.11	0.65 [0.54, 0.77]	
Total events: 102 (St John's wort), 166 (Control)					
Test for heterogeneity: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%					
Test for overall effect: Z = 4.74 (P < 0.00001)					
03 vs Fluoxetine					
Behnke2002 Y M C A	22/35	20/35	8.80	1.10 [0.75, 1.61]	0
Harrer99 E O I A	12/77	17/84	7.15	0.77 [0.39, 1.51]	0
Schrader00 Y O I A	18/126	28/114	12.93	0.58 [0.34, 0.99]	0
Subtotal (95% CI)	238	233	28.89	0.79 [0.58, 1.06]	
Total events: 52 (St John's wort), 65 (Control)					
Test for heterogeneity: Chi² = 4.17, df = 2 (P = 0.12), I² = 52.0%					
Test for overall effect: Z = 1.58 (P = 0.11)					
Total (95% CI)	501	510	100.00	0.69 [0.59, 0.80]	
Total events: 154 (St John's wort), 231 (Control)					
Test for heterogeneity: Chi² = 6.87, df = 4 (P = 0.14), I² = 41.8%					
Test for overall effect: Z = 4.75 (P < 0.00001)					



1

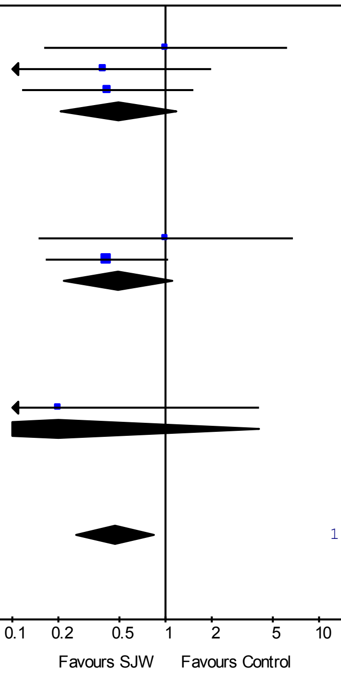
Review: Pharmacology: St John's wort
Comparison: 10 Tolerability against low doses of ADs
Outcome: 01 Leaving the study early

Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Brenner00 Y O I A/L	7/15	3/15	3.46	2.33 [0.74, 7.35]	0
Davidson02 YOI A/L P	31/113	32/111	37.21	0.95 [0.63, 1.45]	0
vanGurp02 Y O I AL	15/44	15/43	17.49	0.98 [0.55, 1.74]	0
Subtotal (95% CI)	172	169	58.15	1.04 [0.75, 1.44]	
Total events: 53 (St John's wort), 50 (Control)					
Test for heterogeneity: Chi² = 2.12, df = 2 (P = 0.35), I² = 5.8%					
Test for overall effect: Z = 0.25 (P = 0.81)					
04 vs Amitriptyline					
Bergmann93 Y O I A	2/40	2/40	2.31	1.00 [0.15, 6.76]	0
Wheatley97 Y O I AL	20/87	24/78	29.17	0.75 [0.45, 1.24]	0
Subtotal (95% CI)	127	118	31.47	0.77 [0.47, 1.25]	
Total events: 22 (St John's wort), 26 (Control)					
Test for heterogeneity: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%					
Test for overall effect: Z = 1.06 (P = 0.29)					
05 vs Maprotiline					
Harrer94 Y O C A/L	7/51	9/51	10.37	0.78 [0.31, 1.93]	0
Subtotal (95% CI)	51	51	10.37	0.78 [0.31, 1.93]	
Total events: 7 (St John's wort), 9 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
Total (95% CI)	350	338	100.00	0.93 [0.72, 1.20]	
Total events: 82 (St John's wort), 85 (Control)					
Test for heterogeneity: Chi² = 3.37, df = 5 (P = 0.64), I² = 0%					
Test for overall effect: Z = 0.57 (P = 0.57)					



2

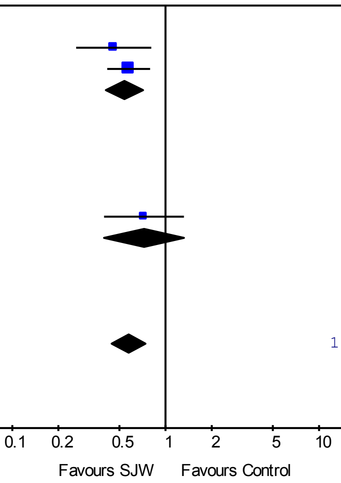
Review: Pharmacology: St John's wort
Comparison: 10 Tolerability against low doses of ADs
Outcome: 02 Leaving the study early due to side effects



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Brenner00 Y O I A/L	2/15	2/15	6.19	1.00 [0.16, 6.20]	0
Davidson02 YOI A/L P	2/113	5/111	15.60	0.39 [0.08, 1.98]	0
vanGurp02 Y O I AL	3/44	7/43	21.90	0.42 [0.12, 1.51]	0
Subtotal (95% CI)	172	169	43.68	0.49 [0.21, 1.17]	
Total events: 7 (St John's wort), 14 (Control)					
Test for heterogeneity: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%					
Test for overall effect: Z = 1.60 (P = 0.11)					
04 vs Amitriptyline					
Bergmann93 Y O I A	2/40	2/40	6.19	1.00 [0.15, 6.76]	0
Wheatley97 Y O I AL	6/87	13/78	42.40	0.41 [0.17, 1.04]	0
Subtotal (95% CI)	127	118	48.58	0.49 [0.22, 1.10]	
Total events: 8 (St John's wort), 15 (Control)					
Test for heterogeneity: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%					
Test for overall effect: Z = 1.72 (P = 0.08)					
05 vs Maprotiline					
Harrer94 Y O C A/L	0/51	2/51	7.73	0.20 [0.01, 4.07]	0
Subtotal (95% CI)	51	51	7.73	0.20 [0.01, 4.07]	
Total events: 0 (St John's wort), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
Total (95% CI)	350	338	100.00	0.47 [0.26, 0.84]	
Total events: 15 (St John's wort), 31 (Control)					
Test for heterogeneity: Chi² = 1.72, df = 5 (P = 0.89), I² = 0%					
Test for overall effect: Z = 2.56 (P = 0.01)					

1

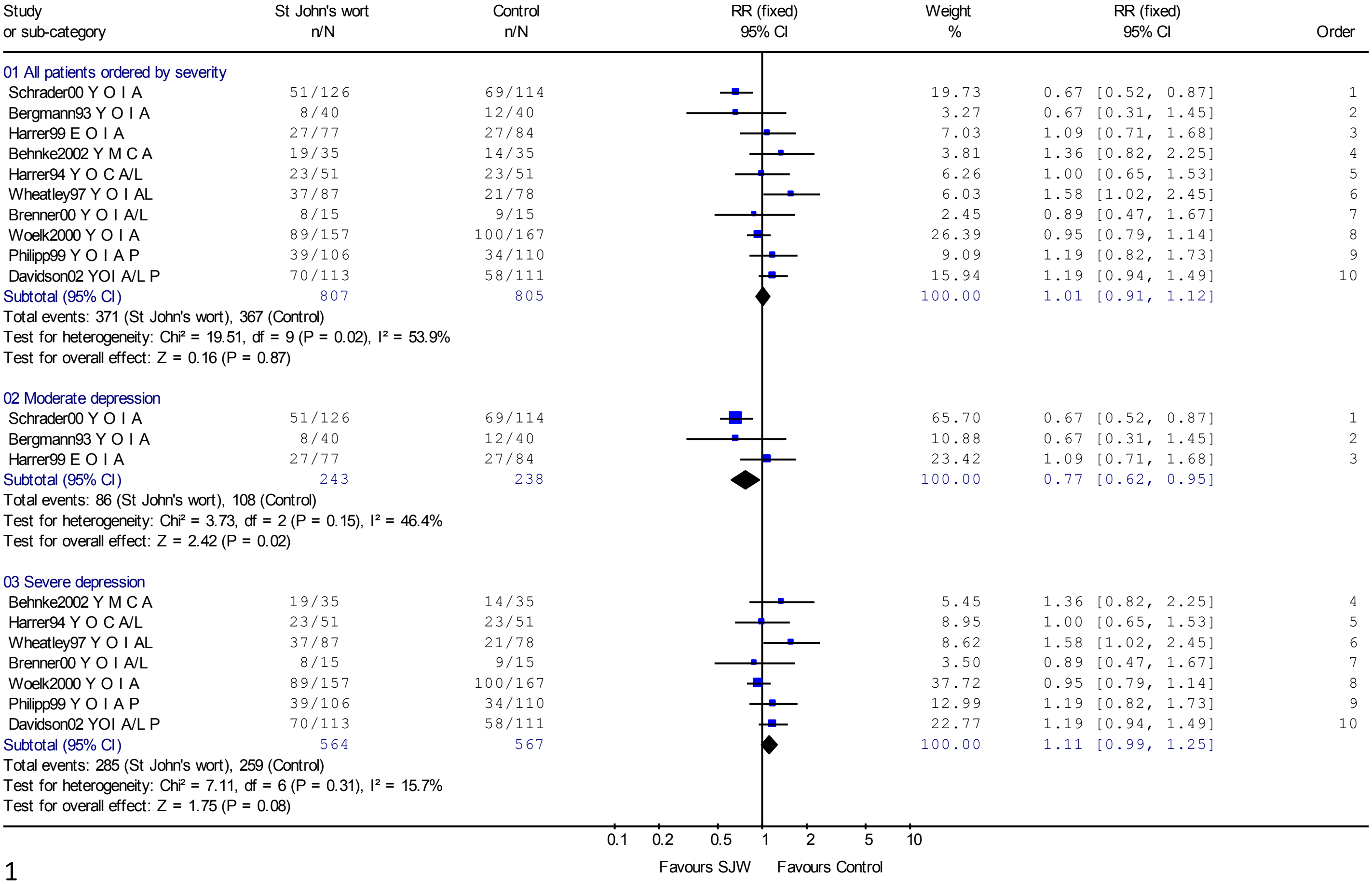
Review: Pharmacology: St John's wort
Comparison: 10 Tolerability against low doses of ADs
Outcome: 03 Patients reporting side effects



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
04 vs Amitriptyline					
Bergmann93 Y O I A	11/40	24/40	25.34	0.46 [0.26, 0.80]	0
Wheatley97 Y O I AL	32/87	50/78	55.66	0.57 [0.42, 0.79]	0
Subtotal (95% CI)	127	118	81.00	0.54 [0.41, 0.71]	
Total events: 43 (St John's wort), 74 (Control)					
Test for heterogeneity: Chi² = 0.47, df = 1 (P = 0.50), I² = 0%					
Test for overall effect: Z = 4.34 (P < 0.0001)					
05 vs Maprotiline					
Harrer94 Y O C A/L	13/51	18/51	19.00	0.72 [0.40, 1.31]	0
Subtotal (95% CI)	51	51	19.00	0.72 [0.40, 1.31]	
Total events: 13 (St John's wort), 18 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.29)					
Total (95% CI)	178	169	100.00	0.57 [0.44, 0.74]	
Total events: 56 (St John's wort), 92 (Control)					
Test for heterogeneity: Chi² = 1.18, df = 2 (P = 0.55), I² = 0%					
Test for overall effect: Z = 4.29 (P < 0.0001)					

2

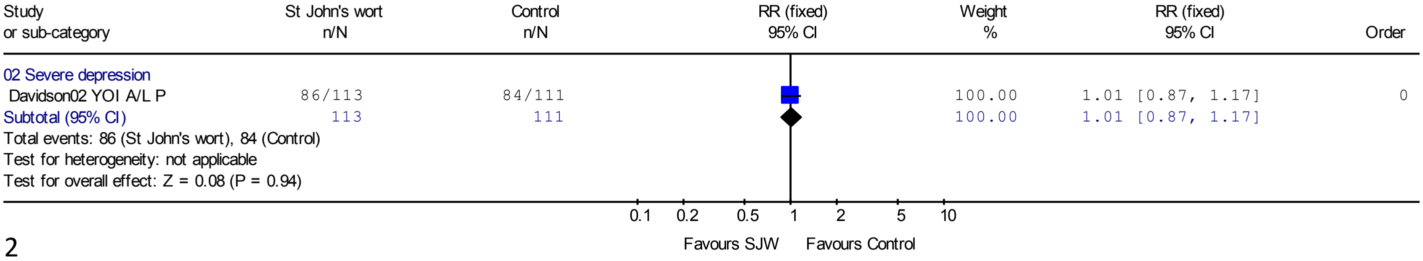
Review: Pharmacology: St John's wort
Comparison: 11 Efficacy against ADs by severity of depression
Outcome: 01 Number of people not achieving at least 50% reduction in depression score



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 All patients ordered by severity					
Schrader00 Y O I A	51/126	69/114	19.73	0.67 [0.52, 0.87]	1
Bergmann93 Y O I A	8/40	12/40	3.27	0.67 [0.31, 1.45]	2
Harrer99 E O I A	27/77	27/84	7.03	1.09 [0.71, 1.68]	3
Behnke2002 Y M C A	19/35	14/35	3.81	1.36 [0.82, 2.25]	4
Harrer94 Y O C A/L	23/51	23/51	6.26	1.00 [0.65, 1.53]	5
Wheatley97 Y O I AL	37/87	21/78	6.03	1.58 [1.02, 2.45]	6
Brenner00 Y O I A/L	8/15	9/15	2.45	0.89 [0.47, 1.67]	7
Woelk2000 Y O I A	89/157	100/167	26.39	0.95 [0.79, 1.14]	8
Philipp99 Y O I A P	39/106	34/110	9.09	1.19 [0.82, 1.73]	9
Davidson02 YOI A/L P	70/113	58/111	15.94	1.19 [0.94, 1.49]	10
Subtotal (95% CI)	807	805	100.00	1.01 [0.91, 1.12]	
Total events: 371 (St John's wort), 367 (Control)					
Test for heterogeneity: Chi² = 19.51, df = 9 (P = 0.02), I² = 53.9%					
Test for overall effect: Z = 0.16 (P = 0.87)					
02 Moderate depression					
Schrader00 Y O I A	51/126	69/114	65.70	0.67 [0.52, 0.87]	1
Bergmann93 Y O I A	8/40	12/40	10.88	0.67 [0.31, 1.45]	2
Harrer99 E O I A	27/77	27/84	23.42	1.09 [0.71, 1.68]	3
Subtotal (95% CI)	243	238	100.00	0.77 [0.62, 0.95]	
Total events: 86 (St John's wort), 108 (Control)					
Test for heterogeneity: Chi² = 3.73, df = 2 (P = 0.15), I² = 46.4%					
Test for overall effect: Z = 2.42 (P = 0.02)					
03 Severe depression					
Behnke2002 Y M C A	19/35	14/35	5.45	1.36 [0.82, 2.25]	4
Harrer94 Y O C A/L	23/51	23/51	8.95	1.00 [0.65, 1.53]	5
Wheatley97 Y O I AL	37/87	21/78	8.62	1.58 [1.02, 2.45]	6
Brenner00 Y O I A/L	8/15	9/15	3.50	0.89 [0.47, 1.67]	7
Woelk2000 Y O I A	89/157	100/167	37.72	0.95 [0.79, 1.14]	8
Philipp99 Y O I A P	39/106	34/110	12.99	1.19 [0.82, 1.73]	9
Davidson02 YOI A/L P	70/113	58/111	22.77	1.19 [0.94, 1.49]	10
Subtotal (95% CI)	564	567	100.00	1.11 [0.99, 1.25]	
Total events: 285 (St John's wort), 259 (Control)					
Test for heterogeneity: Chi² = 7.11, df = 6 (P = 0.31), I² = 15.7%					
Test for overall effect: Z = 1.75 (P = 0.08)					

1

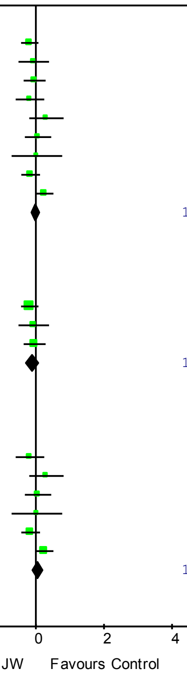
Review: Pharmacology: St John's wort
Comparison: 11 Efficacy against ADs by severity of depression
Outcome: 02 Number of people not achieving remission



Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 Severe depression					
Davidson02 YOI A/L P	86/113	84/111	100.00	1.01 [0.87, 1.17]	0
Subtotal (95% CI)	113	111	100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					

2

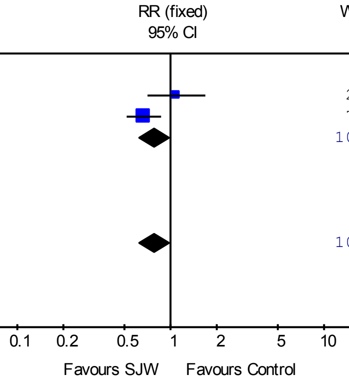
Review: Pharmacology: St John's wort
Comparison: 11 Efficacy against ADs by severity of depression
Outcome: 03 Mean endpoint scores



Study or sub-category	N	St John's wort Mean (SD)	N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 All patients ordered by severity							
Schrader00 Y O I A	125	-8.11(4.85)	113	-7.25(4.61)	20.35	-0.18 [-0.44, 0.07]	1
Bergmann93 Y O I A	38	6.34(4.19)	38	6.65(5.98)	6.54	-0.06 [-0.51, 0.39]	2
Harrer99 E O I A	70	7.91(5.04)	79	8.11(5.67)	12.78	-0.04 [-0.36, 0.28]	3
vanGurp02 Y O I AL	44	-9.50(7.10)	43	-8.20(7.50)	7.46	-0.18 [-0.60, 0.24]	4
Behnke2002 Y M C A	29	-10.00(5.80)	32	-12.00(6.80)	5.17	0.31 [-0.19, 0.82]	5
Harrer94 Y O C A/L	51	12.78(10.19)	51	12.20(7.83)	8.78	0.06 [-0.32, 0.45]	6
Brenner00 Y O I A/L	13	12.70(6.70)	15	12.50(5.60)	2.40	0.03 [-0.71, 0.77]	7
Philipp99 Y O I A P	100	-15.40(8.10)	105	-14.20(7.30)	17.58	-0.16 [-0.43, 0.12]	8
Davidson02 YOI A/L P	113	-8.68(7.23)	109	-10.53(7.52)	18.95	0.25 [-0.01, 0.51]	9
Subtotal (95% CI)	583		585		100.00	-0.02 [-0.13, 0.10]	
Test for heterogeneity: Chi² = 8.89, df = 8 (P = 0.35), I² = 10.0%							
Test for overall effect: Z = 0.27 (P = 0.78)							
02 Moderate depression							
Schrader00 Y O I A	125	-8.11(4.85)	113	-7.25(4.61)	51.30	-0.18 [-0.44, 0.07]	1
Bergmann93 Y O I A	38	6.34(4.19)	38	6.65(5.98)	16.49	-0.06 [-0.51, 0.39]	2
Harrer99 E O I A	70	7.91(5.04)	79	8.11(5.67)	32.21	-0.04 [-0.36, 0.28]	3
Subtotal (95% CI)	233		230		100.00	-0.11 [-0.30, 0.07]	
Test for heterogeneity: Chi² = 0.54, df = 2 (P = 0.76), I² = 0%							
Test for overall effect: Z = 1.23 (P = 0.22)							
03 Severe depression							
vanGurp02 Y O I AL	44	-9.50(7.10)	43	-8.20(7.50)	12.36	-0.18 [-0.60, 0.24]	4
Behnke2002 Y M C A	29	-10.00(5.80)	32	-12.00(6.80)	8.57	0.31 [-0.19, 0.82]	5
Harrer94 Y O C A/L	51	12.78(10.19)	51	12.20(7.83)	14.54	0.06 [-0.32, 0.45]	6
Brenner00 Y O I A/L	13	12.70(6.70)	15	12.50(5.60)	3.97	0.03 [-0.71, 0.77]	7
Philipp99 Y O I A P	100	-15.40(8.10)	105	-14.20(7.30)	29.14	-0.16 [-0.43, 0.12]	8
Davidson02 YOI A/L P	113	-8.68(7.23)	109	-10.53(7.52)	31.41	0.25 [-0.01, 0.51]	9
Subtotal (95% CI)	350		355		100.00	0.05 [-0.10, 0.20]	
Test for heterogeneity: Chi² = 6.50, df = 5 (P = 0.26), I² = 23.0%							
Test for overall effect: Z = 0.64 (P = 0.52)							

1

Review: Pharmacology: St John's wort
Comparison: 12 Therapeutic dose / severity
Outcome: 01 Number of people not achieving at least 50% reduction in depression score / moderate depression

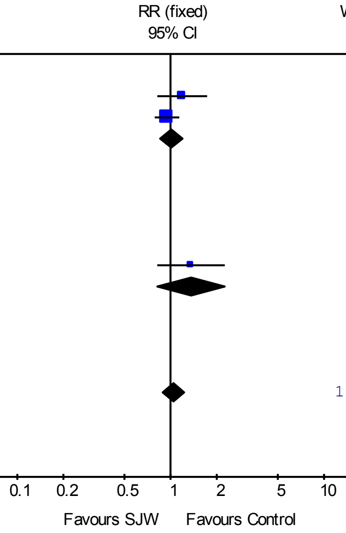


Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
03 vs Fluoxetine					
Harrer99 E O I A	27/77	27/84	26.28	1.09 [0.71, 1.68]	0
Schrader00 Y O I A	51/126	69/114	73.72	0.67 [0.52, 0.87]	0
Subtotal (95% CI)	203	198	100.00	0.78 [0.62, 0.97]	
Total events: 78 (St John's wort), 96 (Control)					
Test for heterogeneity: Chi² = 3.65, df = 1 (P = 0.06), I² = 72.6%					
Test for overall effect: Z = 2.19 (P = 0.03)					
Total (95% CI)	203	198	100.00	0.78 [0.62, 0.97]	
Total events: 78 (St John's wort), 96 (Control)					
Test for heterogeneity: Chi² = 3.65, df = 1 (P = 0.06), I² = 72.6%					
Test for overall effect: Z = 2.19 (P = 0.03)					

2

Review: Pharmacology: St John's wort
Comparison: 12 Therapeutic dose / severity
Outcome: 02 Number of people not achieving at least 50% reduction in depression score / severe depression

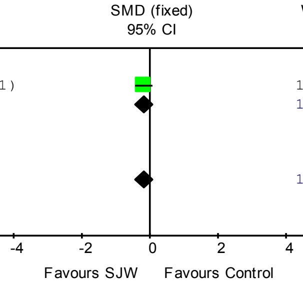
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 vs Imipramine					
Philipp99 Y O I A P	39/106	34/110	23.13	1.19 [0.82, 1.73]	0
Woelk2000 Y O I A	89/157	100/167	67.17	0.95 [0.79, 1.14]	0
Subtotal (95% CI)	263	277	90.30	1.01 [0.85, 1.19]	
Total events: 128 (St John's wort), 134 (Control)					
Test for heterogeneity: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.1%					
Test for overall effect: Z = 0.11 (P = 0.92)					
03 vs Fluoxetine					
Behnke2002 Y M C A	19/35	14/35	9.70	1.36 [0.82, 2.25]	0
Subtotal (95% CI)	35	35	9.70	1.36 [0.82, 2.25]	
Total events: 19 (St John's wort), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					
Total (95% CI)	298	312	100.00	1.04 [0.89, 1.22]	
Total events: 147 (St John's wort), 148 (Control)					
Test for heterogeneity: Chi² = 2.57, df = 2 (P = 0.28), I² = 22.2%					
Test for overall effect: Z = 0.51 (P = 0.61)					



1

Review: Pharmacology: St John's wort
Comparison: 12 Therapeutic dose / severity
Outcome: 03 Mean endpoint scores / moderate depression

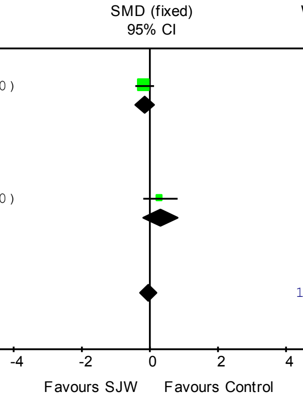
Study or sub-category	N	St John's wort Mean (SD)	N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
03 vs Fluoxetine							
Schrader00 Y O I A	125	-8.11(4.85)	113	-7.25(4.61)	100.00	-0.18 [-0.44, 0.07]	0
Subtotal (95% CI)	125		113		100.00	-0.18 [-0.44, 0.07]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.39 (P = 0.16)							
Total (95% CI)	125		113		100.00	-0.18 [-0.44, 0.07]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.39 (P = 0.16)							



2

Review: Pharmacology: St John's wort
Comparison: 12 Therapeutic dose / severity
Outcome: 04 Mean endpoint scores / severe depression

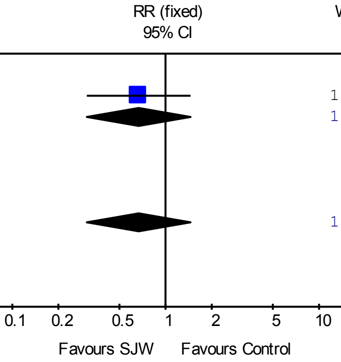
Study or sub-category	N	St John's wort Mean (SD)	N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 vs Imipramine							
Philipp99 Y O I A P	100	-15.40(8.10)	105	-14.20(7.30)	77.27	-0.16 [-0.43, 0.12]	0
Subtotal (95% CI)	100		105		77.27	-0.16 [-0.43, 0.12]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
03 vs Fluoxetine							
Behnke2002 Y M C A	29	-10.00(5.80)	32	-12.00(6.80)	22.73	0.31 [-0.19, 0.82]	0
Subtotal (95% CI)	29		32		22.73	0.31 [-0.19, 0.82]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.21 (P = 0.23)							
Total (95% CI)	129		137		100.00	-0.05 [-0.29, 0.19]	
Test for heterogeneity: Chi² = 2.52, df = 1 (P = 0.11), I² = 60.4%							
Test for overall effect: Z = 0.40 (P = 0.69)							



3

Review: Pharmacology: St John's wort
Comparison: 13 Low dose / severity
Outcome: 01 Number of people not achieving at least 50% reduction in depression score / moderate depression

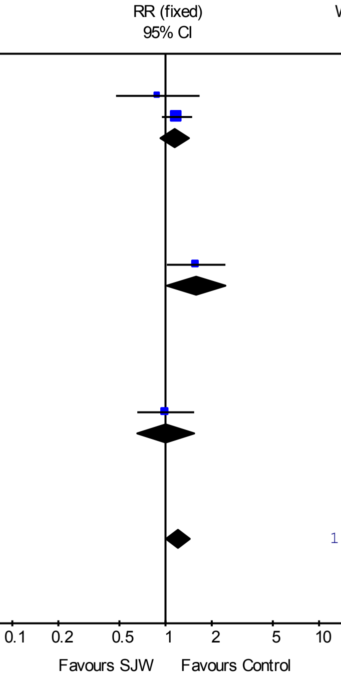
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
04 vs Amitriptyline					
Bergmann93 Y O I A	8/40	12/40	100.00	0.67 [0.31, 1.45]	0
Subtotal (95% CI)	40	40	100.00	0.67 [0.31, 1.45]	
Total events: 8 (St John's wort), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
Total (95% CI)	40	40	100.00	0.67 [0.31, 1.45]	
Total events: 8 (St John's wort), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					



1

Review: Pharmacology: St John's wort
Comparison: 13 Low dose / severity
Outcome: 02 Number of people not achieving at least 50% reduction in depression score / severe depression

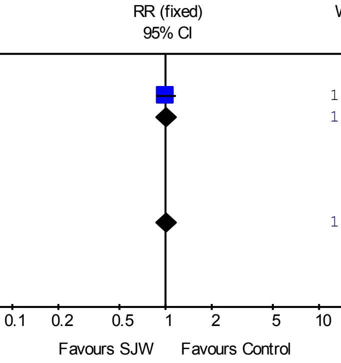
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Brenner00 Y O I A/L	8/15	9/15	7.99	0.89 [0.47, 1.67]	0
Davidson02 YOI A/L P	70/113	58/111	51.94	1.19 [0.94, 1.49]	0
Subtotal (95% CI)	128	126	59.93	1.15 [0.92, 1.42]	
Total events: 78 (St John's wort), 67 (Control)					
Test for heterogeneity: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%					
Test for overall effect: Z = 1.24 (P = 0.21)					
04 vs Amitriptyline					
Wheatley97 Y O I AL	37/87	21/78	19.66	1.58 [1.02, 2.45]	0
Subtotal (95% CI)	87	78	19.66	1.58 [1.02, 2.45]	
Total events: 37 (St John's wort), 21 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.04)					
05 vs Maprotiline					
Harrer94 Y O C A/L	23/51	23/51	20.41	1.00 [0.65, 1.53]	0
Subtotal (95% CI)	51	51	20.41	1.00 [0.65, 1.53]	
Total events: 23 (St John's wort), 23 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					
Total (95% CI)	266	255	100.00	1.20 [1.00, 1.44]	
Total events: 138 (St John's wort), 111 (Control)					
Test for heterogeneity: Chi² = 3.09, df = 3 (P = 0.38), I² = 2.9%					
Test for overall effect: Z = 2.01 (P = 0.04)					



2

Review: Pharmacology: St John's wort
Comparison: 13 Low dose / severity
Outcome: 03 Number of people not achieving remission / severe depression

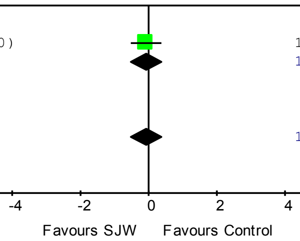
Study or sub-category	St John's wort n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
02 vs Sertraline					
Davidson02 YOI A/L P	86/113	84/111	100.00	1.01 [0.87, 1.17]	0
Subtotal (95% CI)	113	111	100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
Total (95% CI)	113	111	100.00	1.01 [0.87, 1.17]	
Total events: 86 (St John's wort), 84 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					



3

Review: Pharmacology: St John's wort
Comparison: 13 Low dose / severity
Outcome: 04 Mean endpoint scores / moderate depression

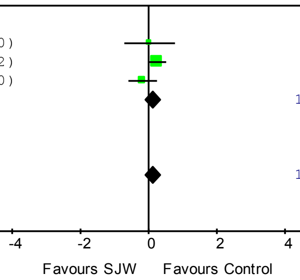
Study or sub-category	St John's wort N	St John's wort Mean (SD)	Control N	Control Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
04 vs Amitriptyline								
Bergmann93 Y O I A	38	6.30(4.20)	38	6.70(6.00)		100.00	-0.08 [-0.53, 0.37]	0
Subtotal (95% CI)	38		38			100.00	-0.08 [-0.53, 0.37]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Total (95% CI)	38		38			100.00	-0.08 [-0.53, 0.37]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								



1

Review: Pharmacology: St John's wort
Comparison: 13 Low dose / severity
Outcome: 05 Mean endpoint scores / severe depression

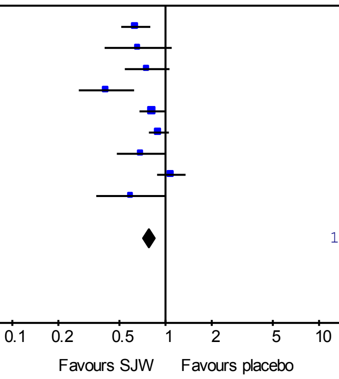
Study or sub-category	St John's wort N	St John's wort Mean (SD)	Control N	Control Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
02 vs Sertraline								
Brenner00 Y O I A/L	13	12.70(6.70)	15	12.50(5.60)		8.32	0.03 [-0.71, 0.77]	0
Davidson02 YOI A/L P	113	-8.68(7.23)	109	-10.53(7.52)		65.79	0.25 [-0.01, 0.51]	0
vanGurp02 Y O I AL	44	-9.50(7.10)	43	-8.20(7.50)		25.89	-0.18 [-0.60, 0.24]	0
Subtotal (95% CI)	170		167			100.00	0.12 [-0.09, 0.34]	
Test for heterogeneity: Chi² = 2.89, df = 2 (P = 0.24), I² = 30.8%								
Test for overall effect: Z = 1.11 (P = 0.27)								
Total (95% CI)	170		167			100.00	0.12 [-0.09, 0.34]	
Test for heterogeneity: Chi² = 2.89, df = 2 (P = 0.24), I² = 30.8%								
Test for overall effect: Z = 1.11 (P = 0.27)								



2

Review: Pharmacology: St John's wort
Comparison: 14 Efficacy against placebo
Outcome: 01 Number of people not achieving at least 50% reduction in depression score

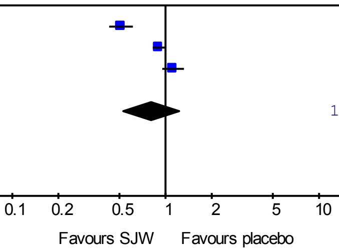
Study or sub-category	St John's wort n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
Schrader98 Y ? I P	44/81	69/81		14.44	0.64 [0.51, 0.79]	1
Kalb2001 Y O I P	14/37	20/35		4.30	0.66 [0.40, 1.09]	2
Laakmann98 Y O I P	25/49	33/49		6.91	0.76 [0.54, 1.06]	3
Hansgen1996 Y M C P	17/53	43/55		8.83	0.41 [0.27, 0.62]	4
Lecrubier02 Y O I P	88/186	109/189		22.63	0.82 [0.68, 1.00]	5
Shelton2001 Y O I P	72/98	83/102		17.03	0.90 [0.78, 1.05]	6
Philipp99 Y O I A P	39/106	25/47		7.25	0.69 [0.48, 1.00]	7
Davidson02 YOI A/L P	70/113	66/116		13.63	1.09 [0.88, 1.35]	8
Witte1995 Y O I P	14/48	24/49		4.97	0.60 [0.35, 1.01]	9
Total (95% CI)	771	723		100.00	0.78 [0.71, 0.85]	
Total events: 383 (St John's wort), 472 (Placebo)						
Test for heterogeneity: Chi² = 27.58, df = 8 (P = 0.0006), I² = 71.0%						
Test for overall effect: Z = 5.67 (P < 0.00001)						



3

Review: Pharmacology: St John's wort
Comparison: 14 Efficacy against placebo
Outcome: 02 Number of people not achieving remission

Study or sub-category	St John's wort n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
Lecrubier02 Y O I P	80/186	159/189		32.75	0.51 [0.43, 0.61]	1
Shelton2001 Y O I P	84/98	97/102		34.20	0.90 [0.82, 0.99]	2
Davidson02 YOI A/L P	86/113	79/116		33.06	1.12 [0.95, 1.31]	3
Total (95% CI)	397	407		100.00	0.80 [0.53, 1.22]	
Total events: 250 (St John's wort), 335 (Placebo)						
Test for heterogeneity: Chi² = 52.99, df = 2 (P < 0.00001), I² = 96.2%						
Test for overall effect: Z = 1.02 (P = 0.31)						

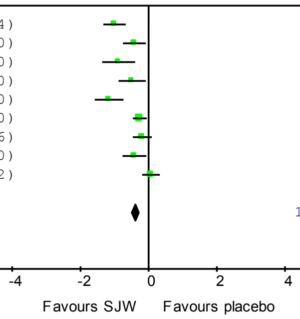


4

Review: Pharmacology: St John's wort
Comparison: 14 Efficacy against placebo
Outcome: 03 Mean endpoint scores

Study or sub-category	N	St John's wort Mean (SD)	N	Placebo Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
Schrader98 Y ? I P	80	-9.60(9.93)	79	-0.77(7.44)	9.73	-1.00 [-1.33, -0.67]	1
Volz2000 Y O I P	70	12.00(5.10)	70	14.30(5.90)	9.46	-0.41 [-0.75, -0.08]	2
Kalb2001 Y O I P	37	-10.80(5.00)	35	-5.70(6.40)	4.51	-0.88 [-1.37, -0.40]	3
Laakmann98 Y O I P	49	-10.30(4.60)	49	-7.90(5.20)	6.57	-0.49 [-0.89, -0.08]	4
Hansgen1996 Y M C P	51	8.90(4.30)	50	14.40(5.10)	5.94	-1.16 [-1.58, -0.74]	5
Lecrubier02 Y O I P	186	-9.90(6.80)	189	-8.10(7.10)	25.69	-0.26 [-0.46, -0.06]	6
Shelton2001 Y O I P	98	15.06(6.93)	102	16.28(6.16)	13.75	-0.19 [-0.46, 0.09]	7
Philipp99 Y O I A P	100	-15.40(8.10)	46	-12.10(7.40)	8.54	-0.42 [-0.77, -0.06]	8
Davidson02 YOI A/L P	113	-8.68(7.23)	116	-9.20(7.22)	15.81	0.07 [-0.19, 0.33]	9
Total (95% CI)	784		736		100.00	-0.39 [-0.50, -0.29]	

Test for heterogeneity: Chi² = 45.90, df = 8 (P < 0.00001), I² = 82.6%
Test for overall effect: Z = 7.48 (P < 0.00001)

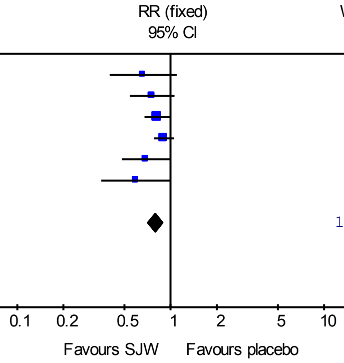


1

Review: Pharmacology: St John's wort
Comparison: 14 Efficacy against placebo
Outcome: 04 Sensitivity analysis: Number of people not achieving at least 50% reduction in depression score

Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (fixed) 95% CI	Order
Kalb2001 Y O I P	14/37	20/35	6.82	0.66 [0.40, 1.09]	2
Laakmann98 Y O I P	25/49	33/49	10.95	0.76 [0.54, 1.06]	3
Lecrubier02 Y O I P	88/186	109/189	35.87	0.82 [0.68, 1.00]	5
Shelton2001 Y O I P	72/98	83/102	26.99	0.90 [0.78, 1.05]	6
Philipp99 Y O I A P	39/106	25/47	11.49	0.69 [0.48, 1.00]	7
Witte1995 Y O I P	14/48	24/49	7.88	0.60 [0.35, 1.01]	9
Total (95% CI)	524	471	100.00	0.79 [0.71, 0.88]	

Total events: 252 (St John's wort), 294 (Placebo)
Test for heterogeneity: Chi² = 5.22, df = 5 (P = 0.39), I² = 4.1%
Test for overall effect: Z = 4.15 (P < 0.0001)

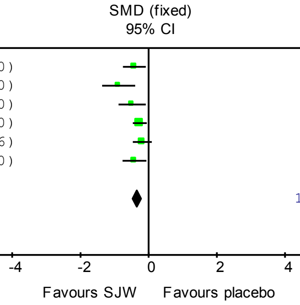


2

Review: Pharmacology: St John's wort
Comparison: 14 Efficacy against placebo
Outcome: 05 Sensitivity analysis: Mean endpoint scores

Study or sub-category	N	St John's wort Mean (SD)	N	Placebo Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
Volz2000 Y O I P	70	12.00(5.10)	70	14.30(5.90)	13.81	-0.41 [-0.75, -0.08]	2
Kalb2001 Y O I P	37	-10.80(5.00)	35	-5.70(6.40)	6.58	-0.88 [-1.37, -0.40]	3
Laakmann98 Y O I P	49	-10.30(4.60)	49	-7.90(5.20)	9.59	-0.49 [-0.89, -0.08]	4
Lecrubier02 Y O I P	186	-9.90(6.80)	189	-8.10(7.10)	37.49	-0.26 [-0.46, -0.06]	6
Shelton2001 Y O I P	98	15.06(6.93)	102	16.28(6.16)	20.07	-0.19 [-0.46, 0.09]	7
Philipp99 Y O I A P	100	-15.40(8.10)	46	-12.10(7.40)	12.47	-0.42 [-0.77, -0.06]	8
Total (95% CI)	540		491		100.00	-0.35 [-0.47, -0.22]	

Test for heterogeneity: Chi² = 7.45, df = 5 (P = 0.19), I² = 32.9%
Test for overall effect: Z = 5.48 (P < 0.00001)

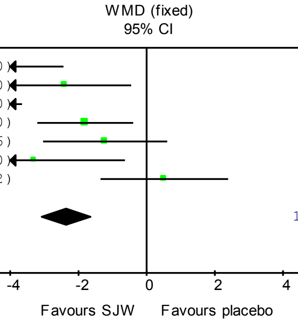


3

Review: Pharmacology: St John's wort
Comparison: 14 Efficacy against placebo
Outcome: 06 Mean endpoint scores (HRSD-17 only)

Study or sub-category	N	St John's wort Mean (SD)	N	Placebo Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
Kalb2001 Y O I P	37	-10.80(5.00)	35	-5.70(6.40)	7.29	-5.10 [-7.76, -2.44]	3
Laakmann98 Y O I P	49	-10.30(4.60)	49	-7.90(5.20)	13.68	-2.40 [-4.34, -0.46]	4
Hansgen1996 Y M C P	51	8.90(4.30)	50	14.40(5.10)	15.25	-5.50 [-7.34, -3.66]	5
Lecrubier02 Y O I P	186	-9.90(6.80)	189	-8.10(7.10)	26.12	-1.80 [-3.21, -0.39]	6
Shelton2001 Y O I P	98	15.06(6.93)	102	16.28(6.16)	15.61	-1.22 [-3.04, 0.60]	7
Philipp99 Y O I A P	100	-15.40(8.10)	46	-12.10(7.40)	7.29	-3.30 [-5.96, -0.64]	8
Davidson02 YOI A/L P	113	-8.68(7.23)	116	-9.20(7.22)	14.76	0.52 [-1.35, 2.39]	9
Total (95% CI)	634		587		100.00	-2.36 [-3.08, -1.64]	

Test for heterogeneity: Chi² = 26.93, df = 6 (P = 0.0001), I² = 77.7%
Test for overall effect: Z = 6.44 (P < 0.00001)

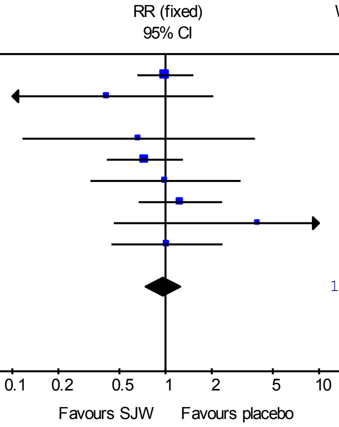


4

Review: Pharmacology: St John's wort
Comparison: 15 Tolerability against placebo
Outcome: 01 Leaving the study early

Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (fixed) 95% CI	Order
Davidson02 YOI A/L P	31/113	32/116	33.44	0.99 [0.65, 1.51]	0
Hansgen1996 Y M C P	2/53	5/55	5.20	0.42 [0.08, 2.05]	0
Kalb2001 Y O I P	0/37	0/35		Not estimable	0
Laakmann98 Y O I P	2/49	3/49	3.18	0.67 [0.12, 3.82]	0
Lecrubier02 Y O I P	18/186	25/189	26.26	0.73 [0.41, 1.30]	0
Philipp99 Y O I A P	9/106	4/47	5.87	1.00 [0.32, 3.08]	0
Shelton2001 Y O I P	18/98	15/102	15.57	1.25 [0.67, 2.34]	0
Volz2000 Y O I P	4/70	1/70	1.06	4.00 [0.46, 34.90]	0
Witte1995 Y O I P	9/48	9/49	9.43	1.02 [0.44, 2.35]	0
Total (95% CI)	760	712	100.00	0.96 [0.74, 1.25]	

Total events: 93 (St John's wort), 94 (Placebo)
Test for heterogeneity: Chi² = 4.50, df = 7 (P = 0.72), I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)

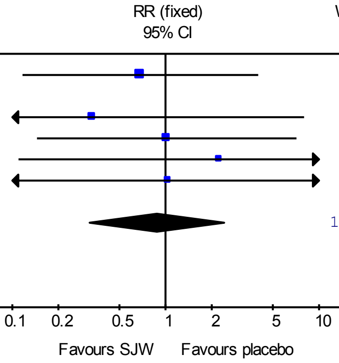


1

Review: Pharmacology: St John's wort
Comparison: 15 Tolerability against placebo
Outcome: 02 Leaving the study early due to side effects

Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (fixed) 95% CI	Order
Davidson02 YOI A/L P	2/113	3/116	36.48	0.68 [0.12, 4.02]	0
Kalb2001 Y O I P	0/37	0/35		Not estimable	0
Laakmann98 Y O I P	0/49	1/49	18.48	0.33 [0.01, 7.99]	0
Lecrubier02 Y O I P	2/186	2/189	24.45	1.02 [0.14, 7.14]	0
Philipp99 Y O I A P	2/106	0/47	8.51	2.24 [0.11, 45.83]	0
Shelton2001 Y O I P	1/98	1/102	12.08	1.04 [0.07, 16.41]	0
Total (95% CI)	589	538	100.00	0.88 [0.32, 2.41]	

Total events: 7 (St John's wort), 7 (Placebo)
Test for heterogeneity: Chi² = 0.84, df = 4 (P = 0.93), I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

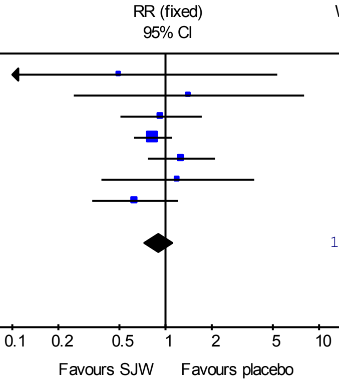


2

Review: Pharmacology: St John's wort
Comparison: 15 Tolerability against placebo
Outcome: 03 Patients reporting side effects

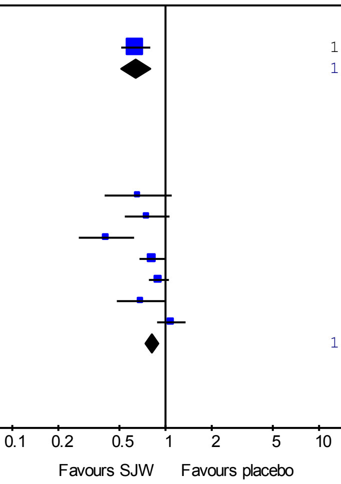
Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (fixed) 95% CI	Order
Hansgen1996 Y M C P	1/53	2/53	1.52	0.50 [0.05, 5.35]	0
Kalb2001 Y O I P	3/37	2/35	1.56	1.42 [0.25, 7.99]	0
Laakmann98 Y O I P	14/49	15/49	11.37	0.93 [0.51, 1.72]	0
Lecrubier02 Y O I P	57/186	70/189	52.65	0.83 [0.62, 1.10]	0
Philipp99 Y O I A P	40/106	14/47	14.71	1.27 [0.77, 2.09]	0
Schrader98 Y ? I P	6/81	5/81	3.79	1.20 [0.38, 3.78]	0
Volz2000 Y O I P	12/70	19/70	14.41	0.63 [0.33, 1.20]	0
Total (95% CI)	582	524	100.00	0.89 [0.72, 1.10]	

Total events: 133 (St John's wort), 127 (Placebo)
Test for heterogeneity: Chi² = 4.03, df = 6 (P = 0.67), I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)



3

Review: Pharmacology: St John's wort
Comparison: 16 Efficacy against placebo by severity
Outcome: 01 Number of people not achieving at least 50% reduction in depression score



Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (fixed) 95% CI	Order
01 Moderate depression					
Schrader98 Y ? I P	44/81	69/81	100.00	0.64 [0.51, 0.79]	1
Subtotal (95% CI)	81	81	100.00	0.64 [0.51, 0.79]	

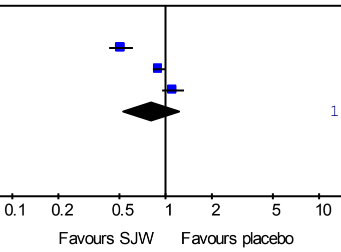
Total events: 44 (St John's wort), 69 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 4.02 (P < 0.0001)

Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (fixed) 95% CI	Order
02 Severe depression					
Kalb2001 Y O I P	14/37	20/35	5.34	0.66 [0.40, 1.09]	2
Laakmann98 Y O I P	25/49	33/49	8.57	0.76 [0.54, 1.06]	3
Hansgen1996 Y M C P	17/53	43/55	10.96	0.41 [0.27, 0.62]	4
Lecrubier02 Y O I P	88/186	109/189	28.08	0.82 [0.68, 1.00]	5
Shelton2001 Y O I P	72/98	83/102	21.13	0.90 [0.78, 1.05]	6
Philipp99 Y O I A P	39/106	25/47	9.00	0.69 [0.48, 1.00]	7
Davidson02 YOI A/L P	70/113	66/116	16.92	1.09 [0.88, 1.35]	8
Subtotal (95% CI)	642	593	100.00	0.81 [0.74, 0.89]	

Total events: 325 (St John's wort), 379 (Placebo)
Test for heterogeneity: Chi² = 20.94, df = 6 (P = 0.002), I² = 71.3%
Test for overall effect: Z = 4.22 (P < 0.0001)

1

Review: Pharmacology: St John's wort
Comparison: 16 Efficacy against placebo by severity
Outcome: 02 Number of people not achieving remission

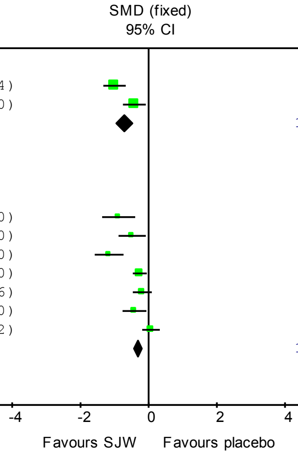


Study or sub-category	St John's wort n/N	Placebo n/N	Weight %	RR (random) 95% CI	Order
01 Severe depression					
Lecrubier02 Y O I P	80/186	159/189	32.75	0.51 [0.43, 0.61]	1
Shelton2001 Y O I P	84/98	97/102	34.20	0.90 [0.82, 0.99]	2
Davidson02 YOI A/L P	86/113	79/116	33.06	1.12 [0.95, 1.31]	3
Subtotal (95% CI)	397	407	100.00	0.80 [0.53, 1.22]	

Total events: 250 (St John's wort), 335 (Placebo)
Test for heterogeneity: Chi² = 52.99, df = 2 (P < 0.00001), I² = 96.2%
Test for overall effect: Z = 1.02 (P = 0.31)

2

Review: Pharmacology: St John's wort
Comparison: 16 Efficacy against placebo by severity
Outcome: 03 Mean endpoint scores



Study or sub-category	St John's wort N	St John's wort Mean (SD)	Placebo N	Placebo Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 Moderate depression							
Schrader98 Y ? I P	80	-9.60(9.93)	79	-0.77(7.44)	50.71	-1.00 [-1.33, -0.67]	1
Volz2000 Y O I P	70	12.00(5.10)	70	14.30(5.90)	49.29	-0.41 [-0.75, -0.08]	2
Subtotal (95% CI)	150		149		100.00	-0.71 [-0.95, -0.48]	

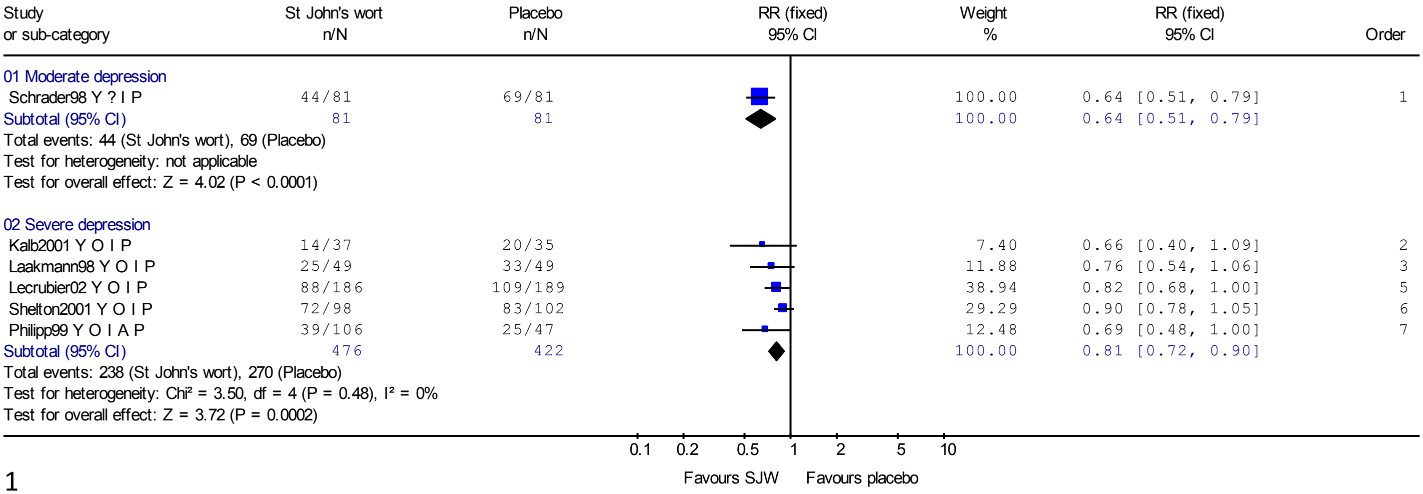
Test for heterogeneity: Chi² = 5.96, df = 1 (P = 0.01), I² = 83.2%
Test for overall effect: Z = 5.93 (P < 0.00001)

Study or sub-category	St John's wort N	St John's wort Mean (SD)	Placebo N	Placebo Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
02 Severe depression							
Kalb2001 Y O I P	37	-10.80(5.00)	35	-5.70(6.40)	5.58	-0.88 [-1.37, -0.40]	3
Laakmann98 Y O I P	49	-10.30(4.60)	49	-7.90(5.20)	8.13	-0.49 [-0.89, -0.08]	4
Hansgen1996 Y M C P	51	8.90(4.30)	50	14.40(5.10)	7.35	-1.16 [-1.58, -0.74]	5
Lecrubier02 Y O I P	186	-9.90(6.80)	189	-8.10(7.10)	31.79	-0.26 [-0.46, -0.06]	6
Shelton2001 Y O I P	98	15.06(6.93)	102	16.28(6.16)	17.02	-0.19 [-0.46, 0.09]	7
Philipp99 Y O I A P	100	-15.40(8.10)	46	-12.10(7.40)	10.57	-0.42 [-0.77, -0.06]	8
Davidson02 YOI A/L P	113	-8.68(7.23)	116	-9.20(7.22)	19.56	0.07 [-0.19, 0.33]	9
Subtotal (95% CI)	634		587		100.00	-0.32 [-0.43, -0.20]	

Test for heterogeneity: Chi² = 31.21, df = 6 (P < 0.0001), I² = 80.8%
Test for overall effect: Z = 5.43 (P < 0.00001)

3

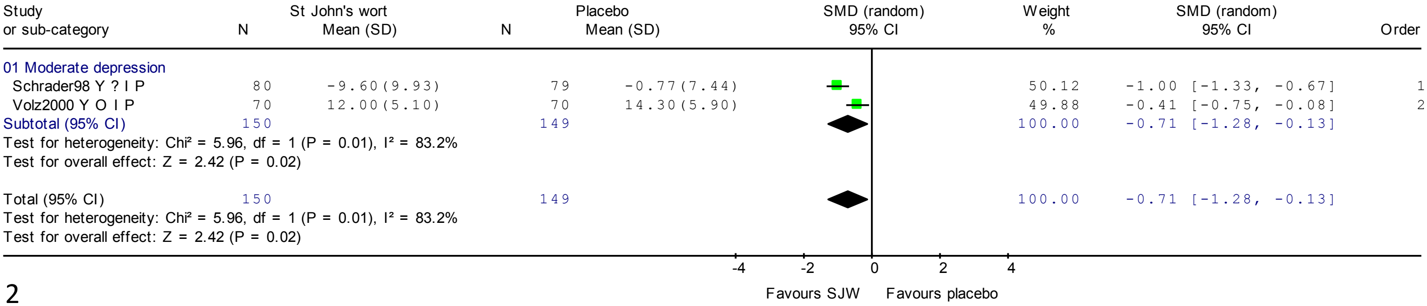
Review: Pharmacology: St John's wort
Comparison: 16 Efficacy against placebo by severity
Outcome: 04 Sensitivity analysis: Number of people not achieving at least 50% reduction in depression score



Study or sub-category	St John's wort n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Moderate depression						
Schrader98 Y ? I P	44/81	69/81		100.00	0.64 [0.51, 0.79]	1
Subtotal (95% CI)	81	81		100.00	0.64 [0.51, 0.79]	
Total events: 44 (St John's wort), 69 (Placebo)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 4.02 (P < 0.0001)						
02 Severe depression						
Kalb2001 Y O I P	14/37	20/35		7.40	0.66 [0.40, 1.09]	2
Laakmann98 Y O I P	25/49	33/49		11.88	0.76 [0.54, 1.06]	3
Lecrubier02 Y O I P	88/186	109/189		38.94	0.82 [0.68, 1.00]	5
Shelton2001 Y O I P	72/98	83/102		29.29	0.90 [0.78, 1.05]	6
Philipp99 Y O I A P	39/106	25/47		12.48	0.69 [0.48, 1.00]	7
Subtotal (95% CI)	476	422		100.00	0.81 [0.72, 0.90]	
Total events: 238 (St John's wort), 270 (Placebo)						
Test for heterogeneity: Chi² = 3.50, df = 4 (P = 0.48), I² = 0%						
Test for overall effect: Z = 3.72 (P = 0.0002)						

1

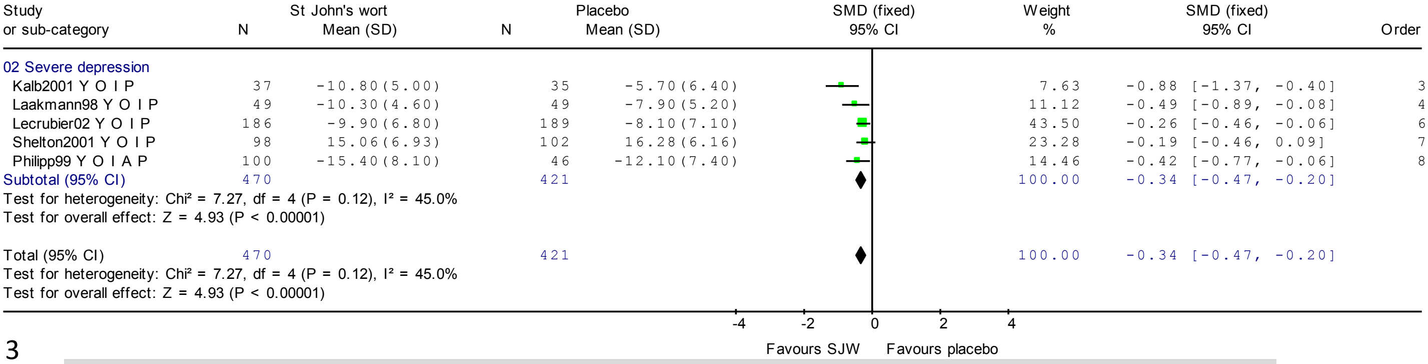
Review: Pharmacology: St John's wort
Comparison: 16 Efficacy against placebo by severity
Outcome: 05 Sensitivity analysis: Mean endpoint scores



Study or sub-category	St John's wort N	St John's wort Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Order
01 Moderate depression								
Schrader98 Y ? I P	80	-9.60(9.93)	79	-0.77(7.44)		50.12	-1.00 [-1.33, -0.67]	1
Volz2000 Y O I P	70	12.00(5.10)	70	14.30(5.90)		49.88	-0.41 [-0.75, -0.08]	2
Subtotal (95% CI)	150		149			100.00	-0.71 [-1.28, -0.13]	
Test for heterogeneity: Chi² = 5.96, df = 1 (P = 0.01), I² = 83.2%								
Test for overall effect: Z = 2.42 (P = 0.02)								
Total (95% CI)	150		149			100.00	-0.71 [-1.28, -0.13]	
Test for heterogeneity: Chi² = 5.96, df = 1 (P = 0.01), I² = 83.2%								
Test for overall effect: Z = 2.42 (P = 0.02)								

2

Review: Pharmacology: St John's wort
Comparison: 16 Efficacy against placebo by severity
Outcome: 06 Sensitivity analysis: Mean endpoint scores



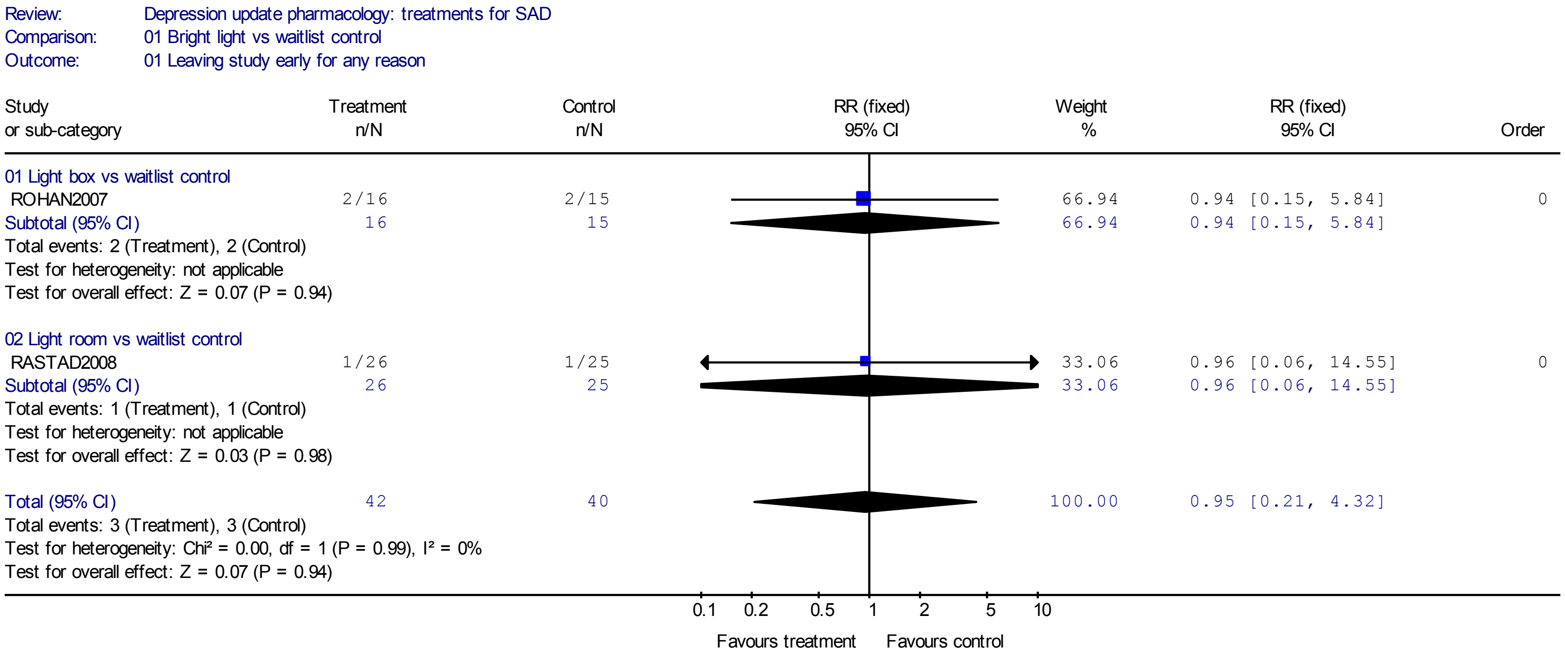
Study or sub-category	St John's wort N	St John's wort Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
02 Severe depression								
Kalb2001 Y O I P	37	-10.80(5.00)	35	-5.70(6.40)		7.63	-0.88 [-1.37, -0.40]	3
Laakmann98 Y O I P	49	-10.30(4.60)	49	-7.90(5.20)		11.12	-0.49 [-0.89, -0.08]	4
Lecrubier02 Y O I P	186	-9.90(6.80)	189	-8.10(7.10)		43.50	-0.26 [-0.46, -0.06]	6
Shelton2001 Y O I P	98	15.06(6.93)	102	16.28(6.16)		23.28	-0.19 [-0.46, 0.09]	7
Philipp99 Y O I A P	100	-15.40(8.10)	46	-12.10(7.40)		14.46	-0.42 [-0.77, -0.06]	8
Subtotal (95% CI)	470		421			100.00	-0.34 [-0.47, -0.20]	
Test for heterogeneity: Chi² = 7.27, df = 4 (P = 0.12), I² = 45.0%								
Test for overall effect: Z = 4.93 (P < 0.00001)								
Total (95% CI)	470		421			100.00	-0.34 [-0.47, -0.20]	
Test for heterogeneity: Chi² = 7.27, df = 4 (P = 0.12), I² = 45.0%								
Test for overall effect: Z = 4.93 (P < 0.00001)								

3
4

Treatments for SAD

bright light versus waitlist control

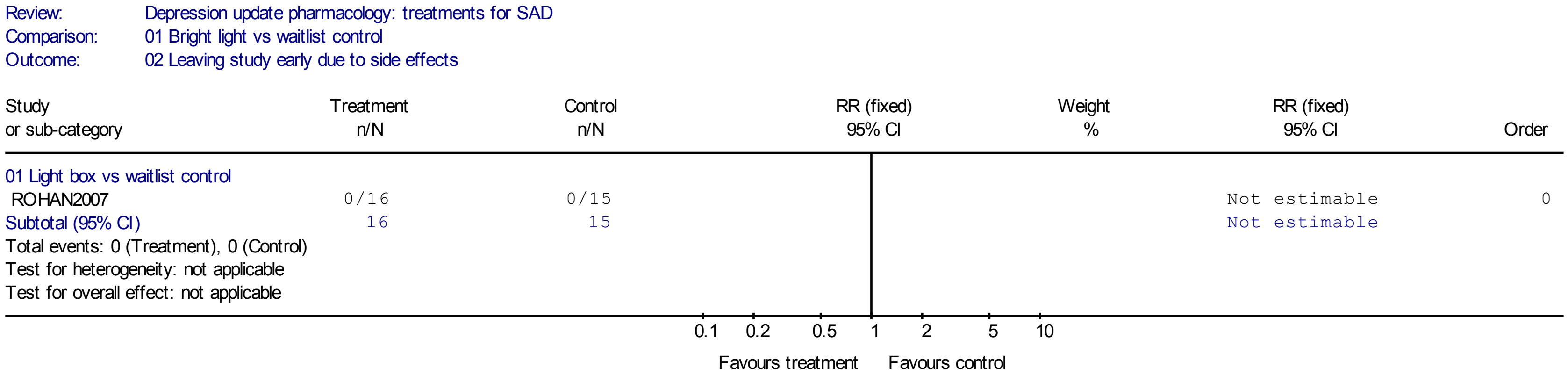
Number leaving the study early for any reason



Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 Light box vs waitlist control					
ROHAN2007	2/16	2/15	66.94	0.94 [0.15, 5.84]	0
Subtotal (95% CI)	16	15	66.94	0.94 [0.15, 5.84]	
Total events: 2 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.07 (P = 0.94)					
02 Light room vs waitlist control					
RASTAD2008	1/26	1/25	33.06	0.96 [0.06, 14.55]	0
Subtotal (95% CI)	26	25	33.06	0.96 [0.06, 14.55]	
Total events: 1 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)	42	40	100.00	0.95 [0.21, 4.32]	
Total events: 3 (Treatment), 3 (Control)					
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%					
Test for overall effect: Z = 0.07 (P = 0.94)					

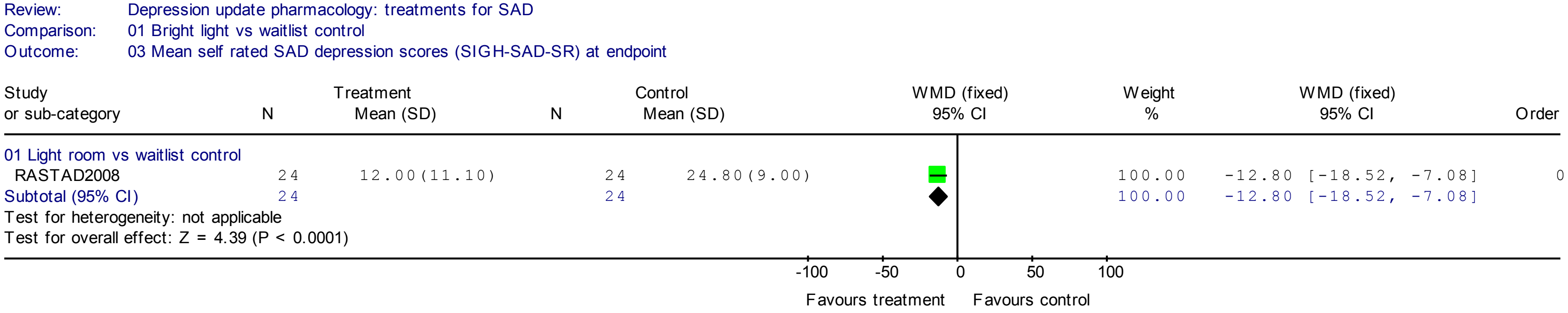
Number leaving the study early due to side effects



Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 02 Leaving study early due to side effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light box vs waitlist control						
ROHAN2007	0/16	0/15			Not estimable	0
Subtotal (95% CI)	16	15			Not estimable	
Total events: 0 (Treatment), 0 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: not applicable						

Mean endpoint SAD depression scores (SIGH-SAD-SR) (self-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 03 Mean self rated SAD depression scores (SIGH-SAD-SR) at endpoint

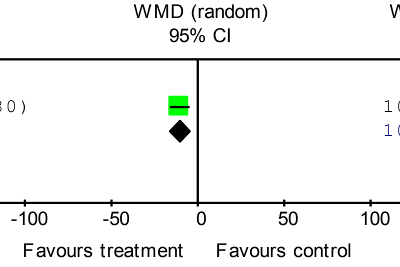
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
01 Light room vs waitlist control								
RASTAD2008	24	12.00(11.10)	24	24.80(9.00)		100.00	-12.80 [-18.52, -7.08]	0
Subtotal (95% CI)	24		24			100.00	-12.80 [-18.52, -7.08]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 4.39 (P < 0.0001)								

Mean endpoint SAD depression scores (SIGH-SAD) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 04 Mean clinician rated SAD depression scores (SIGH-SAD) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI	Order
01 Light box vs waitlist control							
ROHAN2007	16	12.70(6.90)	15	23.10(8.80)	100.00	-10.40 [-15.99, -4.81]	0
Subtotal (95% CI)	16		15		100.00	-10.40 [-15.99, -4.81]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 3.65 (P = 0.0003)

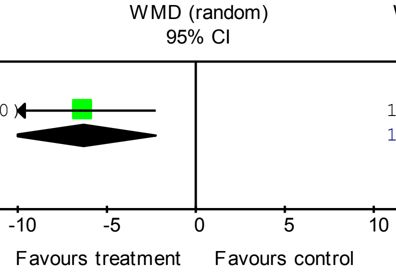


Mean endpoint depression scores (HRSD-21) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 05 Mean clinician rated typical depression scores (HRSD-21) at endpoint

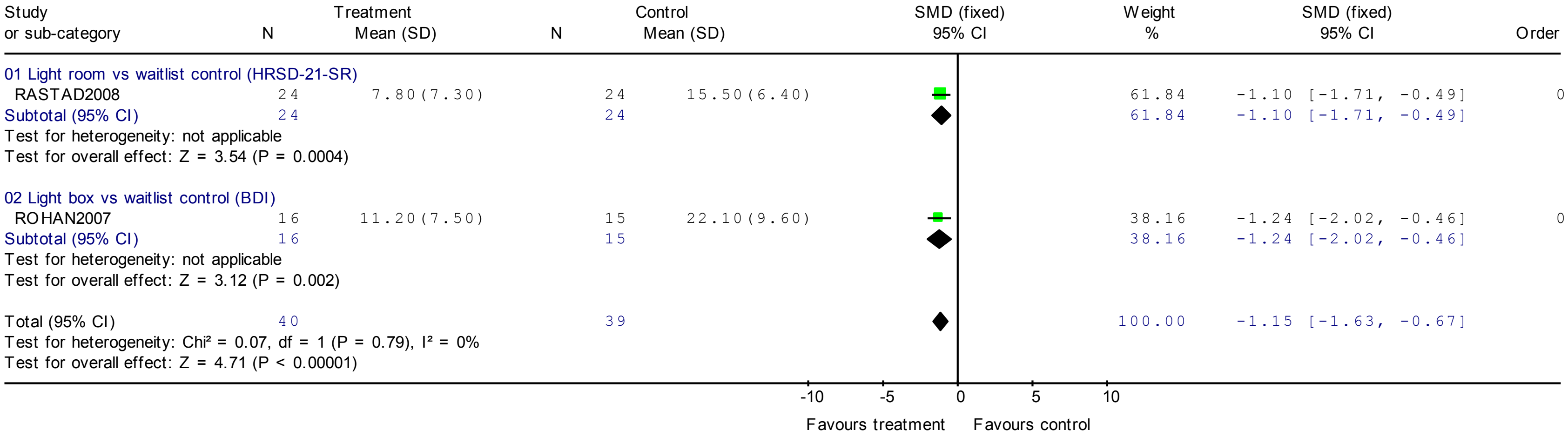
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI	Order
01 Light box vs waitlist control							
ROHAN2007	16	7.60(4.80)	15	13.90(6.50)	100.00	-6.30 [-10.34, -2.26]	0
Subtotal (95% CI)	16		15		100.00	-6.30 [-10.34, -2.26]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 3.05 (P = 0.002)



SAD.01.06. Mean depression scores at endpoint (self-rated)

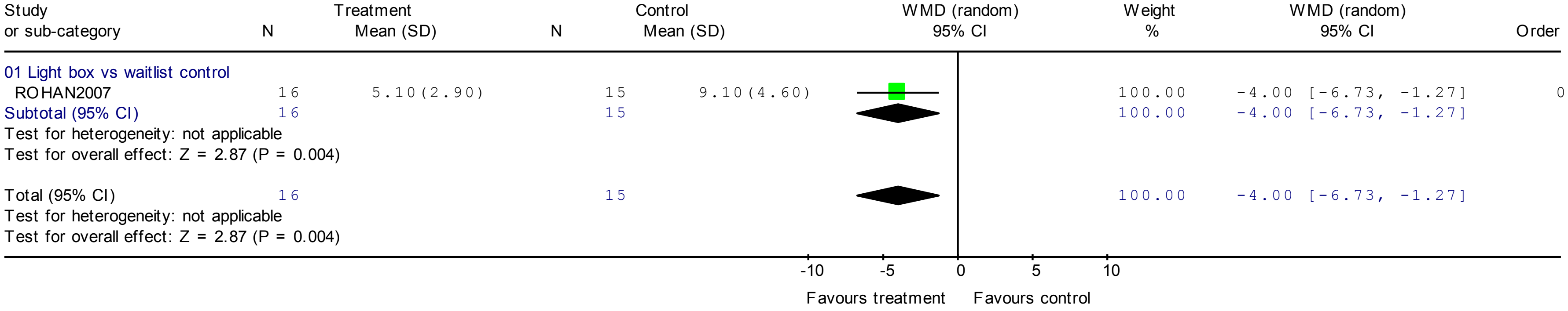
Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 06 Mean self rated depression scores at endpoint



Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
01 Light room vs waitlist control (HRSD-21-SR)								
RASTAD2008	24	7.80(7.30)	24	15.50(6.40)		61.84	-1.10 [-1.71, -0.49]	0
Subtotal (95% CI)	24		24			61.84	-1.10 [-1.71, -0.49]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 3.54 (P = 0.0004)								
02 Light box vs waitlist control (BDI)								
ROHAN2007	16	11.20(7.50)	15	22.10(9.60)		38.16	-1.24 [-2.02, -0.46]	0
Subtotal (95% CI)	16		15			38.16	-1.24 [-2.02, -0.46]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 3.12 (P = 0.002)								
Total (95% CI)	40		39			100.00	-1.15 [-1.63, -0.67]	
Test for heterogeneity: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%								
Test for overall effect: Z = 4.71 (P < 0.00001)								

SAD.01.07. Mean endpoint atypical depression scores (SAD subscale) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 07 Mean clinician rated atypical depression scores (SADsubscale) at endpoint

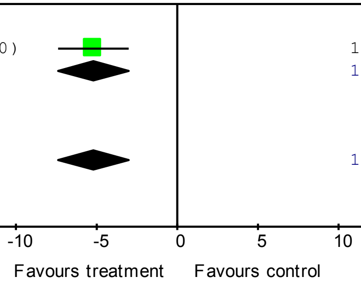


Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Order
01 Light box vs waitlist control								
ROHAN2007	16	5.10(2.90)	15	9.10(4.60)		100.00	-4.00 [-6.73, -1.27]	0
Subtotal (95% CI)	16		15			100.00	-4.00 [-6.73, -1.27]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 2.87 (P = 0.004)								
Total (95% CI)	16		15			100.00	-4.00 [-6.73, -1.27]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 2.87 (P = 0.004)								

Mean endpoint atypical depression scores (SAD-SR subscale) (self-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 08 Mean self rated atypical depression scores (SAD-SR subscale) at endpoint

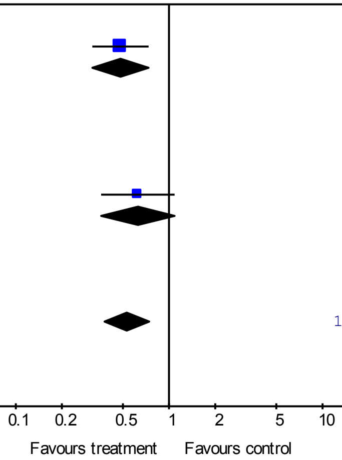
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
01 Light room vs waitlist control								
RASTAD2008	24	4.20(4.20)	24	9.40(3.50)		100.00	-5.20 [-7.39, -3.01]	0
Subtotal (95% CI)	24		24			100.00	-5.20 [-7.39, -3.01]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 4.66 (P < 0.00001)								
Total (95% CI)	24		24			100.00	-5.20 [-7.39, -3.01]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 4.66 (P < 0.00001)								



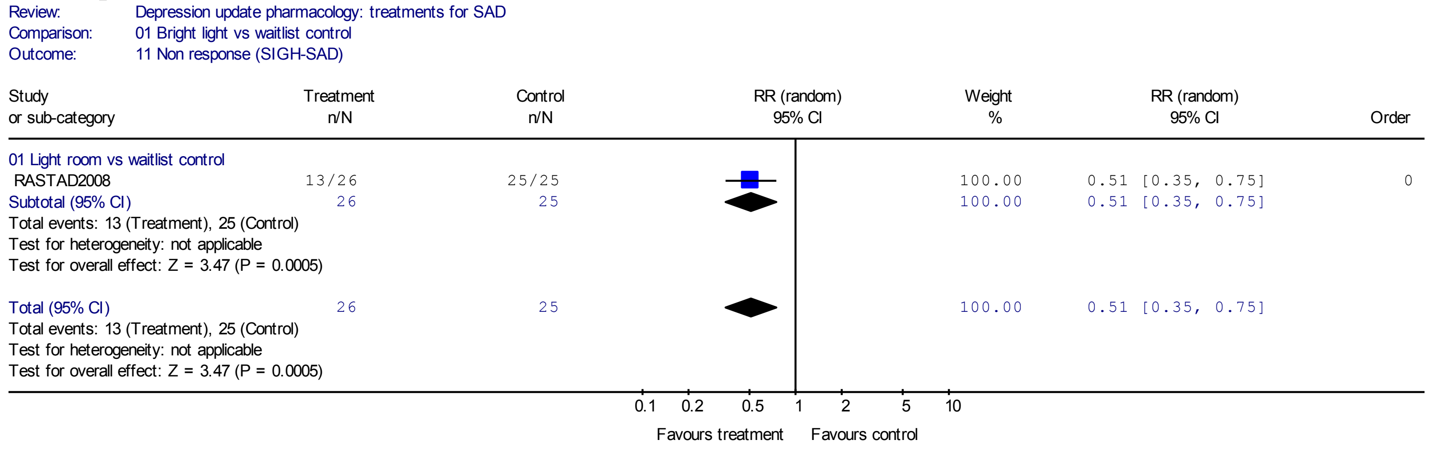
Non-response data (SIGH-SAD)

Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 10 Non remission (SIGH-SAD-SR)

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light room vs waitlist control						
RASTAD2008	12/26	24/25		66.39	0.48 [0.32, 0.73]	0
Subtotal (95% CI)	26	25		66.39	0.48 [0.32, 0.73]	
Total events: 12 (Treatment), 24 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 3.39 (P = 0.0007)						
02 Light box vs waitlist control						
ROHAN2007	8/16	12/15		33.61	0.63 [0.36, 1.08]	0
Subtotal (95% CI)	16	15		33.61	0.63 [0.36, 1.08]	
Total events: 8 (Treatment), 12 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.67 (P = 0.09)						
Total (95% CI)	42	40		100.00	0.53 [0.38, 0.74]	
Total events: 20 (Treatment), 36 (Control)						
Test for heterogeneity: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%						
Test for overall effect: Z = 3.72 (P = 0.0002)						



Non-response data (SIGN-SAD)

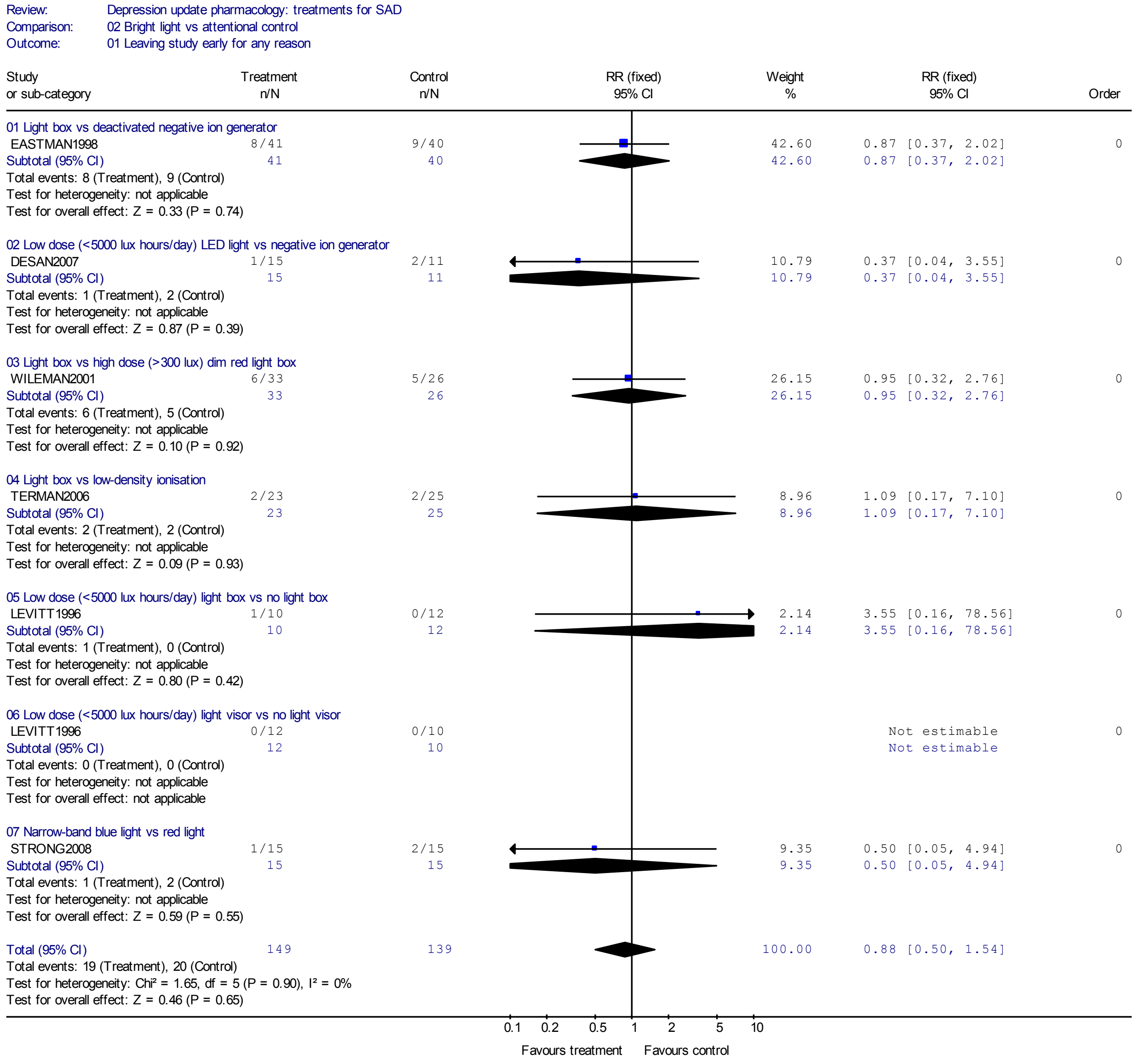


Review: Depression update pharmacology: treatments for SAD
Comparison: 01 Bright light vs waitlist control
Outcome: 11 Non response (SIGH-SAD)

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (random) 95% CI	Order
01 Light room vs waitlist control					
RASTAD2008	13/26	25/25	100.00	0.51 [0.35, 0.75]	0
Subtotal (95% CI)	26	25	100.00	0.51 [0.35, 0.75]	
Total events: 13 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 3.47 (P = 0.0005)					
Total (95% CI)	26	25	100.00	0.51 [0.35, 0.75]	
Total events: 13 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 3.47 (P = 0.0005)					

Bright light versus attentional control

Number leaving study early for any reason



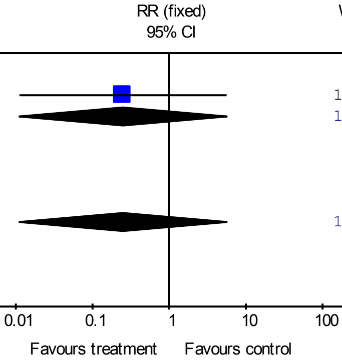
Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light box vs deactivated negative ion generator						
EASTMAN1998	8/41	9/40		42.60	0.87 [0.37, 2.02]	0
Subtotal (95% CI)	41	40		42.60	0.87 [0.37, 2.02]	
Total events: 8 (Treatment), 9 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.33 (P = 0.74)						
02 Low dose (<5000 lux hours/day) LED light vs negative ion generator						
DESAN2007	1/15	2/11		10.79	0.37 [0.04, 3.55]	0
Subtotal (95% CI)	15	11		10.79	0.37 [0.04, 3.55]	
Total events: 1 (Treatment), 2 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.87 (P = 0.39)						
03 Light box vs high dose (>300 lux) dim red light box						
WILEMAN2001	6/33	5/26		26.15	0.95 [0.32, 2.76]	0
Subtotal (95% CI)	33	26		26.15	0.95 [0.32, 2.76]	
Total events: 6 (Treatment), 5 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.10 (P = 0.92)						
04 Light box vs low-density ionisation						
TERMAN2006	2/23	2/25		8.96	1.09 [0.17, 7.10]	0
Subtotal (95% CI)	23	25		8.96	1.09 [0.17, 7.10]	
Total events: 2 (Treatment), 2 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.09 (P = 0.93)						
05 Low dose (<5000 lux hours/day) light box vs no light box						
LEVITT1996	1/10	0/12		2.14	3.55 [0.16, 78.56]	0
Subtotal (95% CI)	10	12		2.14	3.55 [0.16, 78.56]	
Total events: 1 (Treatment), 0 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.80 (P = 0.42)						
06 Low dose (<5000 lux hours/day) light visor vs no light visor						
LEVITT1996	0/12	0/10			Not estimable	0
Subtotal (95% CI)	12	10			Not estimable	
Total events: 0 (Treatment), 0 (Control) Test for heterogeneity: not applicable Test for overall effect: not applicable						
07 Narrow-band blue light vs red light						
STRONG2008	1/15	2/15		9.35	0.50 [0.05, 4.94]	0
Subtotal (95% CI)	15	15		9.35	0.50 [0.05, 4.94]	
Total events: 1 (Treatment), 2 (Control) Test for heterogeneity: not applicable Test for overall effect: Z = 0.59 (P = 0.55)						
Total (95% CI)	149	139		100.00	0.88 [0.50, 1.54]	
Total events: 19 (Treatment), 20 (Control) Test for heterogeneity: Chi² = 1.65, df = 5 (P = 0.90), I² = 0% Test for overall effect: Z = 0.46 (P = 0.65)						

Number leaving study early due to lack of efficacy

Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 02 Leaving study early due to lack of efficacy

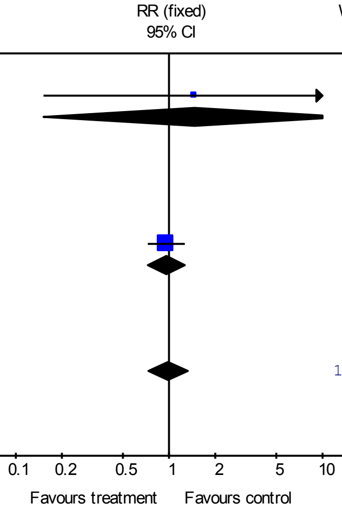
Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 Low dose (<5000 lux hours/day) LED light vs negative ion generator					
DESAN2007	0/15	1/11	100.00	0.25 [0.01, 5.62]	0
Subtotal (95% CI)	15	11	100.00	0.25 [0.01, 5.62]	
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					
Total (95% CI)	15	11	100.00	0.25 [0.01, 5.62]	
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					



Number of reported side effects

Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 03 Reported side effects

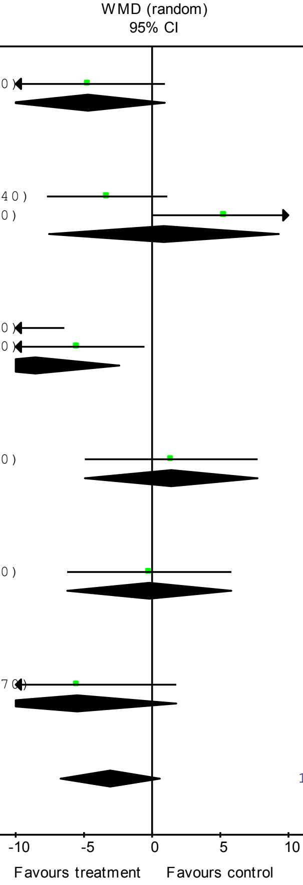
Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 Low dose (<5000 lux hours/day) LED light vs negative ion generator					
DESAN2007	2/15	1/11	5.02	1.47 [0.15, 14.21]	0
Subtotal (95% CI)	15	11	5.02	1.47 [0.15, 14.21]	
Total events: 2 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
02 Light visor vs dim light visor					
ROSENTHAL1993	23/30	20/25	94.98	0.96 [0.73, 1.27]	0
Subtotal (95% CI)	30	25	94.98	0.96 [0.73, 1.27]	
Total events: 23 (Treatment), 20 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
Total (95% CI)	45	36	100.00	0.98 [0.73, 1.32]	
Total events: 25 (Treatment), 21 (Control)					
Test for heterogeneity: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%					
Test for overall effect: Z = 0.11 (P = 0.91)					



Mean endpoint depression scores (SIGH-SAD) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 04 Mean clinician rated SAD depression scores (SIGH-SAD) at endpoint

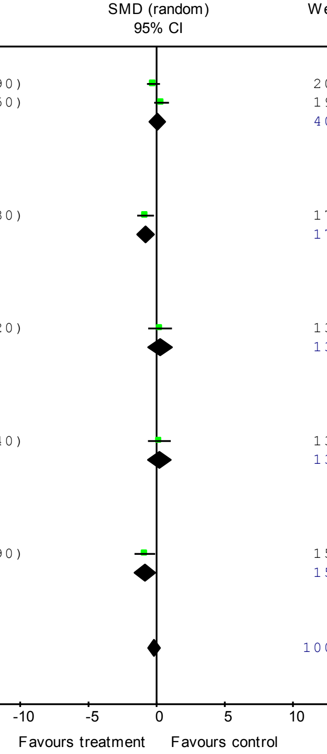
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI	Order
01 Low dose (<5000 lux hours/day) LED light vs negative ion generator							
DESAN2007	14	8.70(8.40)	9	13.40(5.40)	12.52	-4.70 [-10.34, 0.94]	0
Subtotal (95% CI)	14		9		12.52	-4.70 [-10.34, 0.94]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							
02 Light visor vs dim light visor							
JOFFE1993	34	13.10(7.80)	33	16.40(10.40)	14.16	-3.30 [-7.71, 1.11]	0
ROSENTHAL1993	30	19.50(11.40)	25	14.20(8.80)	12.91	5.30 [-0.04, 10.64]	0
Subtotal (95% CI)	64		58		27.08	0.86 [-7.56, 9.29]	
Test for heterogeneity: Chi² = 5.92, df = 1 (P = 0.01), I² = 83.1%							
Test for overall effect: Z = 0.20 (P = 0.84)							
03 Light box vs low-density ionisation							
TERMAN1998	19	10.50(7.60)	19	22.30(9.20)	12.88	-11.80 [-17.17, -6.43]	0
TERMAN2006	21	10.50(7.90)	23	16.00(8.80)	13.46	-5.50 [-10.43, -0.57]	0
Subtotal (95% CI)	40		42		26.34	-8.56 [-14.73, -2.39]	
Test for heterogeneity: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.1%							
Test for overall effect: Z = 2.72 (P = 0.007)							
04 Low dose (<5000 lux hours/day) light box vs no light box							
LEVITT1996	9	14.00(7.70)	12	12.60(6.80)	11.61	1.40 [-4.93, 7.73]	0
Subtotal (95% CI)	9		12		11.61	1.40 [-4.93, 7.73]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.43 (P = 0.66)							
05 Low dose (<5000 lux hours/day) light visor vs no light visor							
LEVITT1996	12	11.30(8.20)	10	11.50(6.20)	12.01	-0.20 [-6.22, 5.82]	0
Subtotal (95% CI)	12		10		12.01	-0.20 [-6.22, 5.82]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.07 (P = 0.95)							
06 Narrow-band blue light vs red light							
STRONG2008	15	-15.70(9.60)	15	-10.20(10.70)	10.44	-5.50 [-12.77, 1.77]	0
Subtotal (95% CI)	15		15		10.44	-5.50 [-12.77, 1.77]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.48 (P = 0.14)							
Total (95% CI)	154		146		100.00	-3.07 [-6.71, 0.58]	
Test for heterogeneity: Chi² = 24.06, df = 7 (P = 0.001), I² = 70.9%							
Test for overall effect: Z = 1.65 (P = 0.10)							



Mean endpoint typical depression scores (HAM-D17/HRSD-21) (clinician-rated)

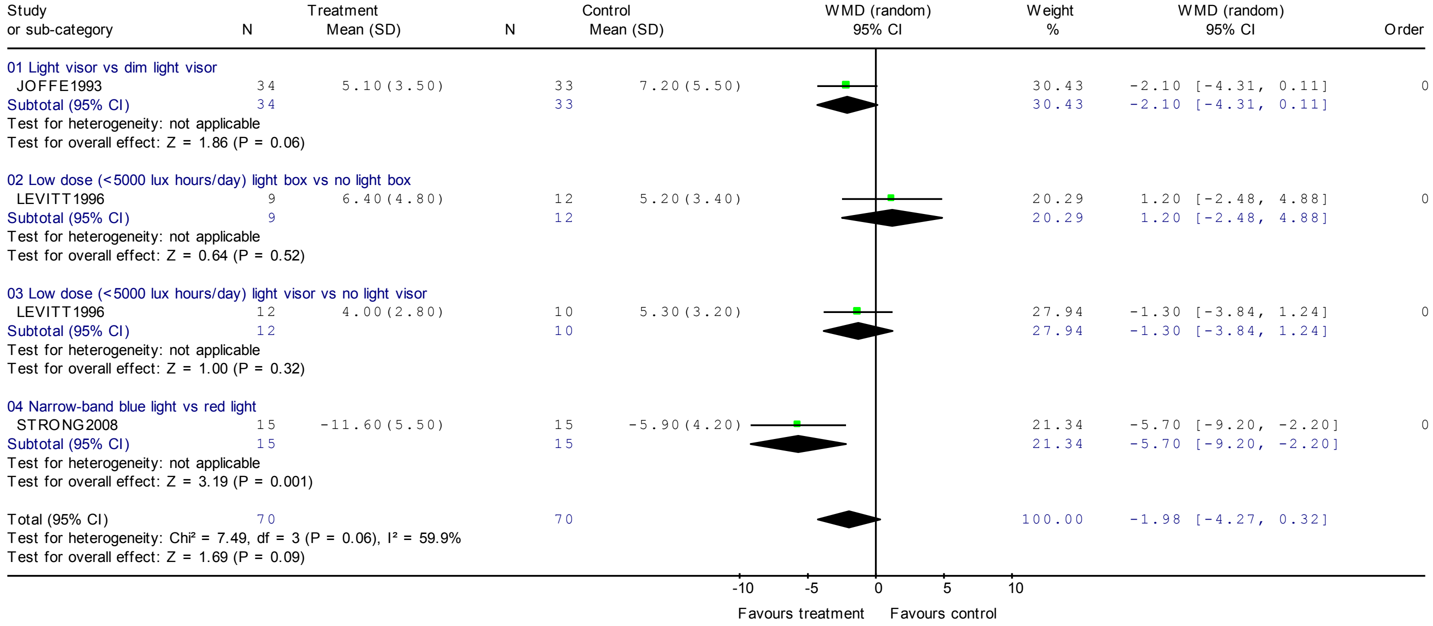
Review:	Depression update pharmacology: treatments for SAD
Comparison:	02 Bright light vs attentional control
Outcome:	05 Mean clinician rated typical depression scores (HAMD-17/HRSD-21) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	SMD (random) 95% CI	Order
01 Light visor vs dim light visor							
JOFFE1993	34	7.90(5.30)	33	9.20(5.90)	20.83	-0.23 [-0.71, 0.25]	0
ROSENTHAL1993	30	11.00(5.90)	25	8.90(5.50)	19.60	0.36 [-0.17, 0.90]	0
Subtotal (95% CI)	64		58		40.44	0.05 [-0.52, 0.63]	
Test for heterogeneity: Chi² = 2.59, df = 1 (P = 0.11), I² = 61.4%							
Test for overall effect: Z = 0.18 (P = 0.85)							
02 Light box vs low-density ionisation							
TERMAN2006	21	5.50(4.60)	23	9.60(5.30)	17.81	-0.81 [-1.43, -0.19]	0
Subtotal (95% CI)	21		23		17.81	-0.81 [-1.43, -0.19]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 2.57 (P = 0.01)							
03 Low dose (<5000 lux hours/day) light box vs no light box							
LEVITT1996	9	7.60(4.00)	12	6.50(4.20)	13.10	0.26 [-0.61, 1.13]	0
Subtotal (95% CI)	9		12		13.10	0.26 [-0.61, 1.13]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
04 Low dose (<5000 lux hours/day) light visor vs no light visor							
LEVITT1996	12	7.30(5.80)	10	6.20(4.40)	13.54	0.20 [-0.64, 1.04]	0
Subtotal (95% CI)	12		10		13.54	0.20 [-0.64, 1.04]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							
05 Narrow-band blue light vs red light							
STRONG2008	15	-10.10(5.30)	15	-6.00(3.90)	15.11	-0.86 [-1.61, -0.10]	0
Subtotal (95% CI)	15		15		15.11	-0.86 [-1.61, -0.10]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 2.23 (P = 0.03)							
Total (95% CI)	121		118		100.00	-0.19 [-0.62, 0.24]	
Test for heterogeneity: Chi² = 12.83, df = 5 (P = 0.03), I² = 61.0%							
Test for overall effect: Z = 0.86 (P = 0.39)							



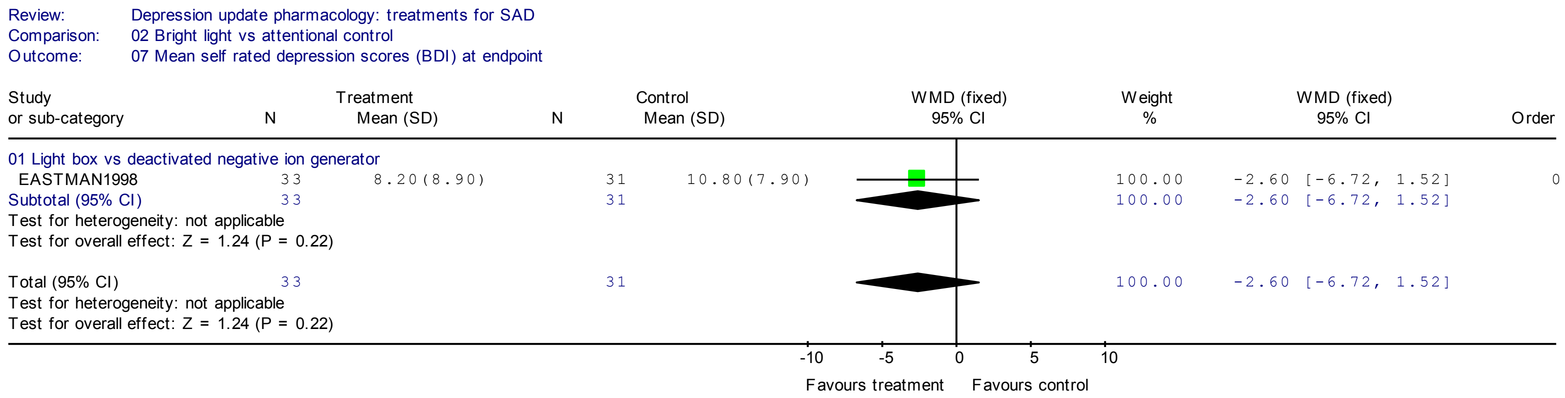
Mean endpoint atypical depression scores (SAD subscale) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 06 Mean clinician rated atypical depression scores (SAD subscale) at endpoint



Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI	Order
01 Light visor vs dim light visor							
JOFFE1993	34	5.10(3.50)	33	7.20(5.50)	30.43	-2.10 [-4.31, 0.11]	0
Subtotal (95% CI)	34		33		30.43	-2.10 [-4.31, 0.11]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.86 (P = 0.06)							
02 Low dose (<5000 lux hours/day) light box vs no light box							
LEVITT1996	9	6.40(4.80)	12	5.20(3.40)	20.29	1.20 [-2.48, 4.88]	0
Subtotal (95% CI)	9		12		20.29	1.20 [-2.48, 4.88]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
03 Low dose (<5000 lux hours/day) light visor vs no light visor							
LEVITT1996	12	4.00(2.80)	10	5.30(3.20)	27.94	-1.30 [-3.84, 1.24]	0
Subtotal (95% CI)	12		10		27.94	-1.30 [-3.84, 1.24]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.00 (P = 0.32)							
04 Narrow-band blue light vs red light							
STRONG2008	15	-11.60(5.50)	15	-5.90(4.20)	21.34	-5.70 [-9.20, -2.20]	0
Subtotal (95% CI)	15		15		21.34	-5.70 [-9.20, -2.20]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 3.19 (P = 0.001)							
Total (95% CI)	70		70		100.00	-1.98 [-4.27, 0.32]	
Test for heterogeneity: Chi² = 7.49, df = 3 (P = 0.06), I² = 59.9%							
Test for overall effect: Z = 1.69 (P = 0.09)							

Mean endpoint depression scores (BDI) (self-rated)



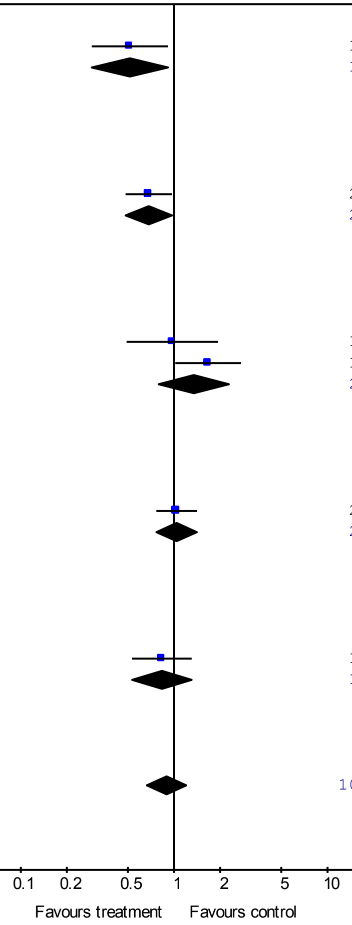
Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 07 Mean self rated depression scores (BDI) at endpoint

Study or sub-category	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
01 Light box vs deactivated negative ion generator								
EASTMAN1998	33	8.20(8.90)	31	10.80(7.90)		100.00	-2.60 [-6.72, 1.52]	0
Subtotal (95% CI)	33		31			100.00	-2.60 [-6.72, 1.52]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 1.24 (P = 0.22)								
Total (95% CI)	33		31			100.00	-2.60 [-6.72, 1.52]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 1.24 (P = 0.22)								

Non-remission data (SIGH-SAD, SIGH-SAD-SR or HDRS)

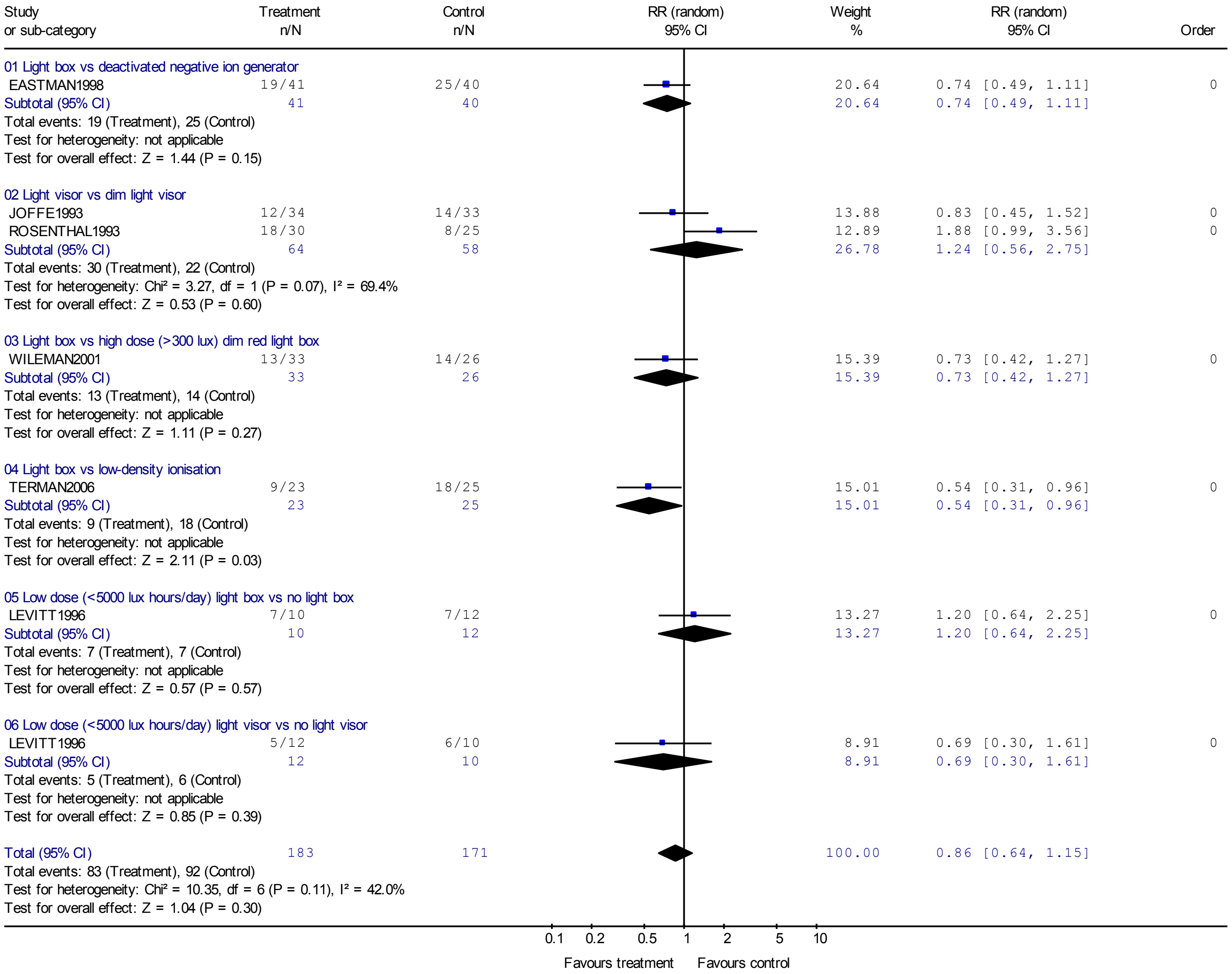
Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 08 Non remission (SIGHSAD or SIGHSAD-SR or HDRS)

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
01 Low dose (<5000 lux hours/day) LED light vs negative ion generator						
DESAN2007	7/15	10/11		13.73	0.51 [0.29, 0.91]	0
Subtotal (95% CI)	15	11		13.73	0.51 [0.29, 0.91]	
Total events: 7 (Treatment), 10 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						
02 Light box vs deactivated negative ion generator						
EASTMAN1998	21/41	30/40		20.28	0.68 [0.48, 0.97]	0
Subtotal (95% CI)	41	40		20.28	0.68 [0.48, 0.97]	
Total events: 21 (Treatment), 30 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 2.15 (P = 0.03)						
03 Light visor vs dim light visor						
JOFFE1993	11/34	11/33		11.24	0.97 [0.49, 1.93]	0
ROSENTHAL1993	22/30	11/25		15.85	1.67 [1.02, 2.73]	0
Subtotal (95% CI)	64	58		27.09	1.34 [0.79, 2.27]	
Total events: 33 (Treatment), 22 (Control)						
Test for heterogeneity: Chi² = 1.62, df = 1 (P = 0.20), I² = 38.2%						
Test for overall effect: Z = 1.09 (P = 0.27)						
04 Light box vs high dose (>300 lux) dim red light box						
WILEMAN2001	25/33	19/26		21.77	1.04 [0.77, 1.40]	0
Subtotal (95% CI)	33	26		21.77	1.04 [0.77, 1.40]	
Total events: 25 (Treatment), 19 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
05 Light box vs low-density ionisation						
TERMAN2006	13/23	17/25		17.13	0.83 [0.53, 1.30]	0
Subtotal (95% CI)	23	25		17.13	0.83 [0.53, 1.30]	
Total events: 13 (Treatment), 17 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)	176	160		100.00	0.89 [0.66, 1.20]	
Total events: 99 (Treatment), 98 (Control)						
Test for heterogeneity: Chi² = 13.16, df = 5 (P = 0.02), I² = 62.0%						
Test for overall effect: Z = 0.76 (P = 0.45)						



Non-response data (SIGH-SAD)

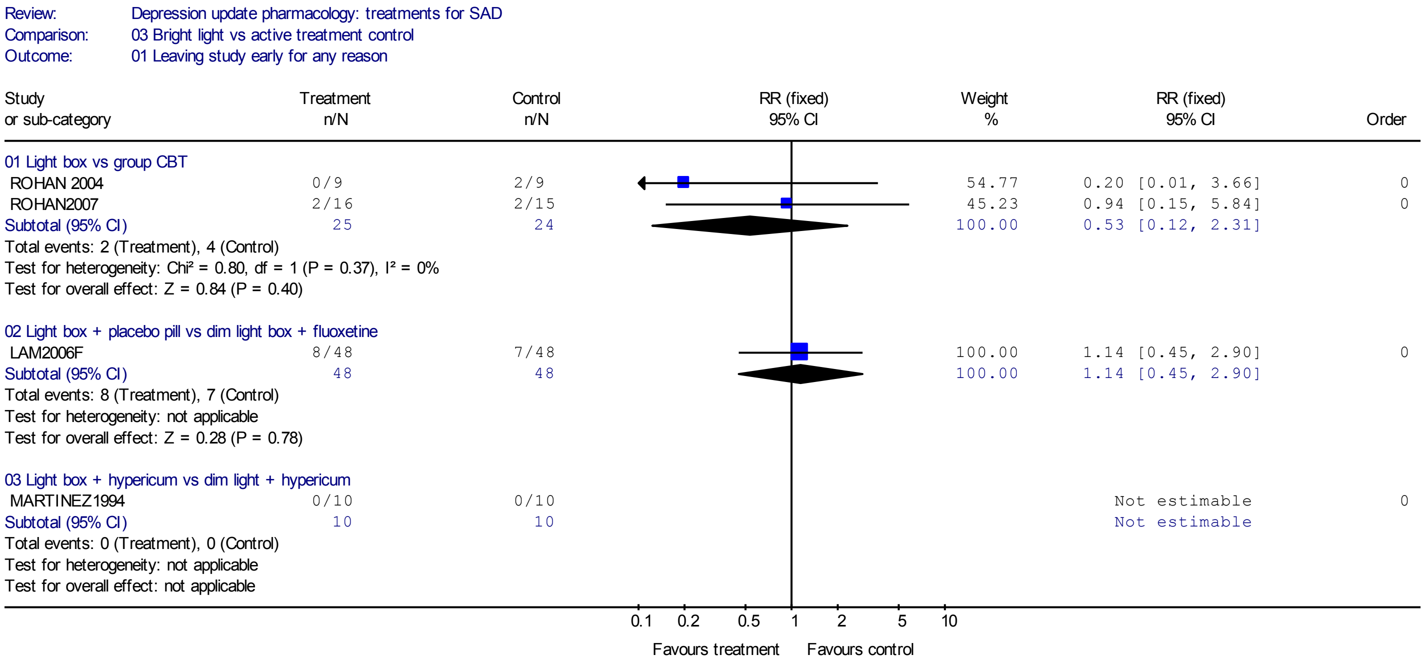
Review: Depression update pharmacology: treatments for SAD
Comparison: 02 Bright light vs attentional control
Outcome: 09 Non response (SIGH-SAD)



Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (random) 95% CI	Order
01 Light box vs deactivated negative ion generator					
EASTMAN1998	19/41	25/40	20.64	0.74 [0.49, 1.11]	0
Subtotal (95% CI)	41	40	20.64	0.74 [0.49, 1.11]	
Total events: 19 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
02 Light visor vs dim light visor					
JOFFE1993	12/34	14/33	13.88	0.83 [0.45, 1.52]	0
ROSENTHAL1993	18/30	8/25	12.89	1.88 [0.99, 3.56]	0
Subtotal (95% CI)	64	58	26.78	1.24 [0.56, 2.75]	
Total events: 30 (Treatment), 22 (Control)					
Test for heterogeneity: Chi² = 3.27, df = 1 (P = 0.07), I² = 69.4%					
Test for overall effect: Z = 0.53 (P = 0.60)					
03 Light box vs high dose (>300 lux) dim red light box					
WILEMAN2001	13/33	14/26	15.39	0.73 [0.42, 1.27]	0
Subtotal (95% CI)	33	26	15.39	0.73 [0.42, 1.27]	
Total events: 13 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
04 Light box vs low-density ionisation					
TERMAN2006	9/23	18/25	15.01	0.54 [0.31, 0.96]	0
Subtotal (95% CI)	23	25	15.01	0.54 [0.31, 0.96]	
Total events: 9 (Treatment), 18 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.11 (P = 0.03)					
05 Low dose (<5000 lux hours/day) light box vs no light box					
LEVITT1996	7/10	7/12	13.27	1.20 [0.64, 2.25]	0
Subtotal (95% CI)	10	12	13.27	1.20 [0.64, 2.25]	
Total events: 7 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
06 Low dose (<5000 lux hours/day) light visor vs no light visor					
LEVITT1996	5/12	6/10	8.91	0.69 [0.30, 1.61]	0
Subtotal (95% CI)	12	10	8.91	0.69 [0.30, 1.61]	
Total events: 5 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
Total (95% CI)	183	171	100.00	0.86 [0.64, 1.15]	
Total events: 83 (Treatment), 92 (Control)					
Test for heterogeneity: Chi² = 10.35, df = 6 (P = 0.11), I² = 42.0%					
Test for overall effect: Z = 1.04 (P = 0.30)					

Bright light versus active treatment control

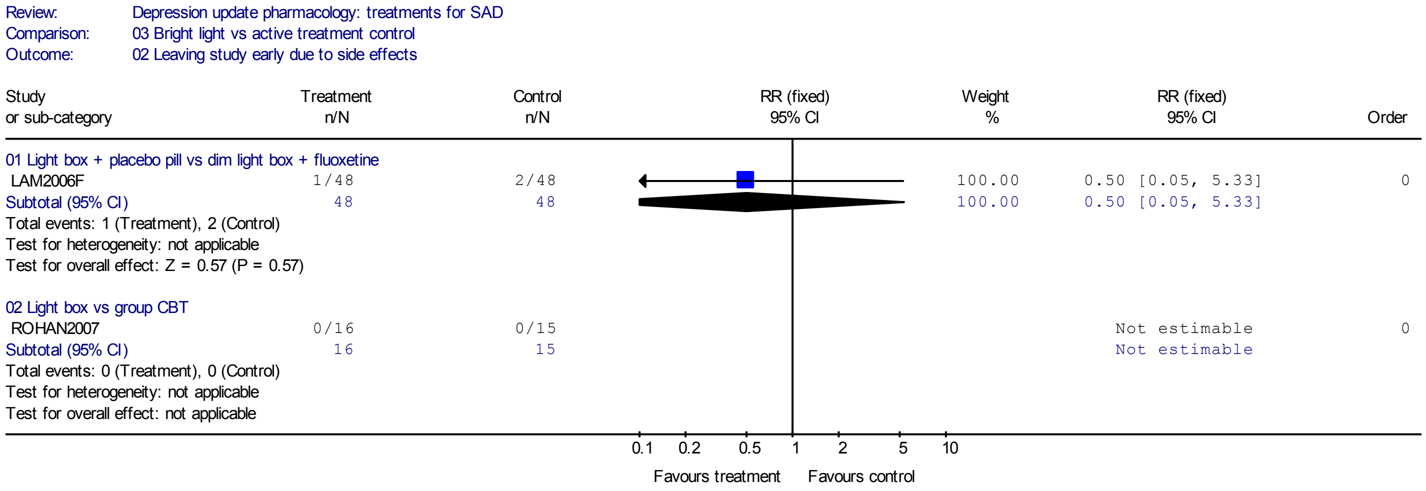
Number leaving study early for any reason



Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light box vs group CBT						
ROHAN 2004	0/9	2/9		54.77	0.20 [0.01, 3.66]	0
ROHAN2007	2/16	2/15		45.23	0.94 [0.15, 5.84]	0
Subtotal (95% CI)	25	24		100.00	0.53 [0.12, 2.31]	
Total events: 2 (Treatment), 4 (Control)						
Test for heterogeneity: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
02 Light box + placebo pill vs dim light box + fluoxetine						
LAM2006F	8/48	7/48		100.00	1.14 [0.45, 2.90]	0
Subtotal (95% CI)	48	48		100.00	1.14 [0.45, 2.90]	
Total events: 8 (Treatment), 7 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
03 Light box + hypericum vs dim light + hypericum						
MARTINEZ1994	0/10	0/10			Not estimable	0
Subtotal (95% CI)	10	10			Not estimable	
Total events: 0 (Treatment), 0 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: not applicable						

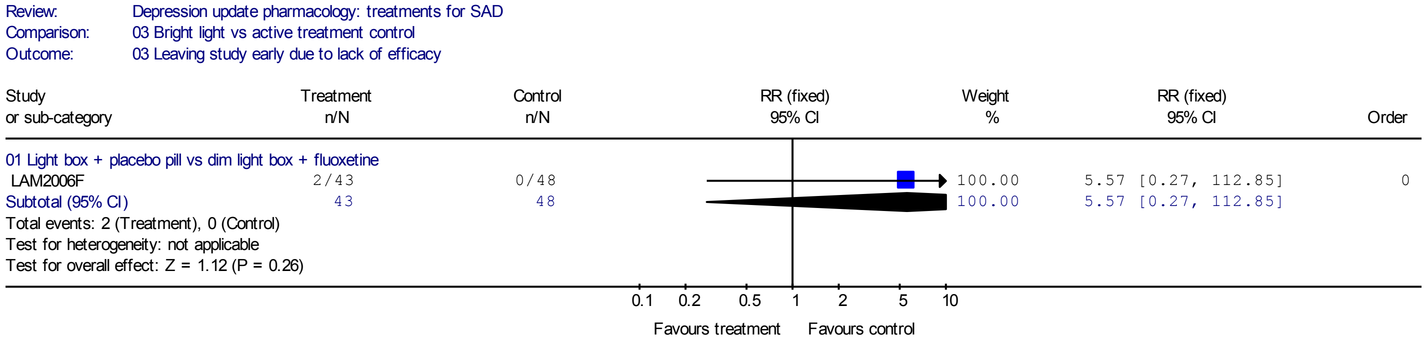
Number leaving study early due to side effects



Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 02 Leaving study early due to side effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light box + placebo pill vs dim light box + fluoxetine						
LAM2006F	1/48	2/48		100.00	0.50 [0.05, 5.33]	0
Subtotal (95% CI)	48	48		100.00	0.50 [0.05, 5.33]	
Total events: 1 (Treatment), 2 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
02 Light box vs group CBT						
ROHAN2007	0/16	0/15			Not estimable	0
Subtotal (95% CI)	16	15			Not estimable	
Total events: 0 (Treatment), 0 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: not applicable						

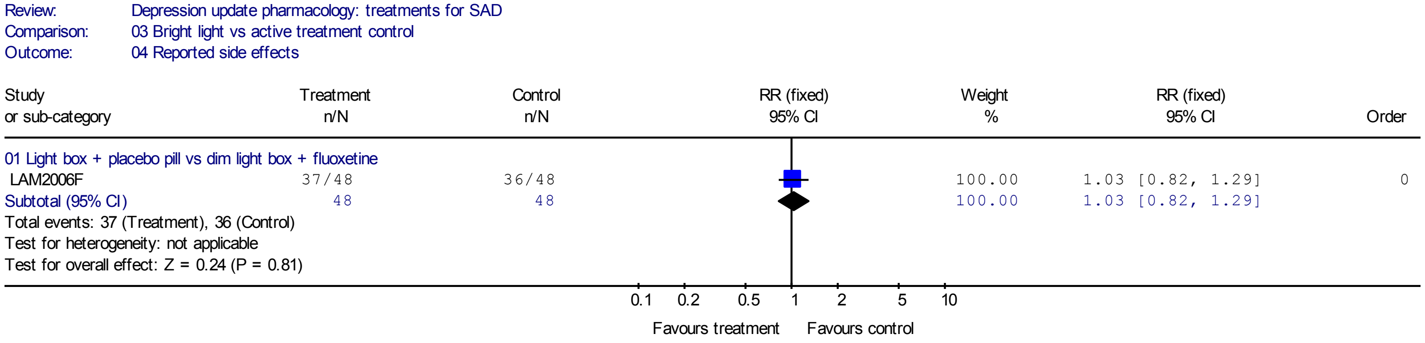
Number leaving study early due to lack of efficacy



Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 03 Leaving study early due to lack of efficacy

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light box + placebo pill vs dim light box + fluoxetine						
LAM2006F	2/43	0/48		100.00	5.57 [0.27, 112.85]	0
Subtotal (95% CI)	43	48		100.00	5.57 [0.27, 112.85]	
Total events: 2 (Treatment), 0 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						

Number of reported side effects

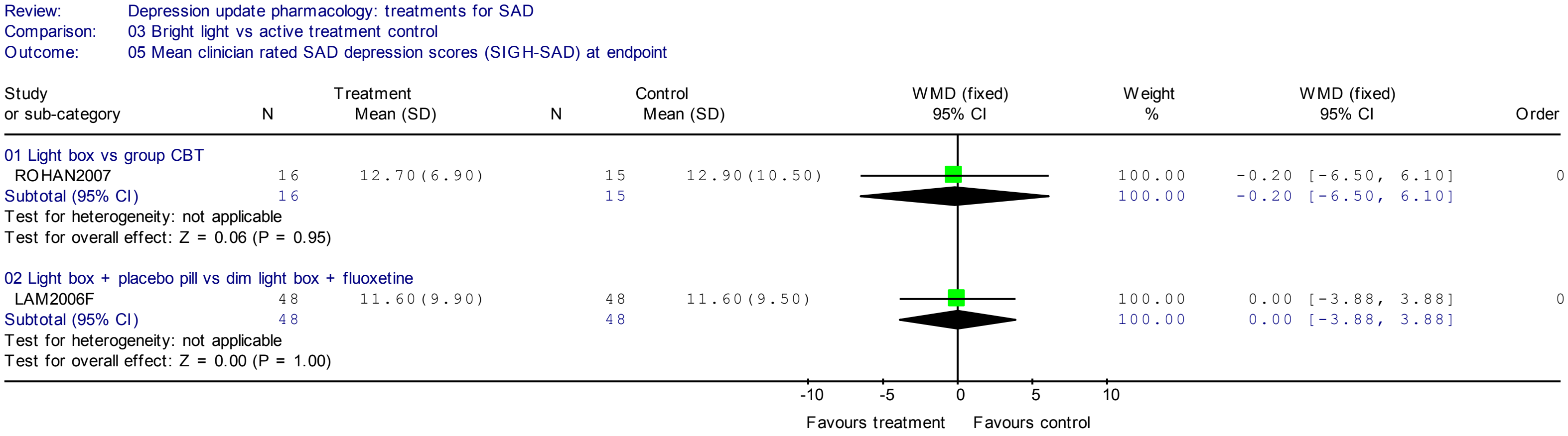


Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 04 Reported side effects

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 Light box + placebo pill vs dim light box + fluoxetine					
LAM2006F	37/48	36/48	100.00	1.03 [0.82, 1.29]	0
Subtotal (95% CI)	48	48	100.00	1.03 [0.82, 1.29]	

Total events: 37 (Treatment), 36 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.24 (P = 0.81)

Mean SAD depression endpoint scores (SIGH-SAD) (clinician-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 05 Mean clinician rated SAD depression scores (SIGH-SAD) at endpoint

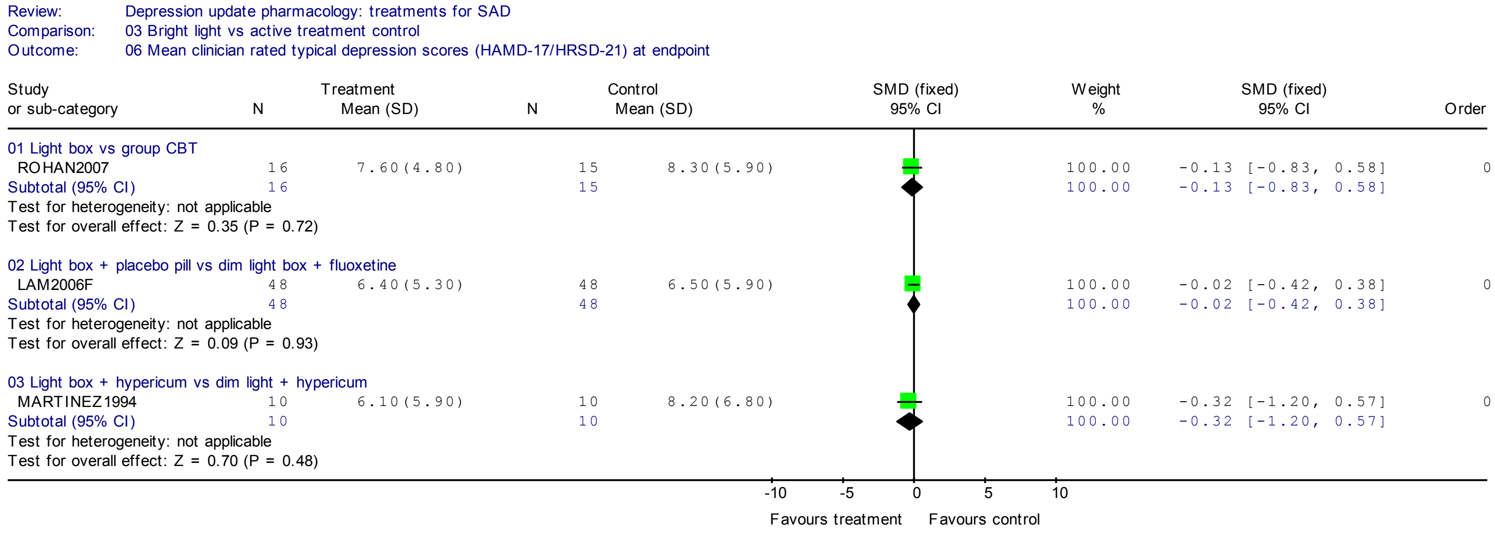
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 Light box vs group CBT							
ROHAN2007	16	12.70(6.90)	15	12.90(10.50)	100.00	-0.20 [-6.50, 6.10]	0
Subtotal (95% CI)	16		15		100.00	-0.20 [-6.50, 6.10]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.06 (P = 0.95)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
02 Light box + placebo pill vs dim light box + fluoxetine							
LAM2006F	48	11.60(9.90)	48	11.60(9.50)	100.00	0.00 [-3.88, 3.88]	0
Subtotal (95% CI)	48		48		100.00	0.00 [-3.88, 3.88]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

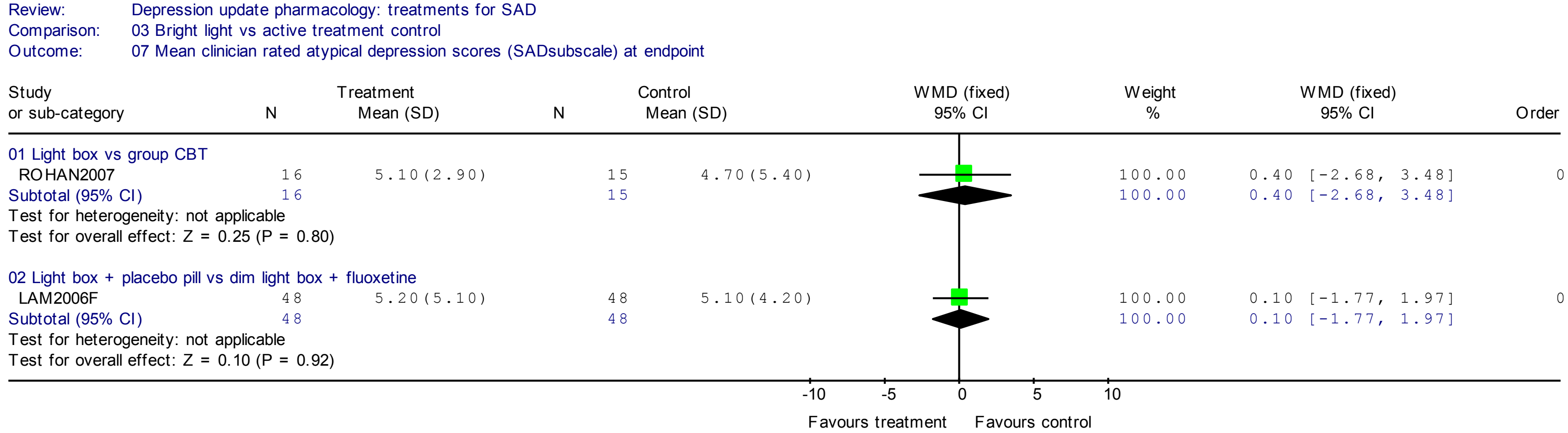
Mean atypical depression endpoint scores (HAM-D17/HRSD-21) (clinician-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 06 Mean clinician rated typical depression scores (HAMD-17/HRSD-21) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 Light box vs group CBT							
ROHAN2007	16	7.60(4.80)	15	8.30(5.90)	100.00	-0.13 [-0.83, 0.58]	0
Subtotal (95% CI)	16		15		100.00	-0.13 [-0.83, 0.58]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.35 (P = 0.72)							
02 Light box + placebo pill vs dim light box + fluoxetine							
LAM2006F	48	6.40(5.30)	48	6.50(5.90)	100.00	-0.02 [-0.42, 0.38]	0
Subtotal (95% CI)	48		48		100.00	-0.02 [-0.42, 0.38]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.09 (P = 0.93)							
03 Light box + hypericum vs dim light + hypericum							
MARTINEZ1994	10	6.10(5.90)	10	8.20(6.80)	100.00	-0.32 [-1.20, 0.57]	0
Subtotal (95% CI)	10		10		100.00	-0.32 [-1.20, 0.57]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.70 (P = 0.48)							

Mean atypical depression endpoint scores (SAD subscale) (clinician-rated)

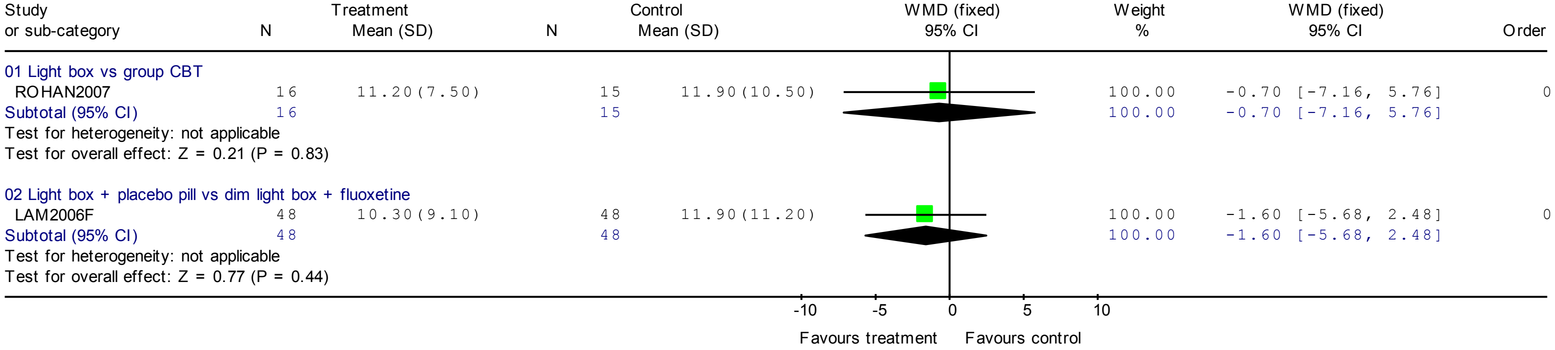


Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 07 Mean clinician rated atypical depression scores (SADsubscale) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 Light box vs group CBT							
ROHAN2007	16	5.10(2.90)	15	4.70(5.40)	100.00	0.40 [-2.68, 3.48]	0
Subtotal (95% CI)	16		15		100.00	0.40 [-2.68, 3.48]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
02 Light box + placebo pill vs dim light box + fluoxetine							
LAM2006F	48	5.20(5.10)	48	5.10(4.20)	100.00	0.10 [-1.77, 1.97]	0
Subtotal (95% CI)	48		48		100.00	0.10 [-1.77, 1.97]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.10 (P = 0.92)							

Mean depression endpoint scores (BDI) (self-rated)

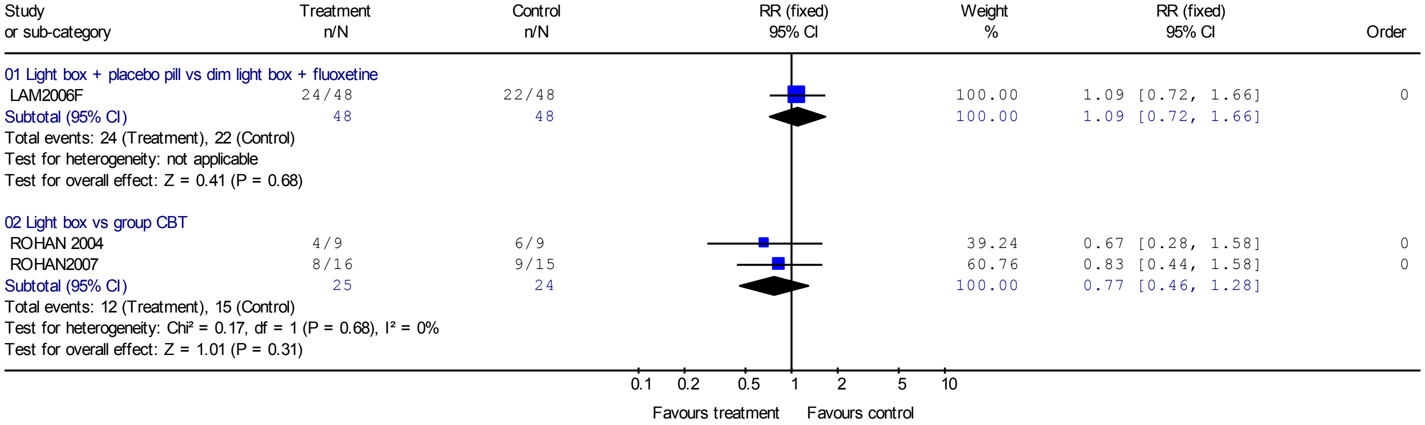
Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 08 Mean self rated depression scores (BDI) at endpoint



Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
01 Light box vs group CBT								
ROHAN2007	16	11.20(7.50)	15	11.90(10.50)		100.00	-0.70 [-7.16, 5.76]	0
Subtotal (95% CI)	16		15			100.00	-0.70 [-7.16, 5.76]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
02 Light box + placebo pill vs dim light box + fluoxetine								
LAM2006F	48	10.30(9.10)	48	11.90(11.20)		100.00	-1.60 [-5.68, 2.48]	0
Subtotal (95% CI)	48		48			100.00	-1.60 [-5.68, 2.48]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								

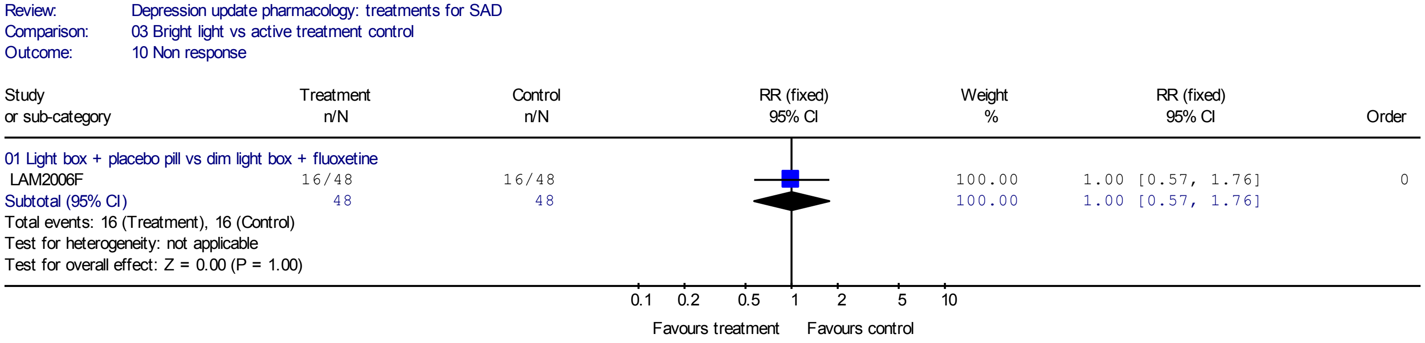
Non-remission data

Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 09 Non remission



Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Light box + placebo pill vs dim light box + fluoxetine						
LAM2006F	24/48	22/48		100.00	1.09 [0.72, 1.66]	0
Subtotal (95% CI)	48	48		100.00	1.09 [0.72, 1.66]	
Total events: 24 (Treatment), 22 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
02 Light box vs group CBT						
ROHAN 2004	4/9	6/9		39.24	0.67 [0.28, 1.58]	0
ROHAN2007	8/16	9/15		60.76	0.83 [0.44, 1.58]	0
Subtotal (95% CI)	25	24		100.00	0.77 [0.46, 1.28]	
Total events: 12 (Treatment), 15 (Control)						
Test for heterogeneity: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						

SAD.03.10. Non-response data



Review: Depression update pharmacology: treatments for SAD
Comparison: 03 Bright light vs active treatment control
Outcome: 10 Non response

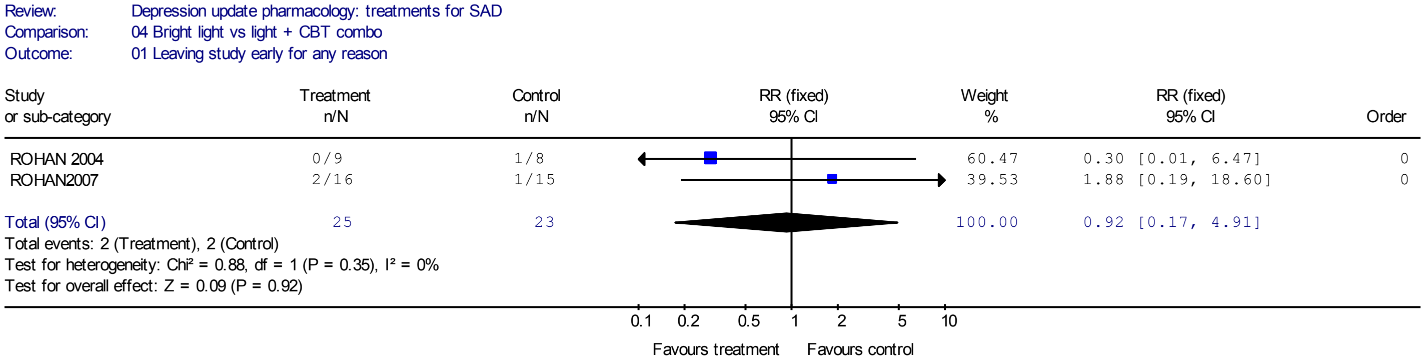
Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 Light box + placebo pill vs dim light box + fluoxetine					
LAM2006F	16/48	16/48	100.00	1.00 [0.57, 1.76]	0
Subtotal (95% CI)	48	48	100.00	1.00 [0.57, 1.76]	

Total events: 16 (Treatment), 16 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

RR (fixed) 95% CI
0.1
0.2
0.5
1
2
5
10
Favours treatment
Favours control

Bright light versus light + CBT combination

Number leaving study early for any reason



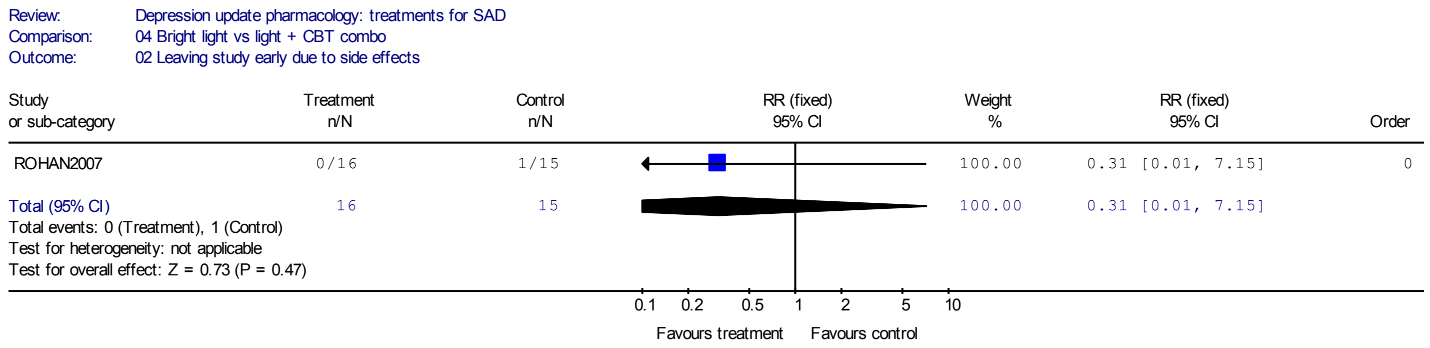
Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
ROHAN 2004	0/9	1/8	60.47	0.30 [0.01, 6.47]	0
ROHAN2007	2/16	1/15	39.53	1.88 [0.19, 18.60]	0
Total (95% CI)	25	23	100.00	0.92 [0.17, 4.91]	

Total events: 2 (Treatment), 2 (Control)
Test for heterogeneity: Chi² = 0.88, df = 1 (P = 0.35), I² = 0%
Test for overall effect: Z = 0.09 (P = 0.92)

RR (fixed) 95% CI
0.1
0.2
0.5
1
2
5
10
Favours treatment
Favours control

Number leaving study early due to side effects

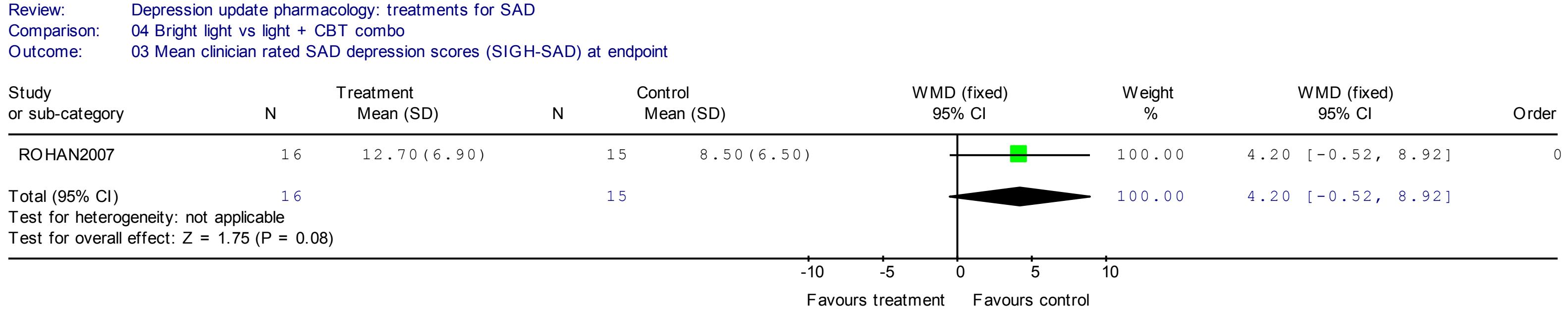


Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 02 Leaving study early due to side effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
ROHAN2007	0/16	1/15		100.00	0.31 [0.01, 7.15]	0
Total (95% CI)	16	15		100.00	0.31 [0.01, 7.15]	

Total events: 0 (Treatment), 1 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.73 (P = 0.47)

Mean SAD depression endpoint scores (SIGH-SAD) (clinician-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 03 Mean clinician rated SAD depression scores (SIGH-SAD) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
ROHAN2007	16	12.70(6.90)	15	8.50(6.50)		100.00	4.20 [-0.52, 8.92]	0
Total (95% CI)	16		15			100.00	4.20 [-0.52, 8.92]	

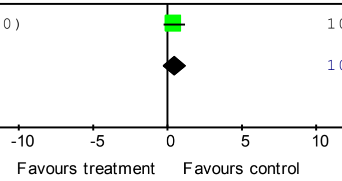
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

Mean typical depression endpoint scores (HAM-D17/HRSD-21) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 04 Mean clinician rated typical depression scores (HAMD-17/HRSD-21) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
ROHAN2007	16	7.60(4.80)	15	5.50(4.10)		100.00	0.46 [-0.26, 1.17]	0
Total (95% CI)	16		15			100.00	0.46 [-0.26, 1.17]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 1.25 (P = 0.21)

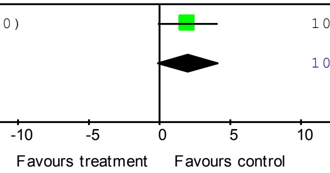


Mean atypical depression endpoint scores (SAD subscale) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 05 Mean clinician rated atypical depression scores (SADsubscale) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
ROHAN2007	16	5.10(2.90)	15	3.10(3.10)		100.00	2.00 [-0.12, 4.12]	0
Total (95% CI)	16		15			100.00	2.00 [-0.12, 4.12]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 1.85 (P = 0.06)

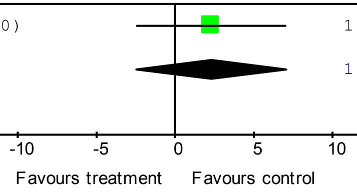


Mean depression endpoint scores (BDI) (self-rated)

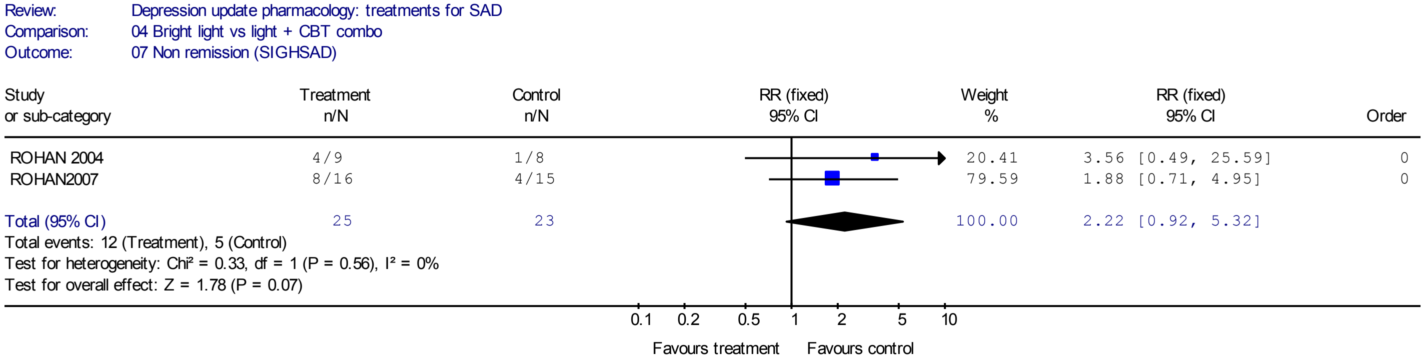
Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 06 Mean self rated depression scores (BDI) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
ROHAN2007	16	11.20(7.50)	15	8.90(6.00)		100.00	2.30 [-2.47, 7.07]	0
Total (95% CI)	16		15			100.00	2.30 [-2.47, 7.07]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



Non-remission data (SIGH-SAD)



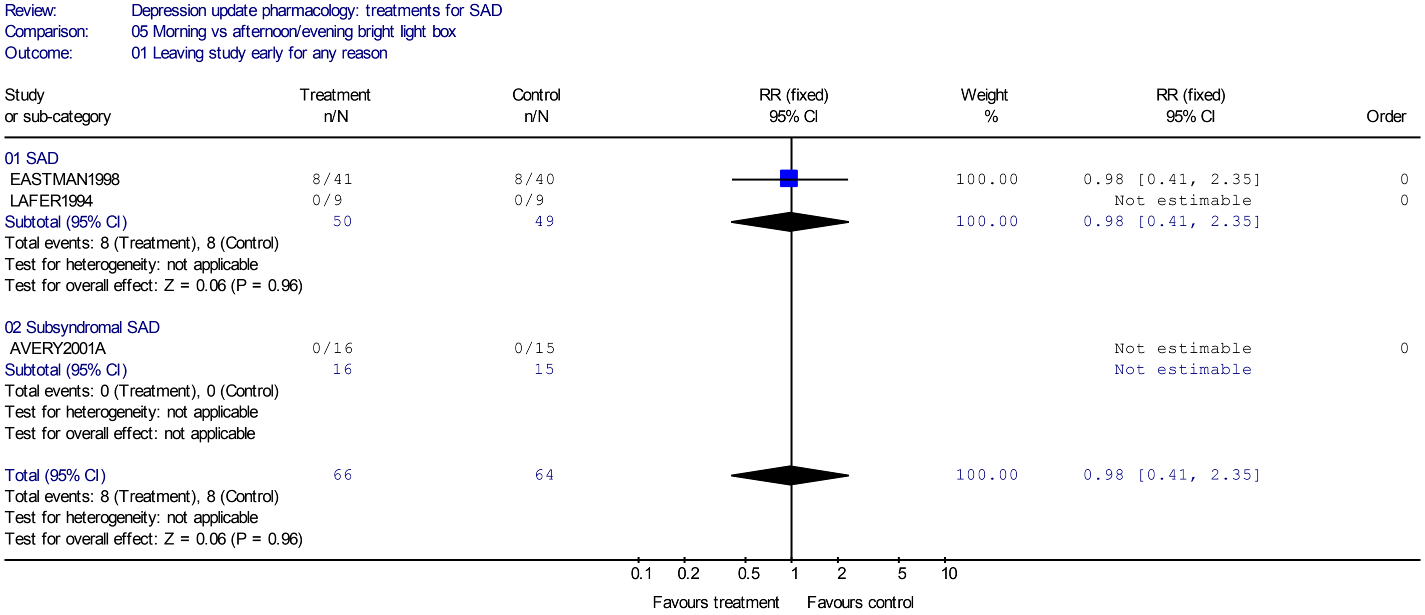
Review: Depression update pharmacology: treatments for SAD
Comparison: 04 Bright light vs light + CBT combo
Outcome: 07 Non remission (SIGHSAD)

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
ROHAN 2004	4/9	1/8		20.41	3.56 [0.49, 25.59]	0
ROHAN2007	8/16	4/15		79.59	1.88 [0.71, 4.95]	0
Total (95% CI)	25	23		100.00	2.22 [0.92, 5.32]	

Total events: 12 (Treatment), 5 (Control)
Test for heterogeneity: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%
Test for overall effect: Z = 1.78 (P = 0.07)

Morning versus afternoon/evening bright light box

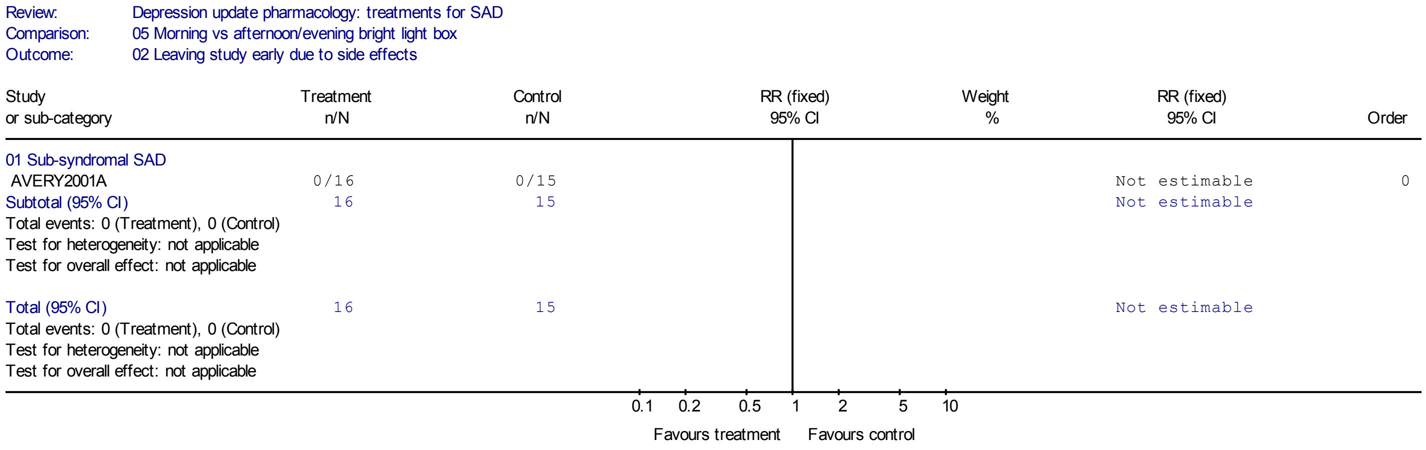
Number leaving study early for any reason



Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 SAD					
EASTMAN1998	8/41	8/40	100.00	0.98 [0.41, 2.35]	0
LAFER1994	0/9	0/9		Not estimable	0
Subtotal (95% CI)	50	49	100.00	0.98 [0.41, 2.35]	
Total events: 8 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.96)					
02 Subsyndromal SAD					
AVERY2001A	0/16	0/15		Not estimable	0
Subtotal (95% CI)	16	15		Not estimable	
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	66	64	100.00	0.98 [0.41, 2.35]	
Total events: 8 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.96)					

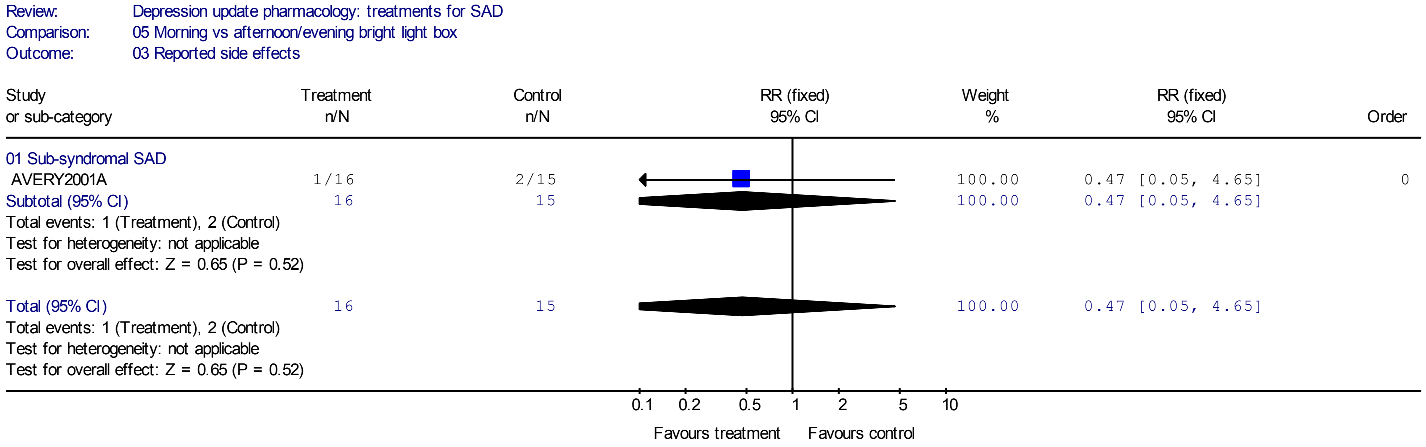
Number leaving study early due to side effects



Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 02 Leaving study early due to side effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Sub-syndromal SAD						
AVERY2001A	0/16	0/15			Not estimable	0
Subtotal (95% CI)	16	15			Not estimable	
Total events: 0 (Treatment), 0 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: not applicable						
Total (95% CI)	16	15			Not estimable	
Total events: 0 (Treatment), 0 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: not applicable						

Number of reported side effects

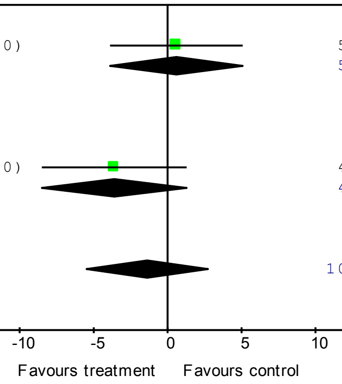


Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 03 Reported side effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Sub-syndromal SAD						
AVERY2001A	1/16	2/15		100.00	0.47 [0.05, 4.65]	0
Subtotal (95% CI)	16	15		100.00	0.47 [0.05, 4.65]	
Total events: 1 (Treatment), 2 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)	16	15		100.00	0.47 [0.05, 4.65]	
Total events: 1 (Treatment), 2 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						

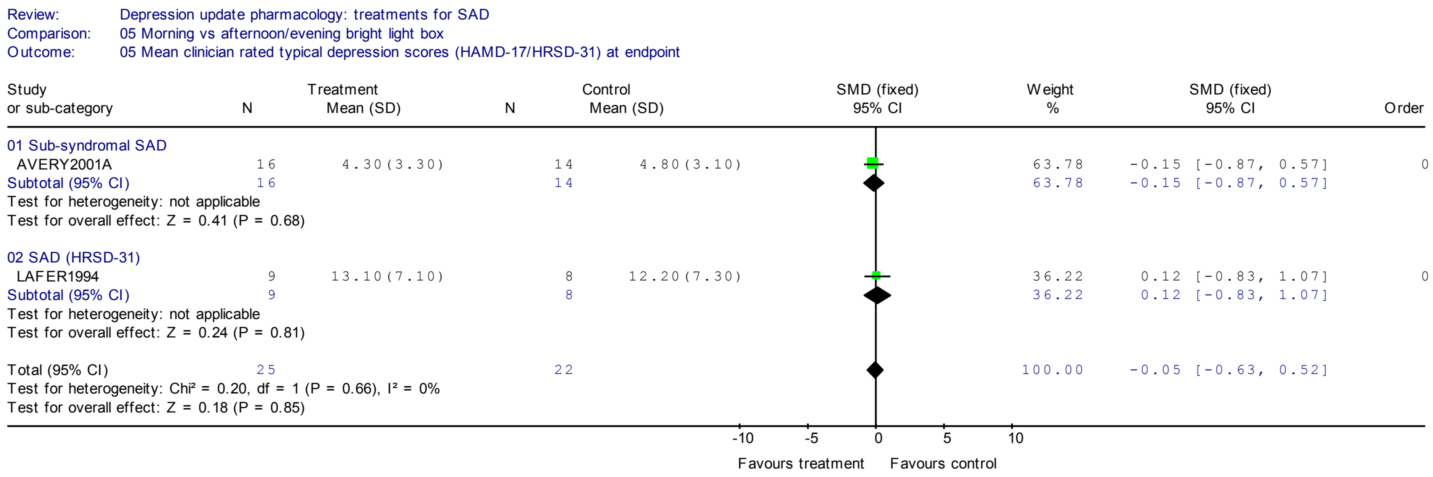
Mean SAD depression endpoint scores (SIGH-SAD) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 04 Mean clinician rated SAD depression scores (SIGH-SAD) at endpoint



Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Order
01 Sub-syndromal SAD								
AVERY2001A	16	10.80(6.20)	14	10.20(6.30)		52.85	0.60 [-3.89, 5.09]	0
Subtotal (95% CI)	16		14			52.85	0.60 [-3.89, 5.09]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.26 (P = 0.79)								
02 SAD								
TERMAN1998	19	10.50(7.60)	19	14.10(7.80)		47.15	-3.60 [-8.50, 1.30]	0
Subtotal (95% CI)	19		19			47.15	-3.60 [-8.50, 1.30]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 1.44 (P = 0.15)								
Total (95% CI)	35		33			100.00	-1.38 [-5.49, 2.73]	
Test for heterogeneity: Chi² = 1.54, df = 1 (P = 0.22), I² = 34.9%								
Test for overall effect: Z = 0.66 (P = 0.51)								

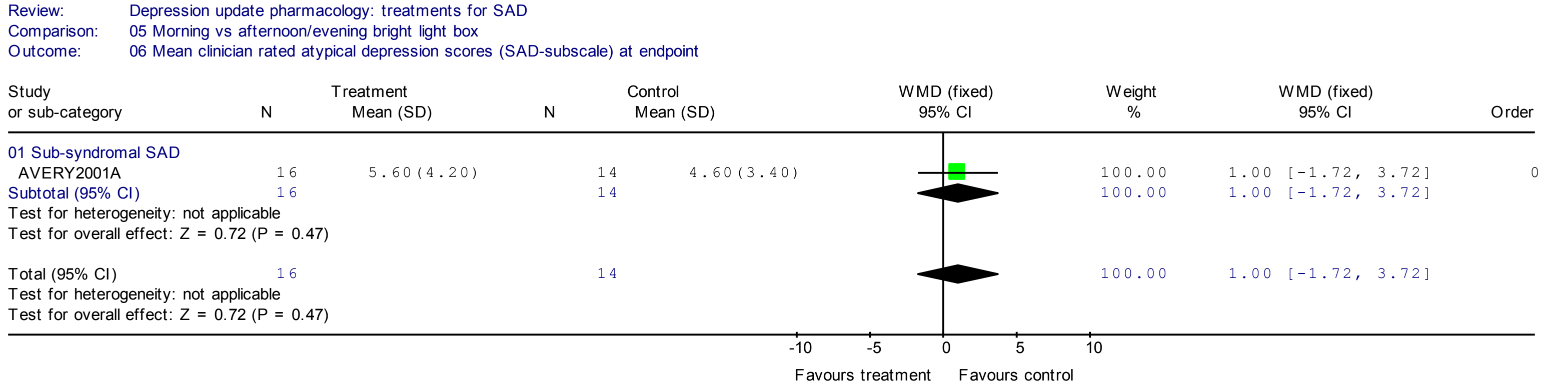
Mean typical depression endpoint scores (HAM-D17/HRSD-31) (clinician-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 05 Mean clinician rated typical depression scores (HAMD-17/HRSD-31) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	SMD (fixed) 95% CI	Order
01 Sub-syndromal SAD							
AVERY2001A	16	4.30(3.30)	14	4.80(3.10)	63.78	-0.15 [-0.87, 0.57]	0
Subtotal (95% CI)	16		14		63.78	-0.15 [-0.87, 0.57]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.41 (P = 0.68)							
02 SAD (HRSD-31)							
LAFER1994	9	13.10(7.10)	8	12.20(7.30)	36.22	0.12 [-0.83, 1.07]	0
Subtotal (95% CI)	9		8		36.22	0.12 [-0.83, 1.07]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.24 (P = 0.81)							
Total (95% CI)	25		22		100.00	-0.05 [-0.63, 0.52]	
Test for heterogeneity: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%							
Test for overall effect: Z = 0.18 (P = 0.85)							

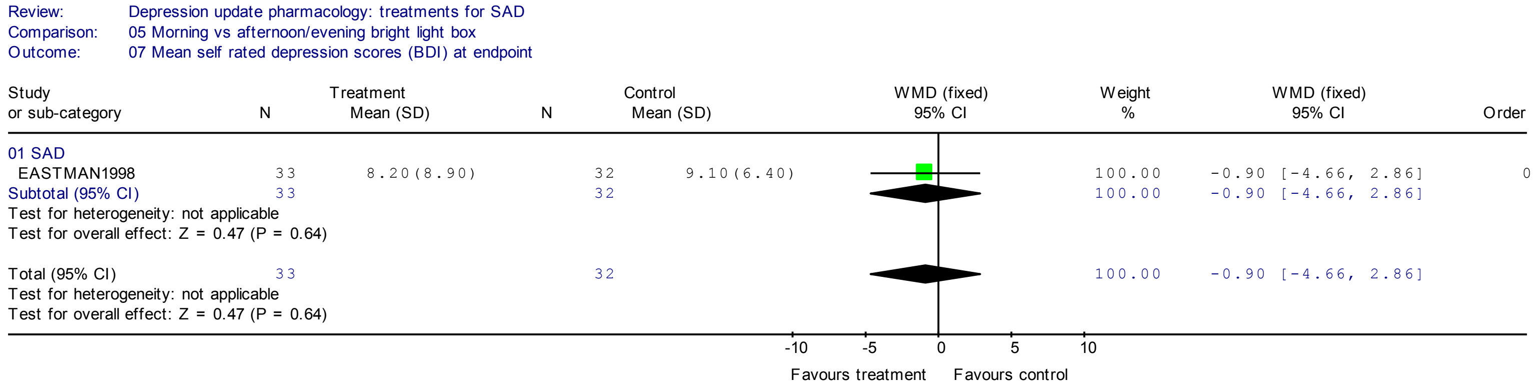
Mean atypical depression endpoint scores (SAD subscale) (clinician-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 06 Mean clinician rated atypical depression scores (SAD-subscale) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 Sub-syndromal SAD							
AVERY2001A	16	5.60(4.20)	14	4.60(3.40)	100.00	1.00 [-1.72, 3.72]	0
Subtotal (95% CI)	16		14		100.00	1.00 [-1.72, 3.72]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
Total (95% CI)	16		14		100.00	1.00 [-1.72, 3.72]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							

Mean depression endpoint scores (BDI) (self-rated)



Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 07 Mean self rated depression scores (BDI) at endpoint

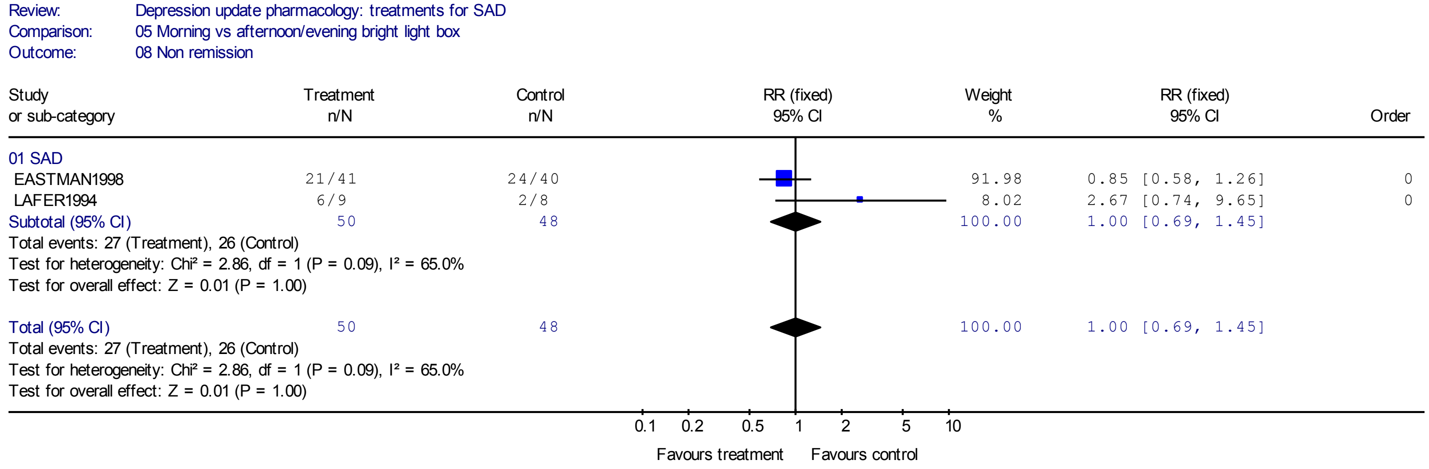
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 SAD							
EASTMAN1998	33	8.20(8.90)	32	9.10(6.40)	100.00	-0.90 [-4.66, 2.86]	0
Subtotal (95% CI)	33		32		100.00	-0.90 [-4.66, 2.86]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
Total (95% CI)	33		32		100.00	-0.90 [-4.66, 2.86]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

Non-remission data



Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 08 Non remission

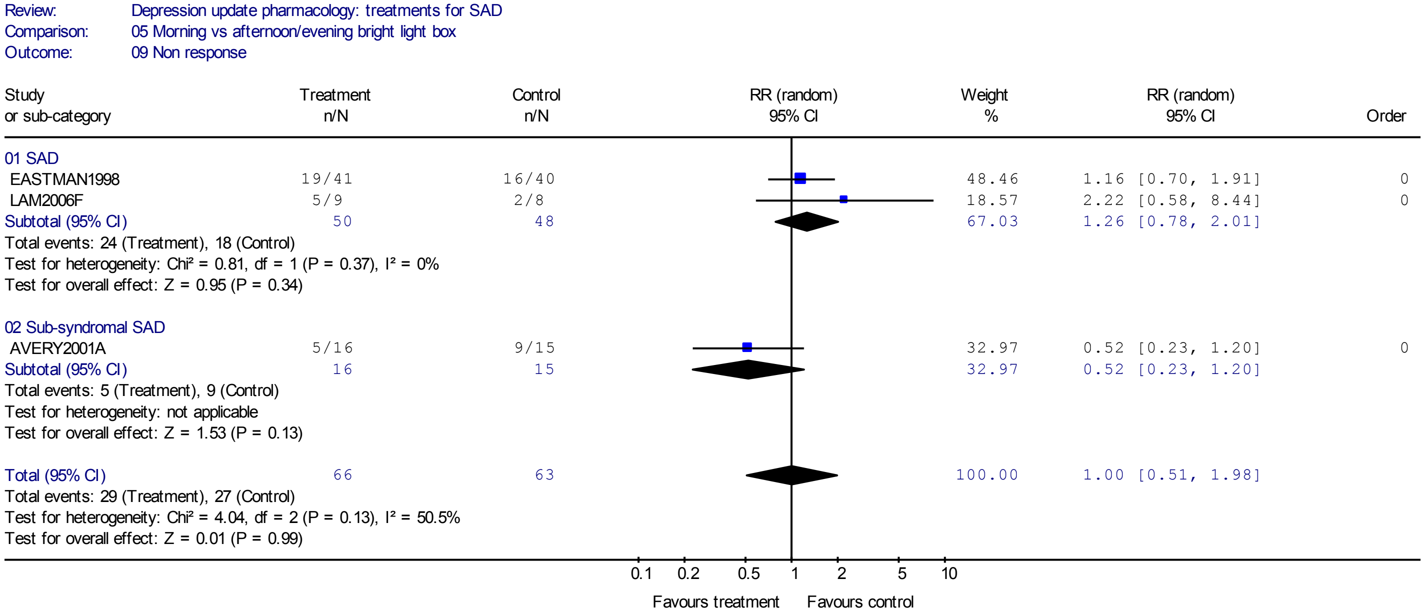
Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 SAD					
EASTMAN1998	21/41	24/40	91.98	0.85 [0.58, 1.26]	0
LAFER1994	6/9	2/8	8.02	2.67 [0.74, 9.65]	0
Subtotal (95% CI)	50	48	100.00	1.00 [0.69, 1.45]	

Total events: 27 (Treatment), 26 (Control)
Test for heterogeneity: Chi² = 2.86, df = 1 (P = 0.09), I² = 65.0%
Test for overall effect: Z = 0.01 (P = 1.00)

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
Total (95% CI)	50	48	100.00	1.00 [0.69, 1.45]	

Total events: 27 (Treatment), 26 (Control)
Test for heterogeneity: Chi² = 2.86, df = 1 (P = 0.09), I² = 65.0%
Test for overall effect: Z = 0.01 (P = 1.00)

Non-response data



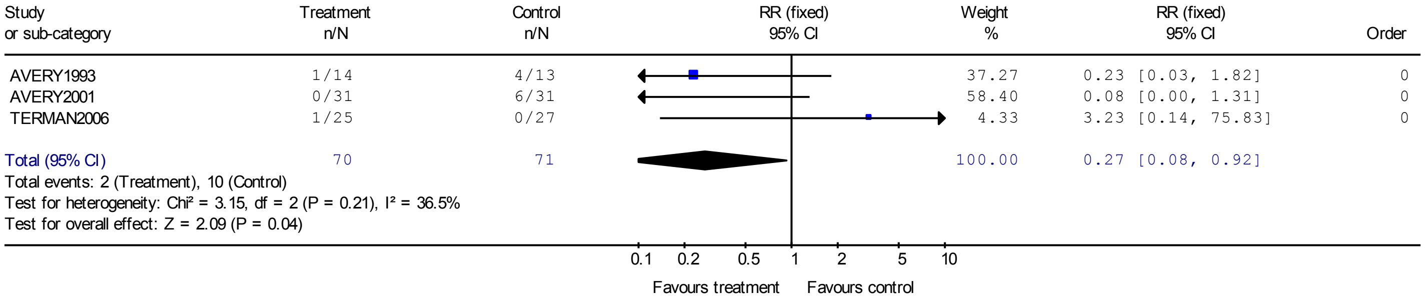
Review: Depression update pharmacology: treatments for SAD
Comparison: 05 Morning vs afternoon/evening bright light box
Outcome: 09 Non response

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
01 SAD						
EASTMAN1998	19/41	16/40		48.46	1.16 [0.70, 1.91]	0
LAM2006F	5/9	2/8		18.57	2.22 [0.58, 8.44]	0
Subtotal (95% CI)	50	48		67.03	1.26 [0.78, 2.01]	
Total events: 24 (Treatment), 18 (Control)						
Test for heterogeneity: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
02 Sub-syndromal SAD						
AVERY2001A	5/16	9/15		32.97	0.52 [0.23, 1.20]	0
Subtotal (95% CI)	16	15		32.97	0.52 [0.23, 1.20]	
Total events: 5 (Treatment), 9 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)	66	63		100.00	1.00 [0.51, 1.98]	
Total events: 29 (Treatment), 27 (Control)						
Test for heterogeneity: Chi² = 4.04, df = 2 (P = 0.13), I² = 50.5%						
Test for overall effect: Z = 0.01 (P = 0.99)						

Dawn simulation versus attentional control

Number leaving study early for any reason

Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 01 Leaving study early for any reason

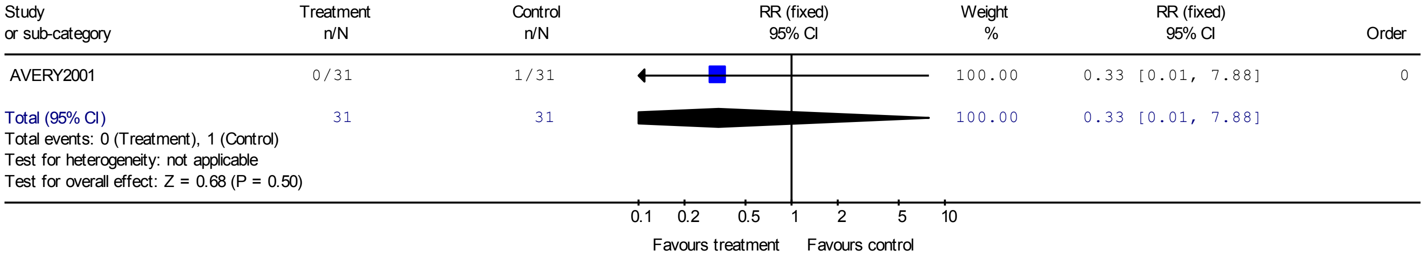


Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
AVERY1993	1/14	4/13	37.27	0.23 [0.03, 1.82]	0
AVERY2001	0/31	6/31	58.40	0.08 [0.00, 1.31]	0
TERMAN2006	1/25	0/27	4.33	3.23 [0.14, 75.83]	0
Total (95% CI)	70	71	100.00	0.27 [0.08, 0.92]	

Total events: 2 (Treatment), 10 (Control)
Test for heterogeneity: Chi² = 3.15, df = 2 (P = 0.21), I² = 36.5%
Test for overall effect: Z = 2.09 (P = 0.04)

Number leaving study early due to side effects

Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 02 Leaving study early due to side effects



Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
AVERY2001	0/31	1/31	100.00	0.33 [0.01, 7.88]	0
Total (95% CI)	31	31	100.00	0.33 [0.01, 7.88]	

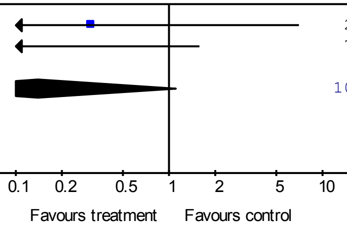
Total events: 0 (Treatment), 1 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

Number leaving study early due to lack of efficacy

Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 03 Leaving study early due to lack of efficacy

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
AVERY1993	0/14	1/13		22.00	0.31 [0.01, 7.02]	0
AVERY2001	0/31	5/31		78.00	0.09 [0.01, 1.58]	0
Total (95% CI)	45	44		100.00	0.14 [0.02, 1.10]	

Total events: 0 (Treatment), 6 (Control)
Test for heterogeneity: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)

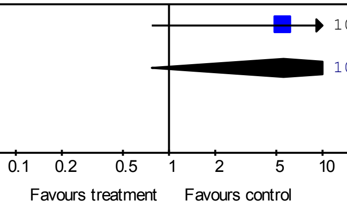


Number of reported side effects

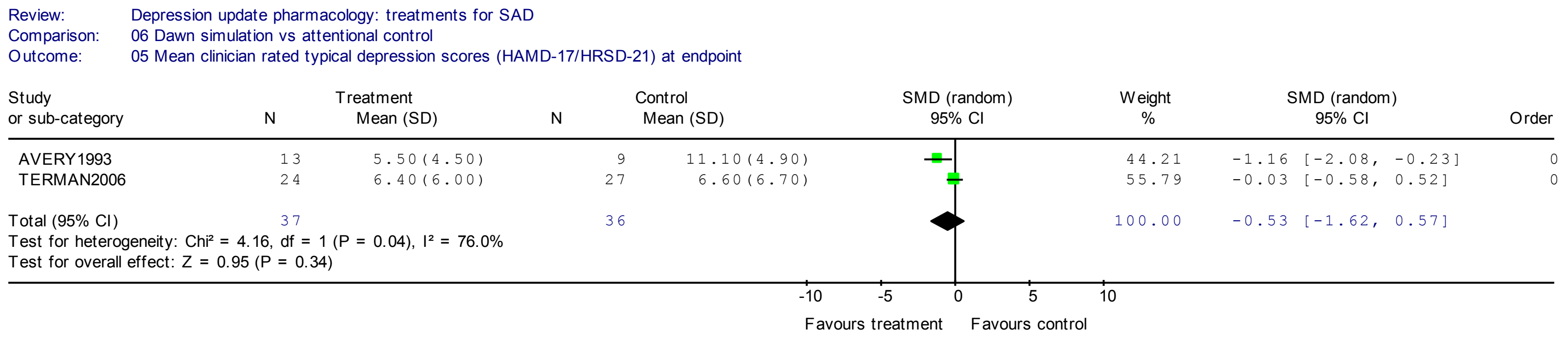
Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 04 Reported side effects

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
AVERY1993	6/14	1/13		100.00	5.57 [0.77, 40.26]	0
Total (95% CI)	14	13		100.00	5.57 [0.77, 40.26]	

Total events: 6 (Treatment), 1 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.70 (P = 0.09)



Mean typical depression endpoint scores (HAM-D17/HRSD-21) (clinician-rated)

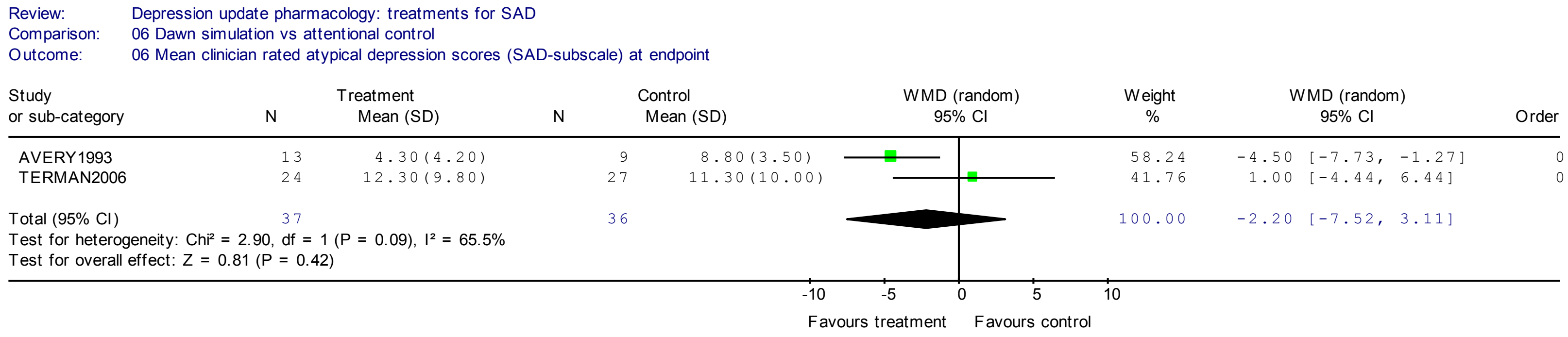


Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 05 Mean clinician rated typical depression scores (HAMD-17/HRSD-21) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	SMD (random) 95% CI	Order
AVERY1993	13	5.50(4.50)	9	11.10(4.90)	44.21	-1.16 [-2.08, -0.23]	0
TERMAN2006	24	6.40(6.00)	27	6.60(6.70)	55.79	-0.03 [-0.58, 0.52]	0
Total (95% CI)	37		36		100.00	-0.53 [-1.62, 0.57]	

Test for heterogeneity: Chi² = 4.16, df = 1 (P = 0.04), I² = 76.0%
Test for overall effect: Z = 0.95 (P = 0.34)

Mean atypical depression endpoint scores (SAD subscale) (clinician-rated)

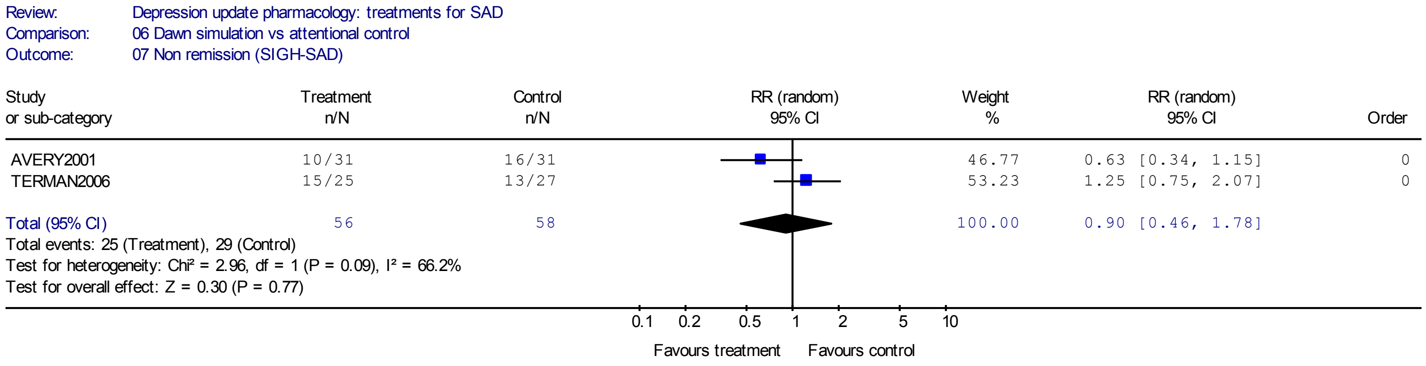


Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 06 Mean clinician rated atypical depression scores (SAD-subscale) at endpoint

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI	Order
AVERY1993	13	4.30(4.20)	9	8.80(3.50)	58.24	-4.50 [-7.73, -1.27]	0
TERMAN2006	24	12.30(9.80)	27	11.30(10.00)	41.76	1.00 [-4.44, 6.44]	0
Total (95% CI)	37		36		100.00	-2.20 [-7.52, 3.11]	

Test for heterogeneity: Chi² = 2.90, df = 1 (P = 0.09), I² = 65.5%
Test for overall effect: Z = 0.81 (P = 0.42)

Non-remission data (SIGH-SAD)



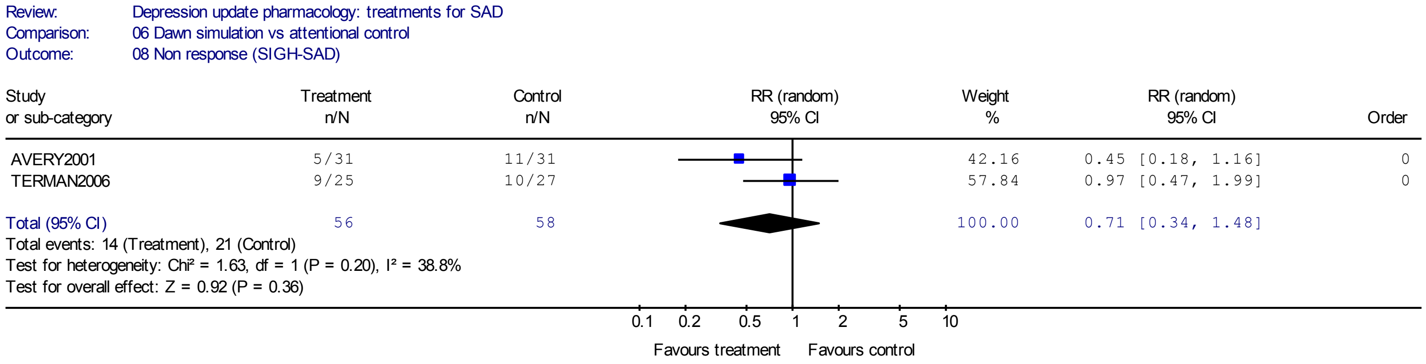
Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 07 Non remission (SIGH-SAD)

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (random) 95% CI	Order
AVERY2001	10/31	16/31	46.77	0.63 [0.34, 1.15]	0
TERMAN2006	15/25	13/27	53.23	1.25 [0.75, 2.07]	0
Total (95% CI)	56	58	100.00	0.90 [0.46, 1.78]	

Total events: 25 (Treatment), 29 (Control)
Test for heterogeneity: Chi² = 2.96, df = 1 (P = 0.09), I² = 66.2%
Test for overall effect: Z = 0.30 (P = 0.77)

RR (random)
95% CI
0.1
0.2
0.5
1
2
5
10
Favours treatment
Favours control

Non-response data (SIGH-SAD)



Review: Depression update pharmacology: treatments for SAD
Comparison: 06 Dawn simulation vs attentional control
Outcome: 08 Non response (SIGH-SAD)

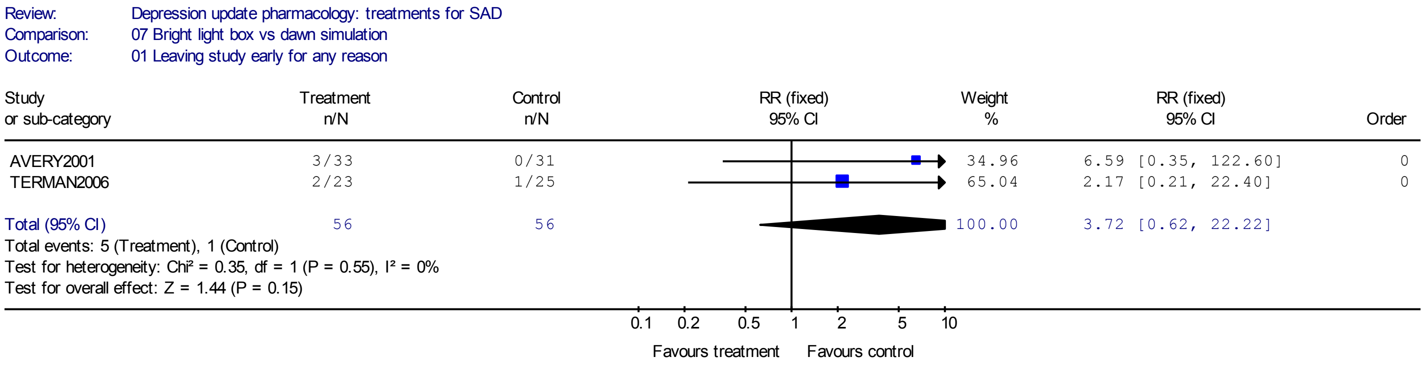
Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (random) 95% CI	Order
AVERY2001	5/31	11/31	42.16	0.45 [0.18, 1.16]	0
TERMAN2006	9/25	10/27	57.84	0.97 [0.47, 1.99]	0
Total (95% CI)	56	58	100.00	0.71 [0.34, 1.48]	

Total events: 14 (Treatment), 21 (Control)
Test for heterogeneity: Chi² = 1.63, df = 1 (P = 0.20), I² = 38.8%
Test for overall effect: Z = 0.92 (P = 0.36)

RR (random)
95% CI
0.1
0.2
0.5
1
2
5
10
Favours treatment
Favours control

Bright light versus dawn simulation

Number leaving study early for any reason

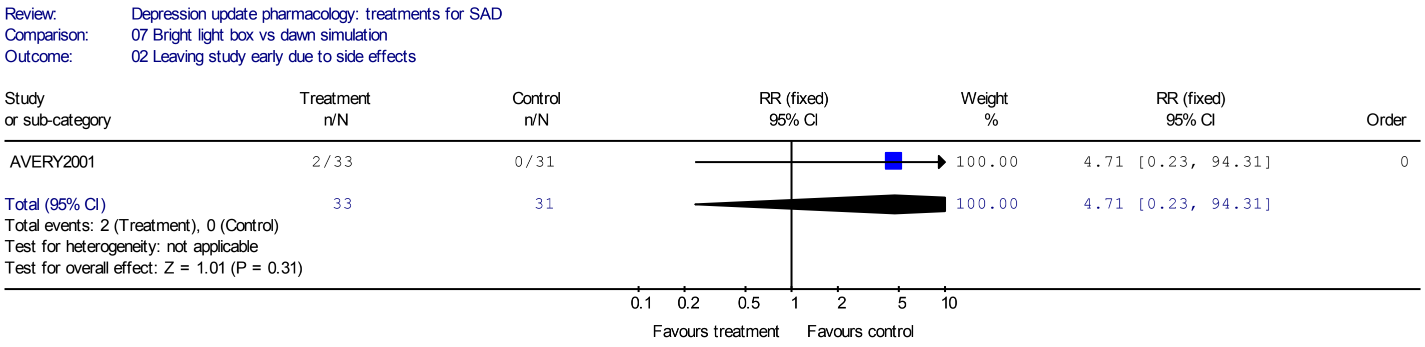

Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
AVERY2001	3/33	0/31	34.96	6.59 [0.35, 122.60]	0
TERMAN2006	2/23	1/25	65.04	2.17 [0.21, 22.40]	0
Total (95% CI)	56	56	100.00	3.72 [0.62, 22.22]	

Total events: 5 (Treatment), 1 (Control)
Test for heterogeneity: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)

RR (fixed)
95% CI
0.1
0.2
0.5
1
2
5
10
Favours treatment
Favours control

Number leaving study early due to side effects

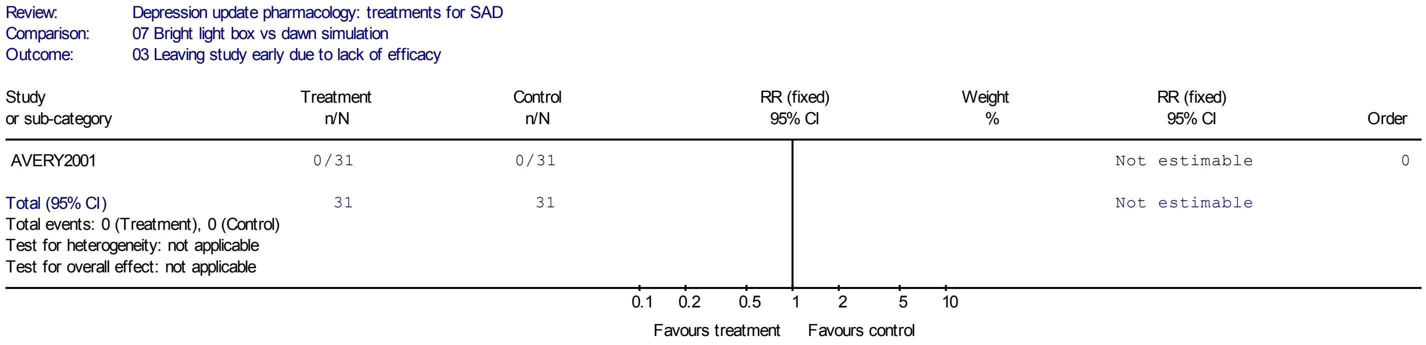

Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 02 Leaving study early due to side effects

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
AVERY2001	2/33	0/31	100.00	4.71 [0.23, 94.31]	0
Total (95% CI)	33	31	100.00	4.71 [0.23, 94.31]	

Total events: 2 (Treatment), 0 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

RR (fixed)
95% CI
0.1
0.2
0.5
1
2
5
10
Favours treatment
Favours control

Number leaving study early due to lack of efficacy

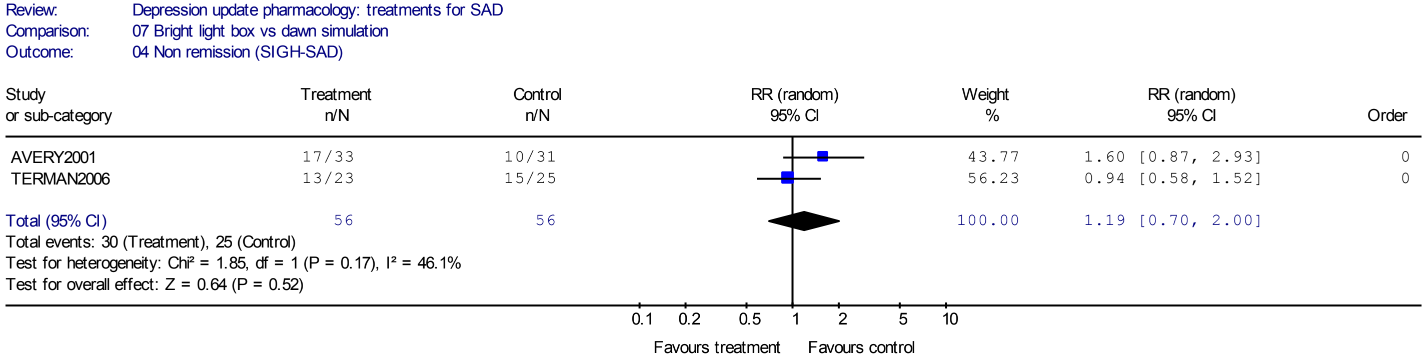


Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 03 Leaving study early due to lack of efficacy

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
AVERY2001	0/31	0/31			Not estimable	0
Total (95% CI)	31	31			Not estimable	

Total events: 0 (Treatment), 0 (Control)
Test for heterogeneity: not applicable
Test for overall effect: not applicable

Non-remission data (SIGH-SAD)



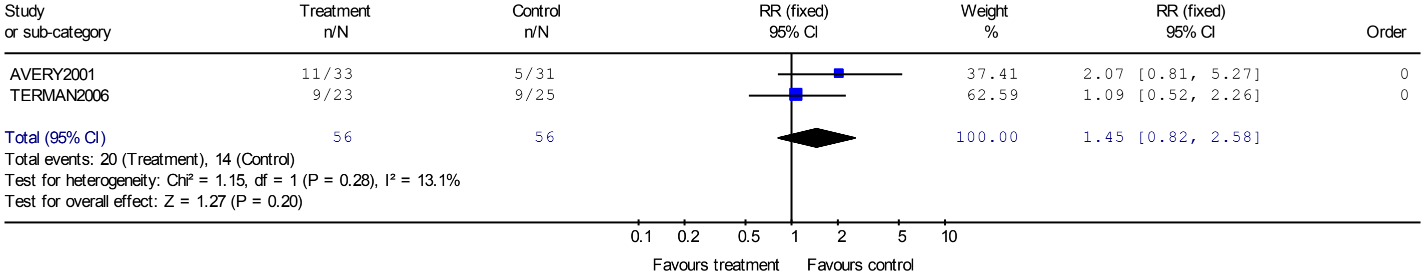
Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 04 Non remission (SIGH-SAD)

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
AVERY2001	17/33	10/31		43.77	1.60 [0.87, 2.93]	0
TERMAN2006	13/23	15/25		56.23	0.94 [0.58, 1.52]	0
Total (95% CI)	56	56		100.00	1.19 [0.70, 2.00]	

Total events: 30 (Treatment), 25 (Control)
Test for heterogeneity: Chi² = 1.85, df = 1 (P = 0.17), I² = 46.1%
Test for overall effect: Z = 0.64 (P = 0.52)

Non-response data (SIGH-SAD

Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 05 Non response (SIGH-SAD)

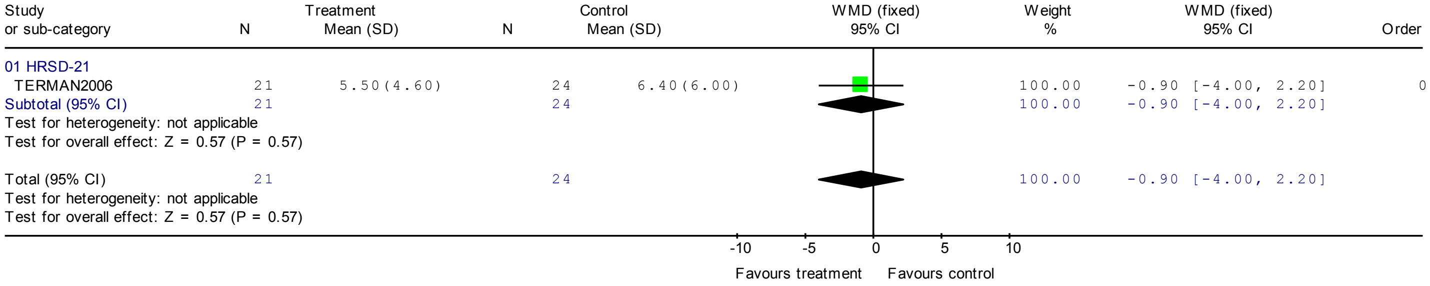


Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
AVERY2001	11/33	5/31	37.41	2.07 [0.81, 5.27]	0
TERMAN2006	9/23	9/25	62.59	1.09 [0.52, 2.26]	0
Total (95% CI)	56	56	100.00	1.45 [0.82, 2.58]	

Total events: 20 (Treatment), 14 (Control)
Test for heterogeneity: Chi² = 1.15, df = 1 (P = 0.28), I² = 13.1%
Test for overall effect: Z = 1.27 (P = 0.20)

Mean depression endpoint scores

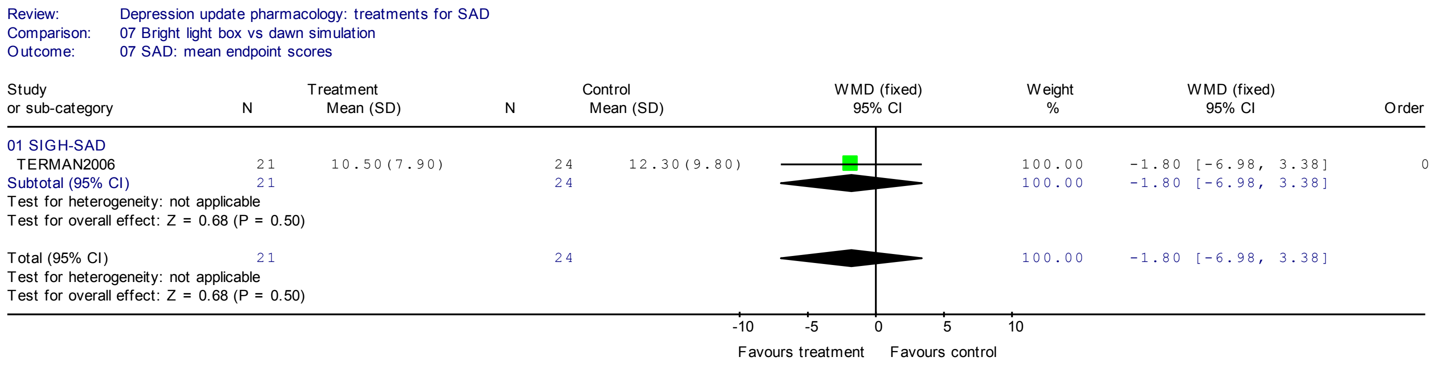
Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 06 Depression: mean endpoint scores



Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 HRSD-21							
TERMAN2006	21	5.50(4.60)	24	6.40(6.00)	100.00	-0.90 [-4.00, 2.20]	0
Subtotal (95% CI)	21		24		100.00	-0.90 [-4.00, 2.20]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							
Total (95% CI)	21		24		100.00	-0.90 [-4.00, 2.20]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

Mean SAD depression endpoint scores

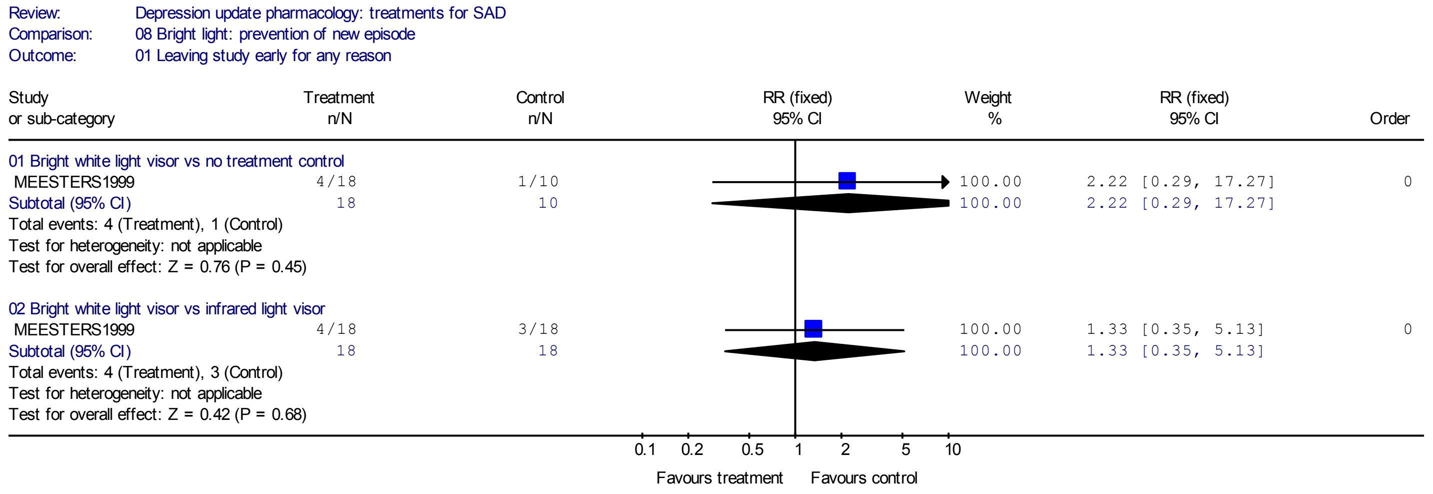


Review: Depression update pharmacology: treatments for SAD
Comparison: 07 Bright light box vs dawn simulation
Outcome: 07 SAD: mean endpoint scores

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
01 SIGH-SAD								
TERMAN2006	21	10.50(7.90)	24	12.30(9.80)		100.00	-1.80 [-6.98, 3.38]	0
Subtotal (95% CI)	21		24			100.00	-1.80 [-6.98, 3.38]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Total (95% CI)	21		24			100.00	-1.80 [-6.98, 3.38]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								

Bright light – prevention of new episode

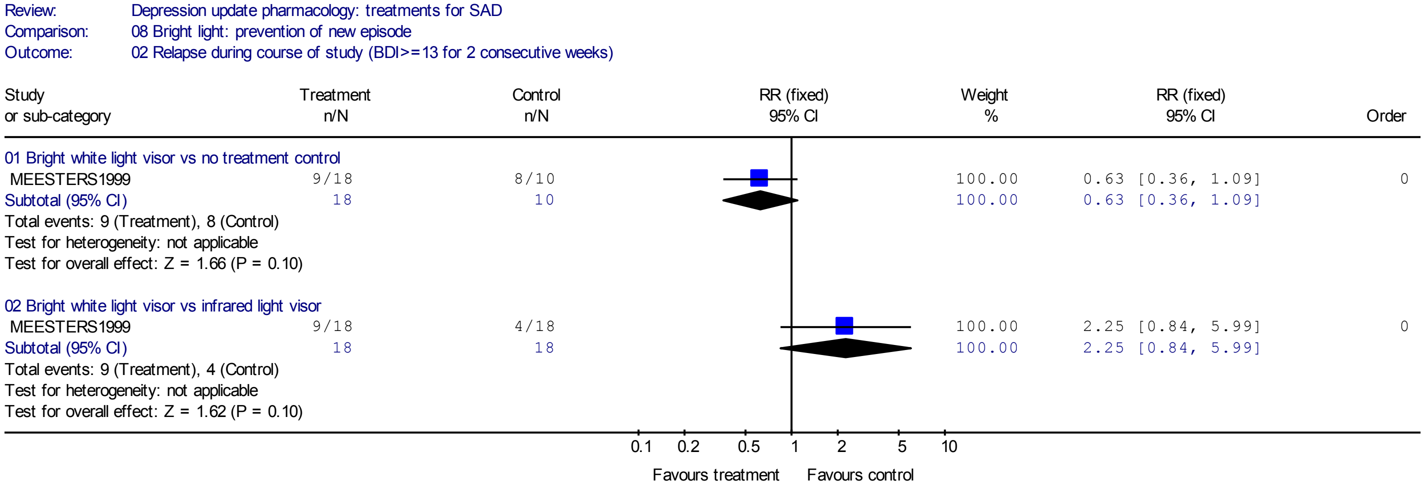
Number leaving study early for any reason



Review: Depression update pharmacology: treatments for SAD
Comparison: 08 Bright light: prevention of new episode
Outcome: 01 Leaving study early for any reason

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Bright white light visor vs no treatment control						
MEESTERS1999	4/18	1/10		100.00	2.22 [0.29, 17.27]	0
Subtotal (95% CI)	18	10		100.00	2.22 [0.29, 17.27]	
Total events: 4 (Treatment), 1 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
02 Bright white light visor vs infrared light visor						
MEESTERS1999	4/18	3/18		100.00	1.33 [0.35, 5.13]	0
Subtotal (95% CI)	18	18		100.00	1.33 [0.35, 5.13]	
Total events: 4 (Treatment), 3 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						

Number who relapsed during course of study (BDI>=13 for 2 consecutive weeks)

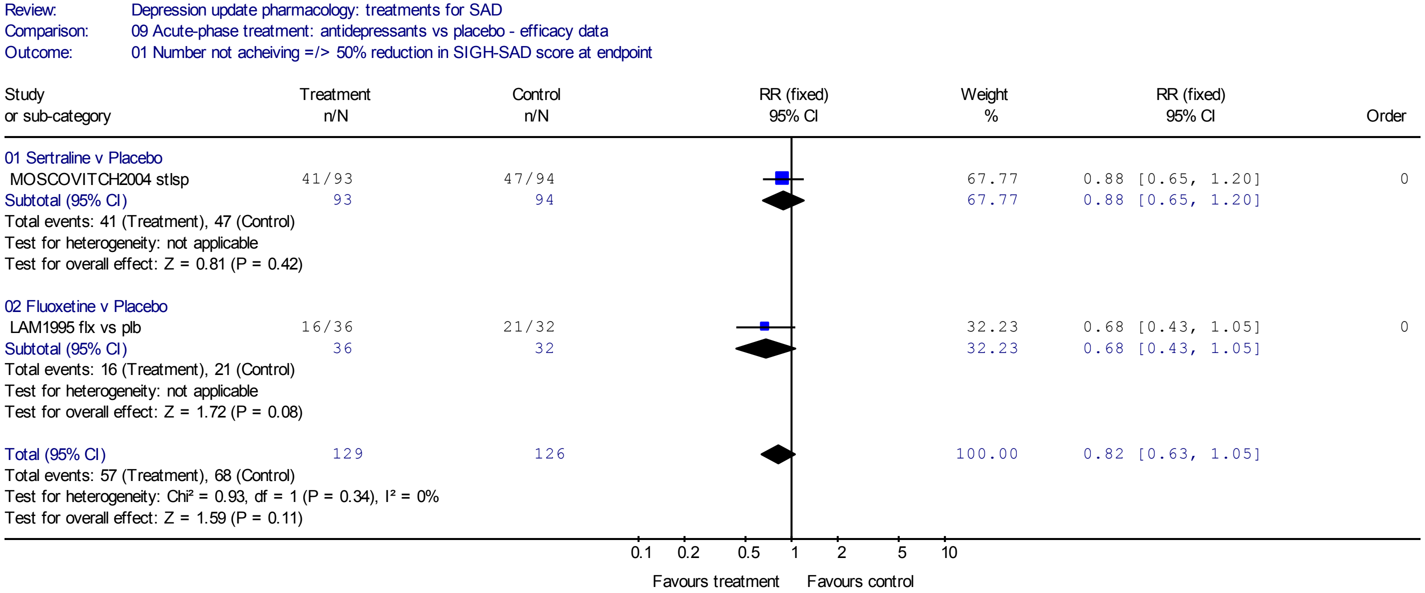


Review: Depression update pharmacology: treatments for SAD
Comparison: 08 Bright light: prevention of new episode
Outcome: 02 Relapse during course of study (BDI>=13 for 2 consecutive weeks)

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Bright white light visor vs no treatment control						
MEESTERS1999	9/18	8/10		100.00	0.63 [0.36, 1.09]	0
Subtotal (95% CI)	18	10		100.00	0.63 [0.36, 1.09]	
Total events: 9 (Treatment), 8 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
02 Bright white light visor vs infrared light visor						
MEESTERS1999	9/18	4/18		100.00	2.25 [0.84, 5.99]	0
Subtotal (95% CI)	18	18		100.00	2.25 [0.84, 5.99]	
Total events: 9 (Treatment), 4 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						

Acute-phase treatment – antidepressants versus placebo (efficacy data)

Non-response data (SIGH-SAD)



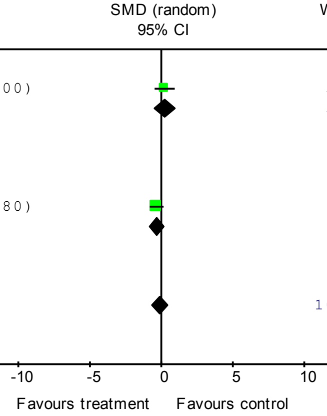
Review: Depression update pharmacology: treatments for SAD
Comparison: 09 Acute-phase treatment: antidepressants vs placebo - efficacy data
Outcome: 01 Number not acheiving =/> 50% reduction in SIGH-SAD score at endpoint

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Sertraline v Placebo						
MOSCOVITCH2004 stlsp	41/93	47/94		67.77	0.88 [0.65, 1.20]	0
Subtotal (95% CI)	93	94		67.77	0.88 [0.65, 1.20]	
Total events: 41 (Treatment), 47 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
02 Fluoxetine v Placebo						
LAM1995 flx vs plb	16/36	21/32		32.23	0.68 [0.43, 1.05]	0
Subtotal (95% CI)	36	32		32.23	0.68 [0.43, 1.05]	
Total events: 16 (Treatment), 21 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.72 (P = 0.08)						
Total (95% CI)	129	126		100.00	0.82 [0.63, 1.05]	
Total events: 57 (Treatment), 68 (Control)						
Test for heterogeneity: Chi² = 0.93, df = 1 (P = 0.34), I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						

Mean endpoint depression scores (SIGH-SAD) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 09 Acute-phase treatment: antidepressants vs placebo - efficacy data
Outcome: 02 Mean endpoint (clinician rated) (antidepressants) SIGH-SAD

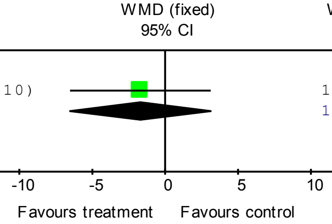
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	SMD (random) 95% CI	Order
01 Moclobemide vs Placebo							
LINGJAERDE93ml vs pl	16	24.00(14.00)	15	21.00(11.00)	38.79	0.23 [-0.48, 0.94]	0
Subtotal (95% CI)	16		15		38.79	0.23 [-0.48, 0.94]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
02 Fluoxetine vs Placebo							
LAM1995 flx vs plb	36	15.10(10.50)	32	18.80(11.80)	61.21	-0.33 [-0.81, 0.15]	0
Subtotal (95% CI)	36		32		61.21	-0.33 [-0.81, 0.15]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.34 (P = 0.18)							
Total (95% CI)	52		47		100.00	-0.11 [-0.65, 0.42]	
Test for heterogeneity: Chi² = 1.65, df = 1 (P = 0.20), I² = 39.4%							
Test for overall effect: Z = 0.41 (P = 0.68)							



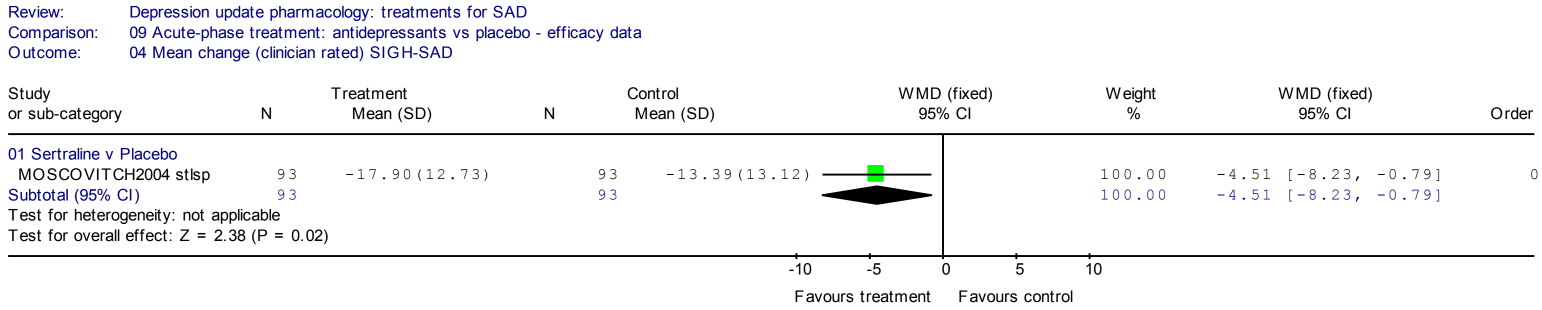
Mean endpoint depression scores (BDI) (self-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 09 Acute-phase treatment: antidepressants vs placebo - efficacy data
Outcome: 03 Mean endpoint (self rated) BDI

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 Fluoxetine vs Placebo							
LAM1995 flx vs plb	36	11.60(10.20)	32	13.30(10.10)	100.00	-1.70 [-6.53, 3.13]	0
Subtotal (95% CI)	36		32		100.00	-1.70 [-6.53, 3.13]	
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							



Mean change depression scores (SIGH-SAD) (clinician-rated)



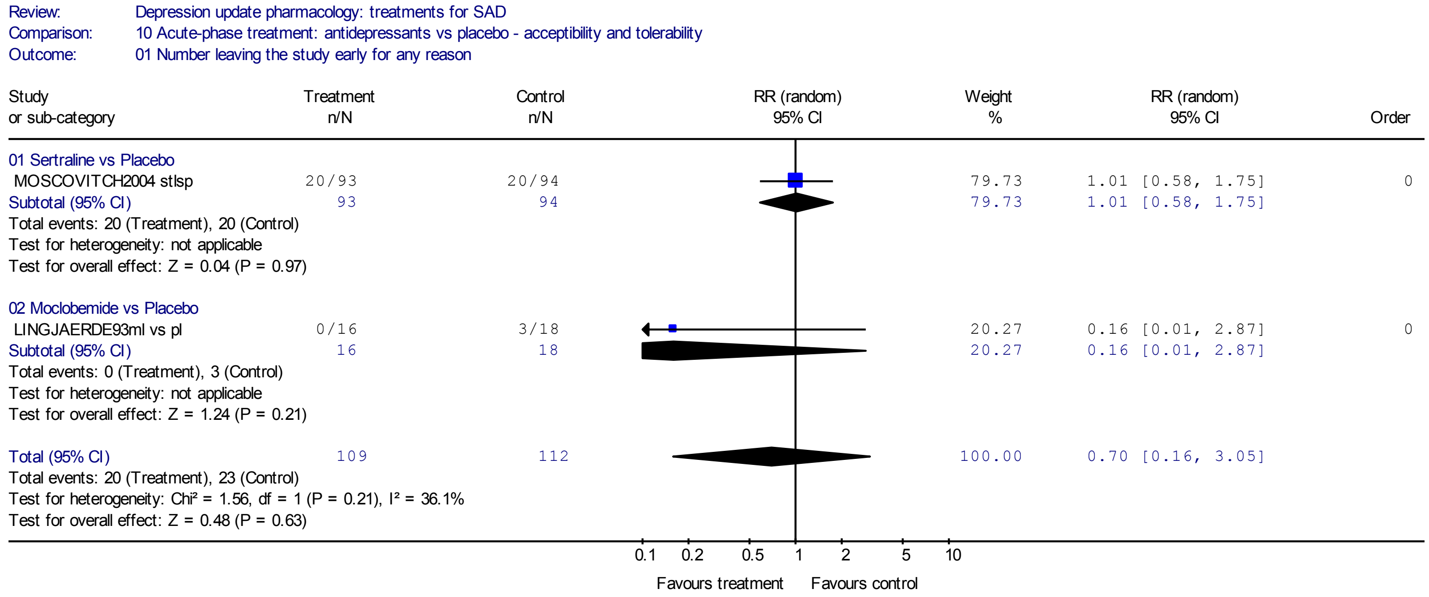
Review: Depression update pharmacology: treatments for SAD
Comparison: 09 Acute-phase treatment: antidepressants vs placebo - efficacy data
Outcome: 04 Mean change (clinician rated) SIGH-SAD

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 Sertraline v Placebo							
MOSCOVITCH2004 stlsp	93	-17.90(12.73)	93	-13.39(13.12)	100.00	-4.51 [-8.23, -0.79]	0
Subtotal (95% CI)	93		93		100.00	-4.51 [-8.23, -0.79]	

Test for heterogeneity: not applicable
Test for overall effect: Z = 2.38 (P = 0.02)

Acute-phase treatment – antidepressants versus placebo (acceptability and tolerability data)

Number leaving the study early for any reason



Review: Depression update pharmacology: treatments for SAD
Comparison: 10 Acute-phase treatment: antidepressants vs placebo - acceptibility and tolerability
Outcome: 01 Number leaving the study early for any reason

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (random) 95% CI	Order
01 Sertraline vs Placebo					
MOSCOVITCH2004 stlsp	20/93	20/94	79.73	1.01 [0.58, 1.75]	0
Subtotal (95% CI)	93	94	79.73	1.01 [0.58, 1.75]	

Total events: 20 (Treatment), 20 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (random) 95% CI	Order
02 Moclobemide vs Placebo					
LINGJAERDE93ml vs pl	0/16	3/18	20.27	0.16 [0.01, 2.87]	0
Subtotal (95% CI)	16	18	20.27	0.16 [0.01, 2.87]	

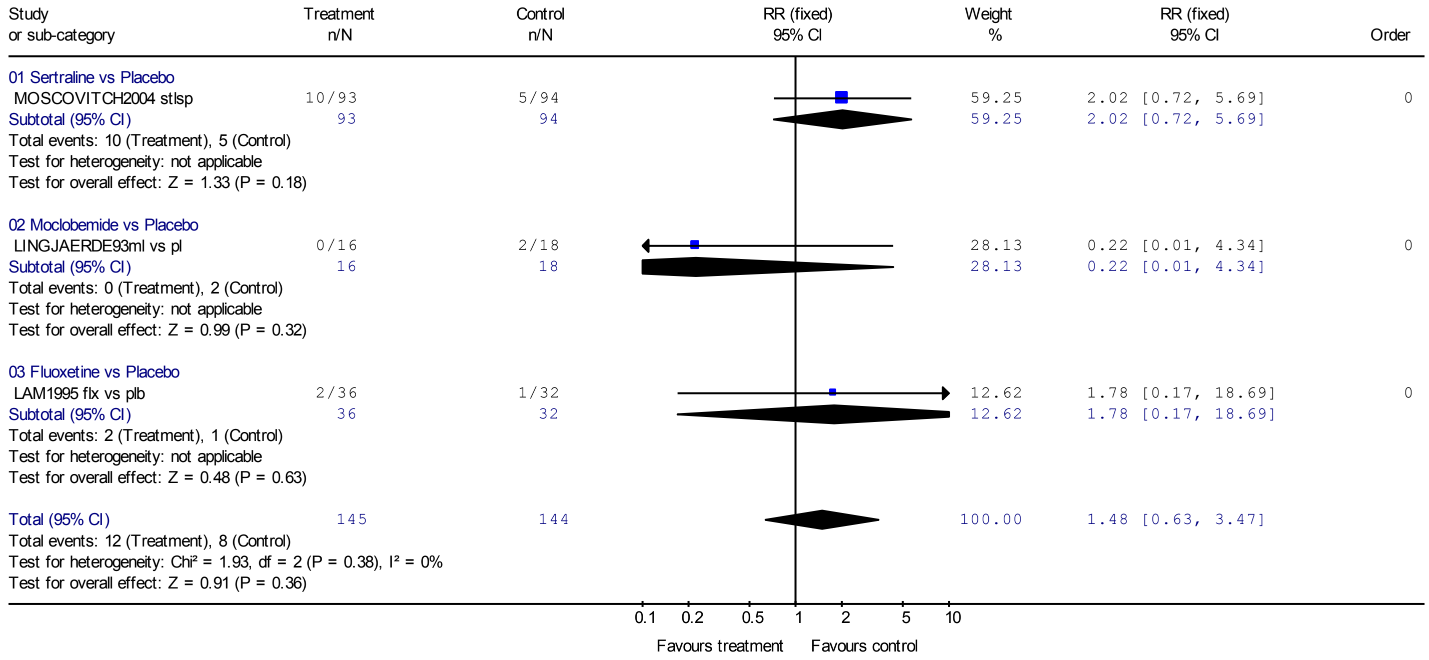
Total events: 0 (Treatment), 3 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.24 (P = 0.21)

	Treatment	Control	Weight	RR (random)	
Total (95% CI)	109	112	100.00	0.70 [0.16, 3.05]	

Total events: 20 (Treatment), 23 (Control)
Test for heterogeneity: Chi² = 1.56, df = 1 (P = 0.21), I² = 36.1%
Test for overall effect: Z = 0.48 (P = 0.63)

Number leaving the study early due to side effects

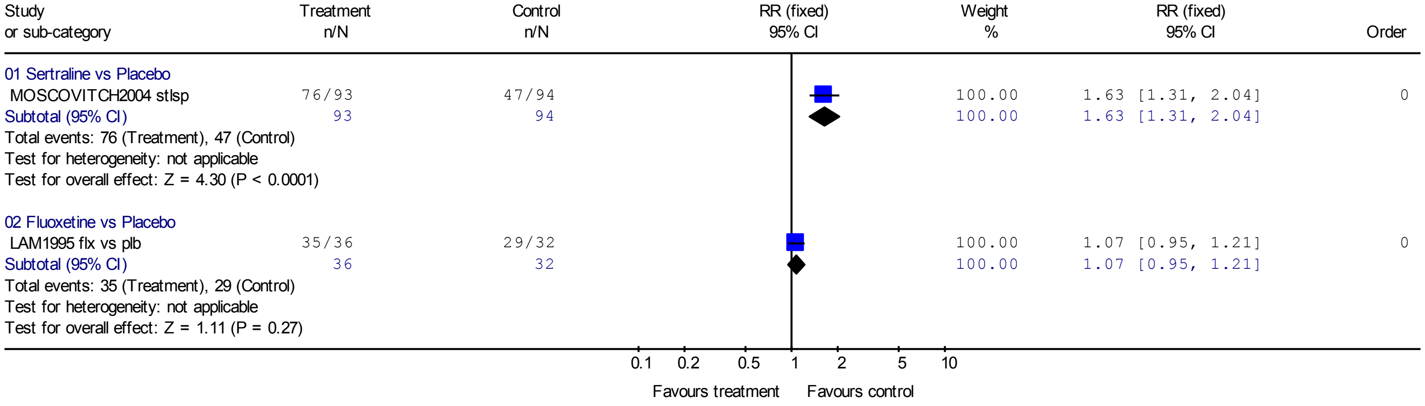
Review: Depression update pharmacology: treatments for SAD
Comparison: 10 Acute-phase treatment: antidepressants vs placebo - acceptibility and tolerability
Outcome: 02 Number leaving the study early due to side effects



Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 Sertraline vs Placebo					
MOSCOVITCH2004 stlsp	10/93	5/94	59.25	2.02 [0.72, 5.69]	0
Subtotal (95% CI)	93	94	59.25	2.02 [0.72, 5.69]	
Total events: 10 (Treatment), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
02 Moclobemide vs Placebo					
LINGJAERDE93ml vs pl	0/16	2/18	28.13	0.22 [0.01, 4.34]	0
Subtotal (95% CI)	16	18	28.13	0.22 [0.01, 4.34]	
Total events: 0 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
03 Fluoxetine vs Placebo					
LAM1995 flx vs plb	2/36	1/32	12.62	1.78 [0.17, 18.69]	0
Subtotal (95% CI)	36	32	12.62	1.78 [0.17, 18.69]	
Total events: 2 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
Total (95% CI)	145	144	100.00	1.48 [0.63, 3.47]	
Total events: 12 (Treatment), 8 (Control)					
Test for heterogeneity: Chi² = 1.93, df = 2 (P = 0.38), I² = 0%					
Test for overall effect: Z = 0.91 (P = 0.36)					

Number reporting side effects

Review: Depression update pharmacology: treatments for SAD
Comparison: 10 Acute-phase treatment: antidepressants vs placebo - acceptibility and tolerability
Outcome: 03 Number reporting side effects

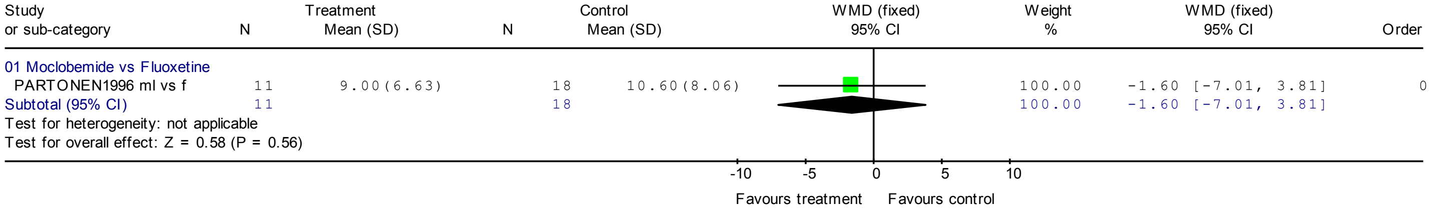


Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Sertraline vs Placebo						
MOSCOVITCH2004 stlsp	76/93	47/94		100.00	1.63 [1.31, 2.04]	0
Subtotal (95% CI)	93	94		100.00	1.63 [1.31, 2.04]	
Total events: 76 (Treatment), 47 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 4.30 (P < 0.0001)						
02 Fluoxetine vs Placebo						
LAM1995 flx vs plb	35/36	29/32		100.00	1.07 [0.95, 1.21]	0
Subtotal (95% CI)	36	32		100.00	1.07 [0.95, 1.21]	
Total events: 35 (Treatment), 29 (Control)						
Test for heterogeneity: not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						

Acute-phase treatment – antidepressants versus active control (efficacy data)

Mean endpoint depression data (SIGH-SAD) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 11 Acute-phase treatment: antidepressants vs active control - efficacy data
Outcome: 01 Mean endpoint (clinician rated) SIGH-SAD

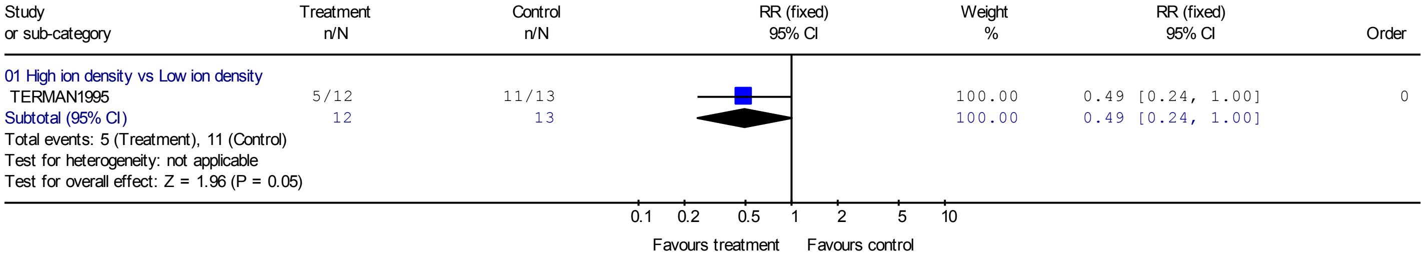


Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI	Order
01 Moclobemide vs Fluoxetine								
PARTONEN1996 ml vs f	11	9.00(6.63)	18	10.60(8.06)		100.00	-1.60 [-7.01, 3.81]	0
Subtotal (95% CI)	11		18			100.00	-1.60 [-7.01, 3.81]	
Test for heterogeneity: not applicable								
Test for overall effect: Z = 0.58 (P = 0.56)								

Overall efficacy (other interventions)

Non-response data (SIGH-SAD)

Review: Depression update pharmacology: treatments for SAD
Comparison: 12 Overall efficacy (other interventions)
Outcome: 01 Number not acheiving =/> 50% reduction in outcome score at endpoint SIGH-SAD



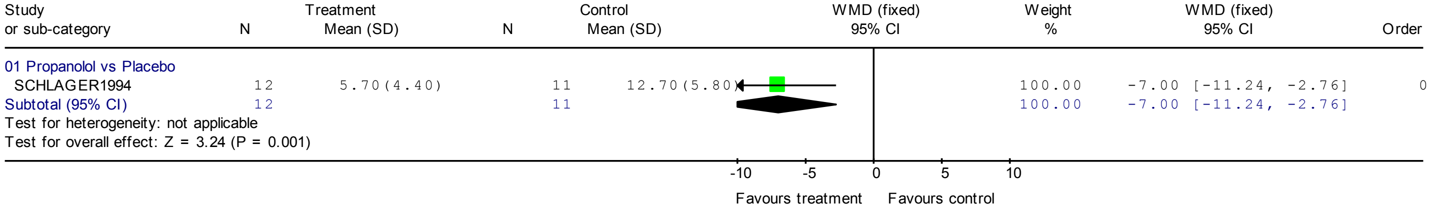
Study or sub-category	Treatment n/N	Control n/N	Weight %	RR (fixed) 95% CI	Order
01 High ion density vs Low ion density					
TERMAN1995	5/12	11/13	100.00	0.49 [0.24, 1.00]	0
Subtotal (95% CI)	12	13	100.00	0.49 [0.24, 1.00]	

Total events: 5 (Treatment), 11 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.96 (P = 0.05)

Continuation treatment

Mean endpoint depression scores (HAM-D21) (clinician-rated)

Review: Depression update pharmacology: treatments for SAD
Comparison: 13 Continuation treatment
Outcome: 01 Mean endpoint (clinician-rated) HAMD-21



Study or sub-category	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI	Order
01 Propanolol vs Placebo							
SCHLAGER1994	12	5.70(4.40)	11	12.70(5.80)	100.00	-7.00 [-11.24, -2.76]	0
Subtotal (95% CI)	12		11		100.00	-7.00 [-11.24, -2.76]	

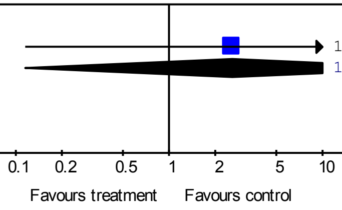
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.24 (P = 0.001)

Number leaving the study early for any reason

Review: Depression update pharmacology: treatments for SAD
Comparison: 13 Continuation treatment
Outcome: 02 Number leaving the study early for any reason

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Propanolol vs Placebo						
SCHLAGER1994	1/13	0/11		100.00	2.57 [0.12, 57.44]	0
Subtotal (95% CI)	13	11		100.00	2.57 [0.12, 57.44]	

Total events: 1 (Treatment), 0 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.60 (P = 0.55)



Antidepressants – prevention of a new episode

Number of patients experiencing a recurrence

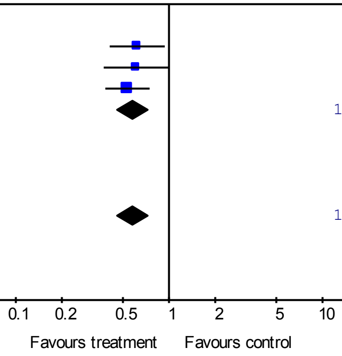
Review: Depression update pharmacology: treatments for SAD
Comparison: 14 Antidepressants: prevention of new episode
Outcome: 01 Buspirone vs placebo

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Number of patients expriencing a recurrence						
MODELL05 bpn v plb 1	28/142	43/135		28.19	0.62 [0.41, 0.94]	0
MODELL05 bpn v plb 2	22/158	35/153		22.74	0.61 [0.37, 0.99]	0
MODELL05 bpn v plb 3	42/242	75/231		49.07	0.53 [0.38, 0.74]	0
Subtotal (95% CI)	542	519		100.00	0.58 [0.46, 0.72]	

Total events: 92 (Treatment), 153 (Control)
Test for heterogeneity: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%
Test for overall effect: Z = 4.75 (P < 0.00001)

Total (95% CI)	542	519		100.00	0.58 [0.46, 0.72]	

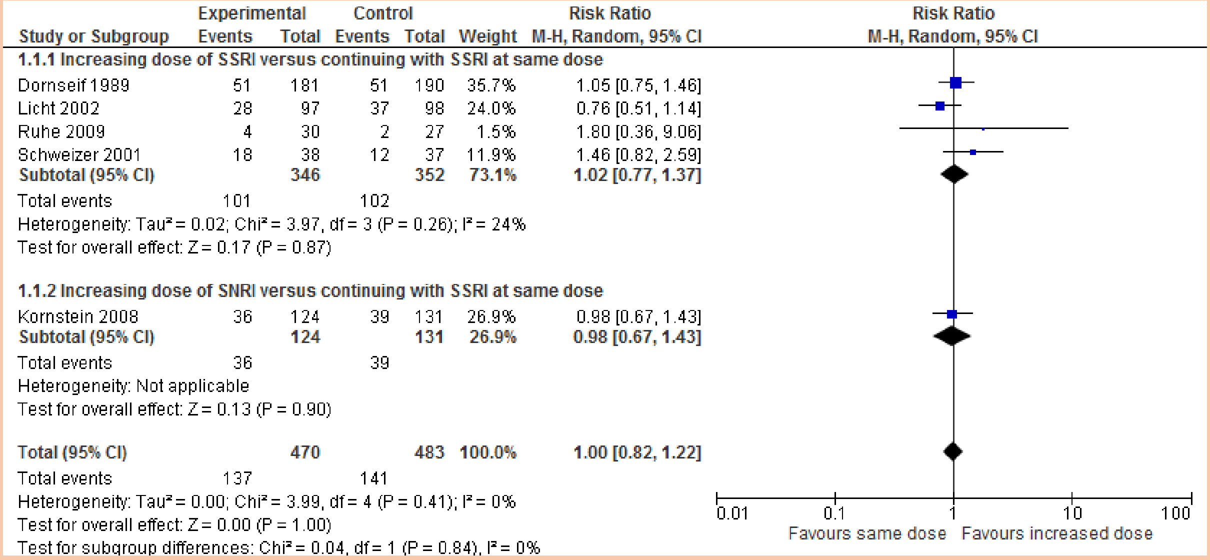
Total events: 92 (Treatment), 153 (Control)
Test for heterogeneity: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%
Test for overall effect: Z = 4.75 (P < 0.00001)



Further-line treatment (chapter 8)

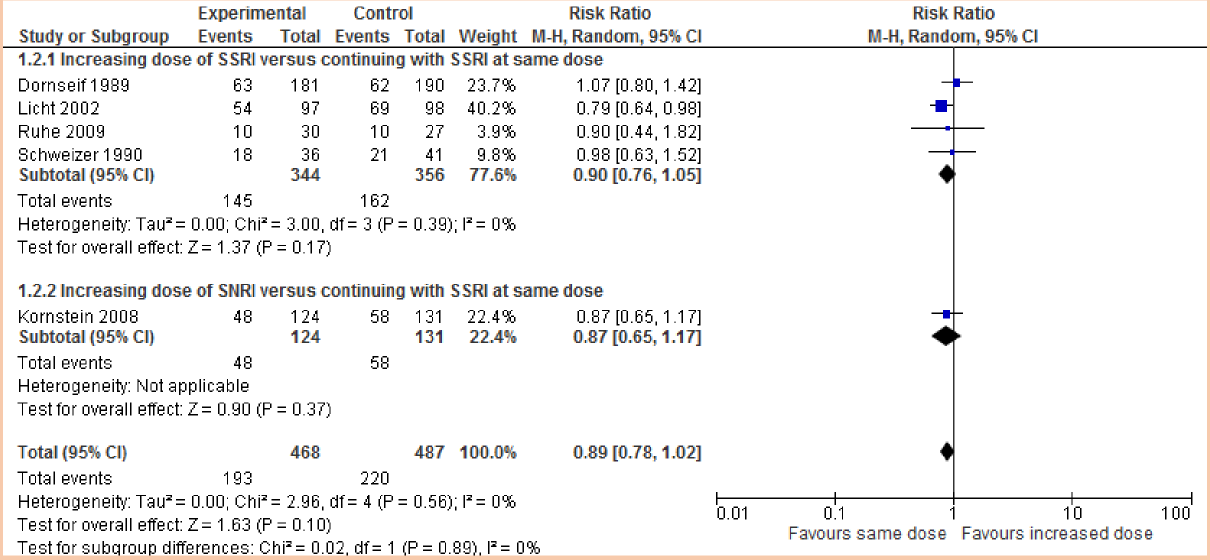
Increasing the dose of antidepressant versus continuing with the antidepressant at the same dose

Remission (≤7 on HAMD)



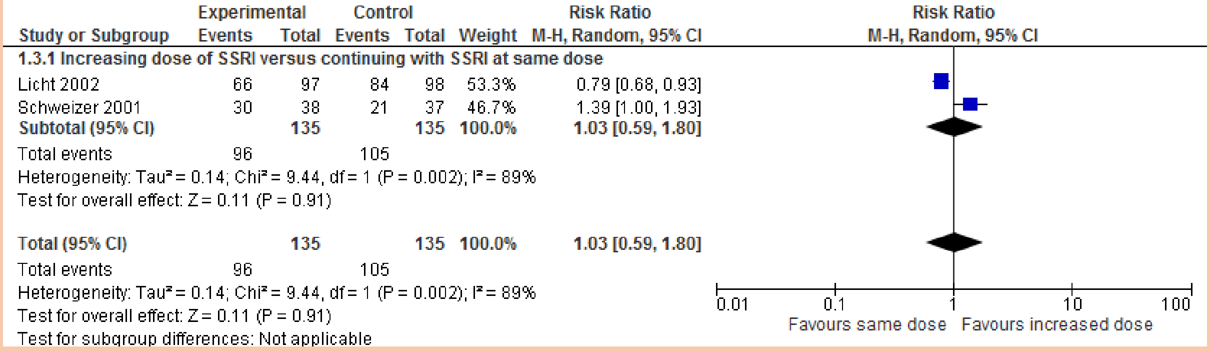
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Increasing dose of SSRI versus continuing with SSRI at same dose						
Dornseif 1989	51	181	51	190	35.7%	1.05 [0.75, 1.46]
Licht 2002	28	97	37	98	24.0%	0.76 [0.51, 1.14]
Ruhe 2009	4	30	2	27	1.5%	1.80 [0.36, 9.06]
Schweizer 2001	18	38	12	37	11.9%	1.46 [0.82, 2.59]
Subtotal (95% CI)		**346**		**352**	**73.1%**	**1.02 [0.77, 1.37]**
Total events	101		102			
Heterogeneity: Tau² = 0.02; Chi² = 3.97, df = 3 (P = 0.26); I² = 24%						
Test for overall effect: Z = 0.17 (P = 0.87)						
1.1.2 Increasing dose of SNRI versus continuing with SSRI at same dose						
Kornstein 2008	36	124	39	131	26.9%	0.98 [0.67, 1.43]
Subtotal (95% CI)		**124**		**131**	**26.9%**	**0.98 [0.67, 1.43]**
Total events	36		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**470**		**483**	**100.0%**	**1.00 [0.82, 1.22]**
Total events	137		141			
Heterogeneity: Tau² = 0.00; Chi² = 3.99, df = 4 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						

Response (≥50% improvement on HAMD)



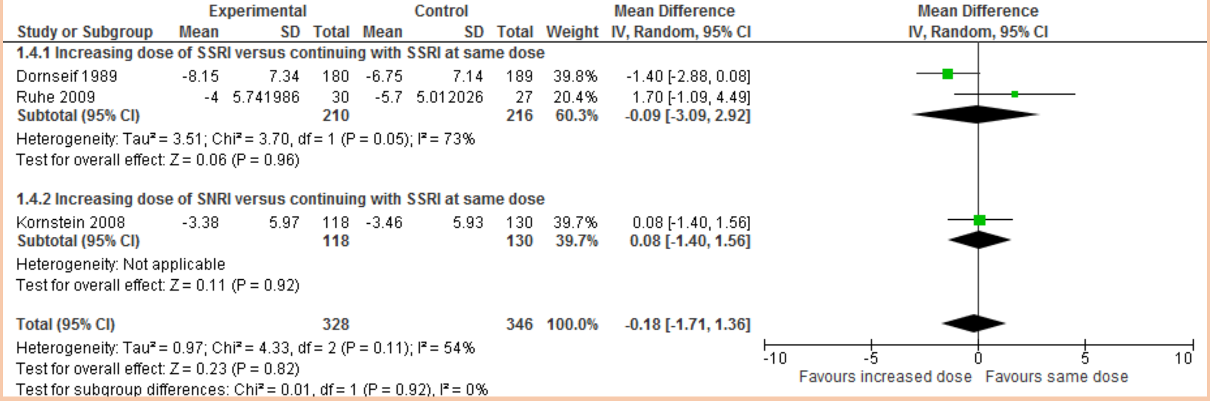
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Increasing dose of SSRI versus continuing with SSRI at same dose						
Dornseif 1989	63	181	62	190	23.7%	1.07 [0.80, 1.42]
Licht 2002	54	97	69	98	40.2%	0.79 [0.64, 0.98]
Ruhe 2009	10	30	10	27	3.9%	0.90 [0.44, 1.82]
Schweizer 1990	18	36	21	41	9.8%	0.98 [0.63, 1.52]
Subtotal (95% CI)		**344**		**356**	**77.6%**	**0.90 [0.76, 1.05]**
Total events	145		162			
Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 3 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.2.2 Increasing dose of SNRI versus continuing with SSRI at same dose						
Kornstein 2008	48	124	58	131	22.4%	0.87 [0.65, 1.17]
Subtotal (95% CI)		**124**		**131**	**22.4%**	**0.87 [0.65, 1.17]**
Total events	48		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**468**		**487**	**100.0%**	**0.89 [0.78, 1.02]**
Total events	193		220			
Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						

Response (much/very much improved on CGI-I)



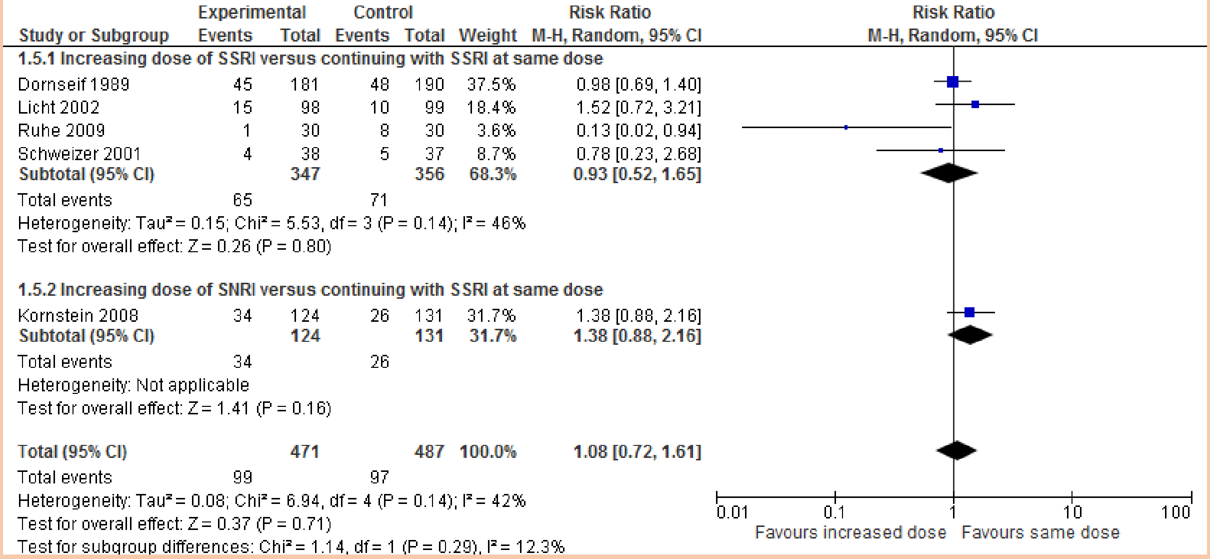
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Increasing dose of SSRI versus continuing with SSRI at same dose						
Licht 2002	66	97	84	98	53.3%	0.79 [0.68, 0.93]
Schweizer 2001	30	38	21	37	46.7%	1.39 [1.00, 1.93]
Subtotal (95% CI)		**135**		**135**	**100.0%**	**1.03 [0.59, 1.80]**
Total events	96		105			
Heterogeneity: Tau² = 0.14; Chi² = 9.44, df = 1 (P = 0.002); I² = 89%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**135**		**135**	**100.0%**	**1.03 [0.59, 1.80]**
Total events	96		105			
Heterogeneity: Tau² = 0.14; Chi² = 9.44, df = 1 (P = 0.002); I² = 89%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Test for subgroup differences: Not applicable						

Depression symptomatology (HAMD change score)



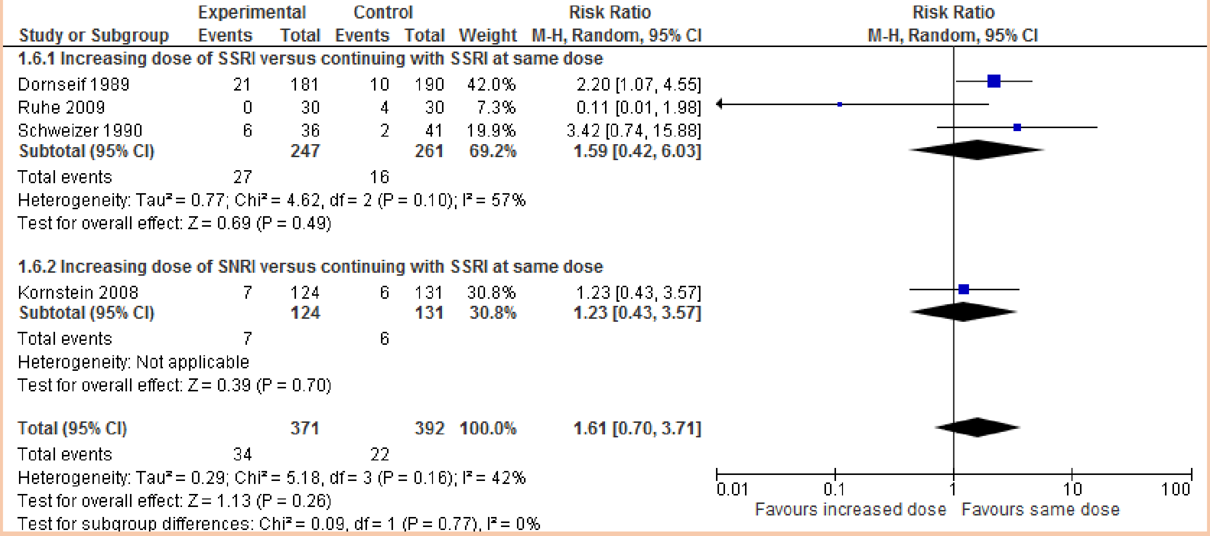
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Increasing dose of SSRI versus continuing with SSRI at same dose								
Dornseif 1989	-8.15	7.34	180	-6.75	7.14	189	39.8%	-1.40 [-2.88, 0.08]
Ruhe 2009	-4	5.741986	30	-5.7	5.012026	27	20.4%	1.70 [-1.09, 4.49]
Subtotal (95% CI)			**210**			**216**	**60.3%**	**-0.09 [-3.09, 2.92]**
Heterogeneity: Tau² = 3.51; Chi² = 3.70, df = 1 (P = 0.05); I² = 73%								
Test for overall effect: Z = 0.06 (P = 0.96)								
1.4.2 Increasing dose of SNRI versus continuing with SSRI at same dose								
Kornstein 2008	-3.38	5.97	118	-3.46	5.93	130	39.7%	0.08 [-1.40, 1.56]
Subtotal (95% CI)			**118**			**130**	**39.7%**	**0.08 [-1.40, 1.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.92)								
Total (95% CI)			**328**			**346**	**100.0%**	**-0.18 [-1.71, 1.36]**
Heterogeneity: Tau² = 0.97; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%								
Test for overall effect: Z = 0.23 (P = 0.82)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%								

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Increasing dose of SSRI versus continuing with SSRI at same dose						
Dornseif 1989	45	181	48	190	37.5%	0.98 [0.69, 1.40]
Licht 2002	15	98	10	99	18.4%	1.52 [0.72, 3.21]
Ruhe 2009	1	30	8	30	3.6%	0.13 [0.02, 0.94]
Schweizer 2001	4	38	5	37	8.7%	0.78 [0.23, 2.68]
Subtotal (95% CI)		**347**		**356**	**68.3%**	**0.93 [0.52, 1.65]**
Total events	65		71			
Heterogeneity: Tau² = 0.15; Chi² = 5.53, df = 3 (P = 0.14); I² = 46%						
Test for overall effect: Z = 0.26 (P = 0.80)						
1.5.2 Increasing dose of SNRI versus continuing with SSRI at same dose						
Kornstein 2008	34	124	26	131	31.7%	1.38 [0.88, 2.16]
Subtotal (95% CI)		**124**		**131**	**31.7%**	**1.38 [0.88, 2.16]**
Total events	34		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Total (95% CI)		**471**		**487**	**100.0%**	**1.08 [0.72, 1.61]**
Total events	99		97			
Heterogeneity: Tau² = 0.08; Chi² = 6.94, df = 4 (P = 0.14); I² = 42%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.3%						

Discontinuation due to adverse events

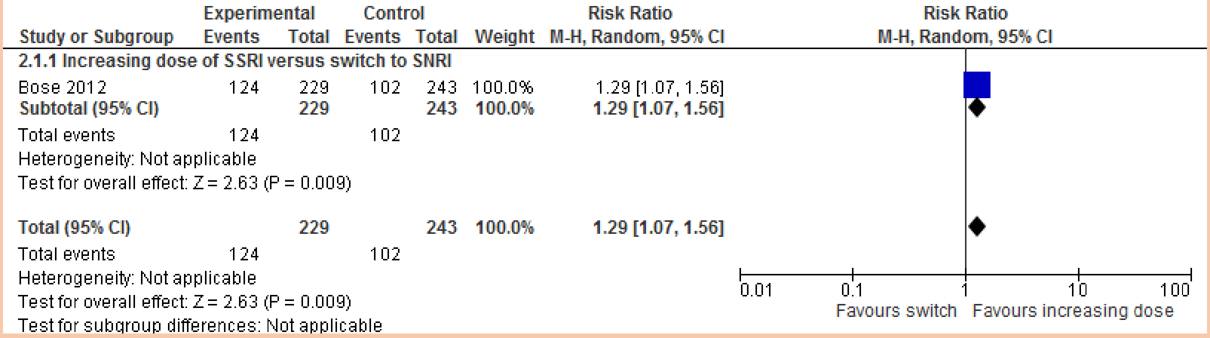


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Increasing dose of SSRI versus continuing with SSRI at same dose						
Dornseif 1989	21	181	10	190	42.0%	2.20 [1.07, 4.55]
Ruhe 2009	0	30	4	30	7.3%	0.11 [0.01, 1.98]
Schweizer 1990	6	36	2	41	19.9%	3.42 [0.74, 15.88]
Subtotal (95% CI)		**247**		**261**	**69.2%**	**1.59 [0.42, 6.03]**
Total events	27		16			
Heterogeneity: Tau² = 0.77; Chi² = 4.62, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.6.2 Increasing dose of SNRI versus continuing with SSRI at same dose						
Kornstein 2008	7	124	6	131	30.8%	1.23 [0.43, 3.57]
Subtotal (95% CI)		**124**		**131**	**30.8%**	**1.23 [0.43, 3.57]**
Total events	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**371**		**392**	**100.0%**	**1.61 [0.70, 3.71]**
Total events	34		22			
Heterogeneity: Tau² = 0.29; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours increased dose
Favours same dose

Increasing the dose of antidepressant versus switching to another antidepressant

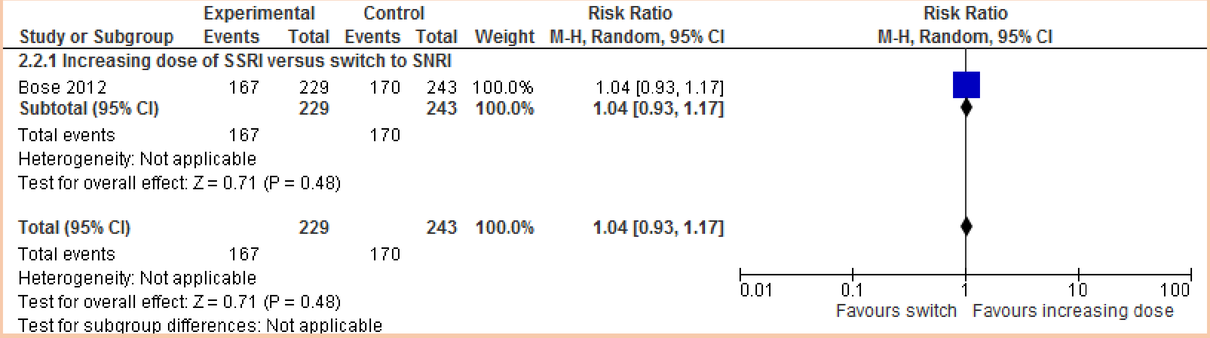
Remission (≤10 on MADRS)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Increasing dose of SSRI versus switch to SNRI						
Bose 2012	124	229	102	243	100.0%	1.29 [1.07, 1.56]
Subtotal (95% CI)		**229**		**243**	**100.0%**	**1.29 [1.07, 1.56]**
Total events	124		102			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
Total (95% CI)		**229**		**243**	**100.0%**	**1.29 [1.07, 1.56]**
Total events	124		102			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours switch
Favours increasing dose

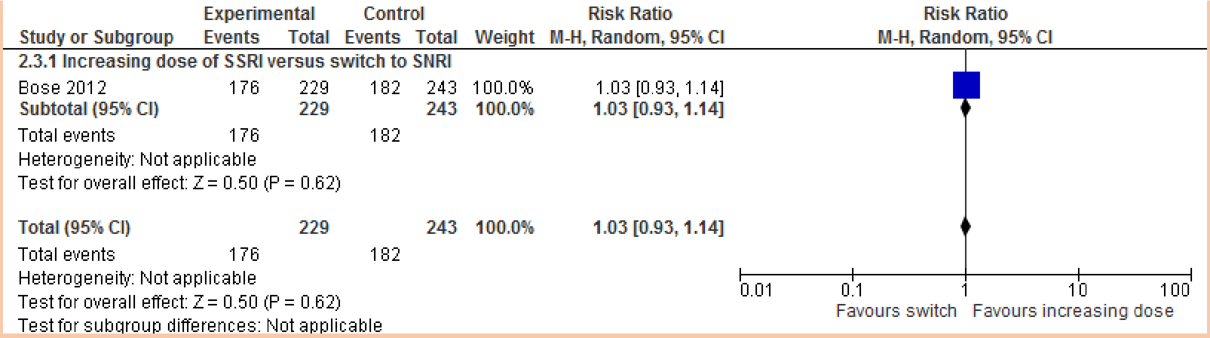
Response (≥50% improvement on MADRS)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Increasing dose of SSRI versus switch to SNRI						
Bose 2012	167	229	170	243	100.0%	1.04 [0.93, 1.17]
Subtotal (95% CI)		**229**		**243**	**100.0%**	**1.04 [0.93, 1.17]**
Total events	167		170			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**229**		**243**	**100.0%**	**1.04 [0.93, 1.17]**
Total events	167		170			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours switch
Favours increasing dose

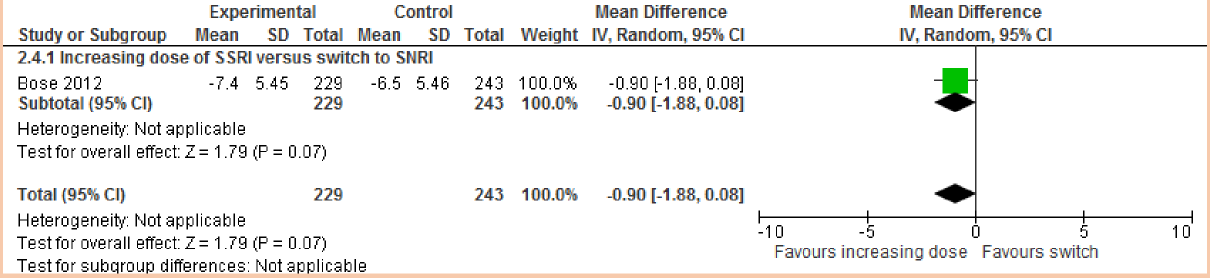
Response (much/very much improved on CGI-I)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Increasing dose of SSRI versus switch to SNRI						
Bose 2012	176	229	182	243	100.0%	1.03 [0.93, 1.14]
Subtotal (95% CI)		**229**		**243**	**100.0%**	**1.03 [0.93, 1.14]**
Total events	176		182			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
Total (95% CI)		**229**		**243**	**100.0%**	**1.03 [0.93, 1.14]**
Total events	176		182			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours switch
Favours increasing dose

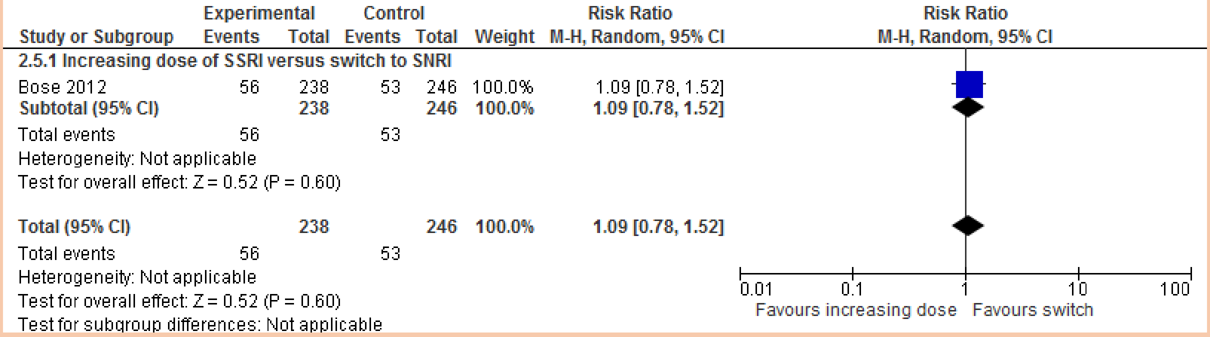
Depression symptomatology (QIDS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Increasing dose of SSRI versus switch to SNRI								
Bose 2012	-7.4	5.45	229	-6.5	5.46	243	100.0%	-0.90 [-1.88, 0.08]
Subtotal (95% CI)			**229**			**243**	**100.0%**	**-0.90 [-1.88, 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.79 (P = 0.07)								
Total (95% CI)			**229**			**243**	**100.0%**	**-0.90 [-1.88, 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.79 (P = 0.07)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours increasing dose
Favours switch

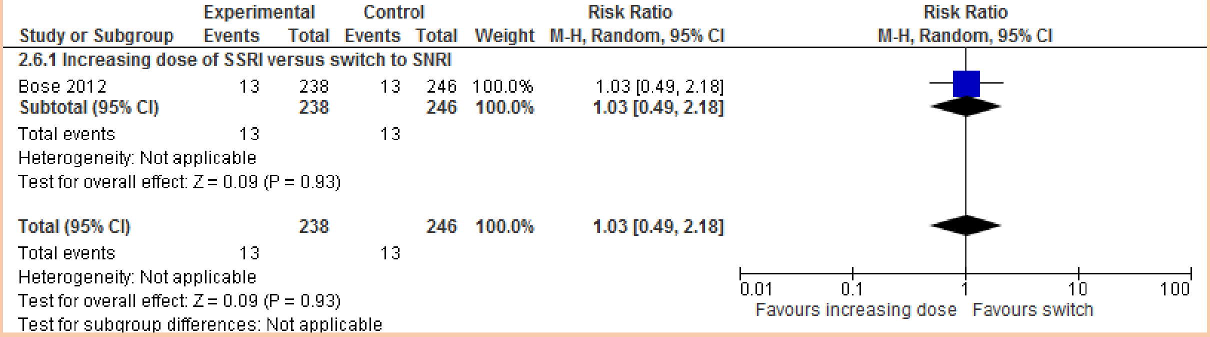
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Increasing dose of SSRI versus switch to SNRI						
Bose 2012	56	238	53	246	100.0%	1.09 [0.78, 1.52]
Subtotal (95% CI)		**238**		**246**	**100.0%**	**1.09 [0.78, 1.52]**
Total events	56		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
Total (95% CI)		**238**		**246**	**100.0%**	**1.09 [0.78, 1.52]**
Total events	56		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours increasing dose
Favours switch

Discontinuation due to adverse events

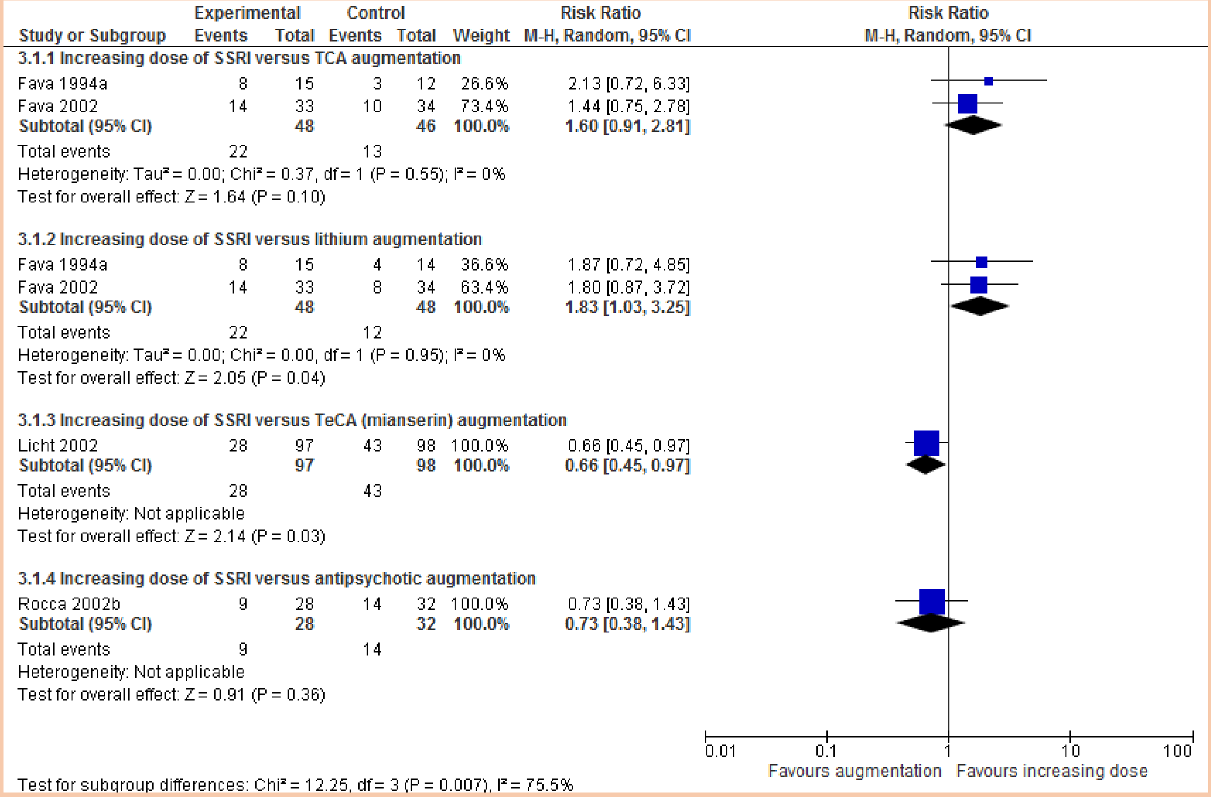


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Increasing dose of SSRI versus switch to SNRI						
Bose 2012	13	238	13	246	100.0%	1.03 [0.49, 2.18]
Subtotal (95% CI)		**238**		**246**	**100.0%**	**1.03 [0.49, 2.18]**
Total events	13		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**238**		**246**	**100.0%**	**1.03 [0.49, 2.18]**
Total events	13		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours increasing dose
Favours switch

Increasing the dose of antidepressant versus augmenting with another antidepressant/non-antidepressant agent

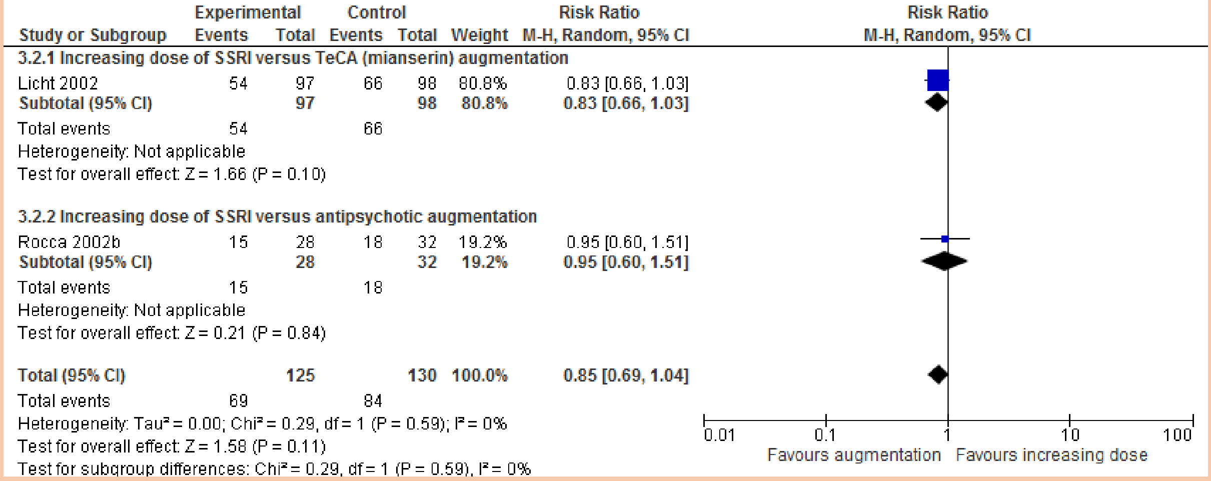
Remission (≤7 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Increasing dose of SSRI versus TCA augmentation						
Fava 1994a	8	15	3	12	26.6%	2.13 [0.72, 6.33]
Fava 2002	14	33	10	34	73.4%	1.44 [0.75, 2.78]
Subtotal (95% CI)		**48**		**46**	**100.0%**	**1.60 [0.91, 2.81]**
Total events	22		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
3.1.2 Increasing dose of SSRI versus lithium augmentation						
Fava 1994a	8	15	4	14	36.6%	1.87 [0.72, 4.85]
Fava 2002	14	33	8	34	63.4%	1.80 [0.87, 3.72]
Subtotal (95% CI)		**48**		**48**	**100.0%**	**1.83 [1.03, 3.25]**
Total events	22		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
3.1.3 Increasing dose of SSRI versus TeCA (mianserin) augmentation						
Licht 2002	28	97	43	98	100.0%	0.66 [0.45, 0.97]
Subtotal (95% CI)		**97**		**98**	**100.0%**	**0.66 [0.45, 0.97]**
Total events	28		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.14 (P = 0.03)						
3.1.4 Increasing dose of SSRI versus antipsychotic augmentation						
Rocca 2002b	9	28	14	32	100.0%	0.73 [0.38, 1.43]
Subtotal (95% CI)		**28**		**32**	**100.0%**	**0.73 [0.38, 1.43]**
Total events	9		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						

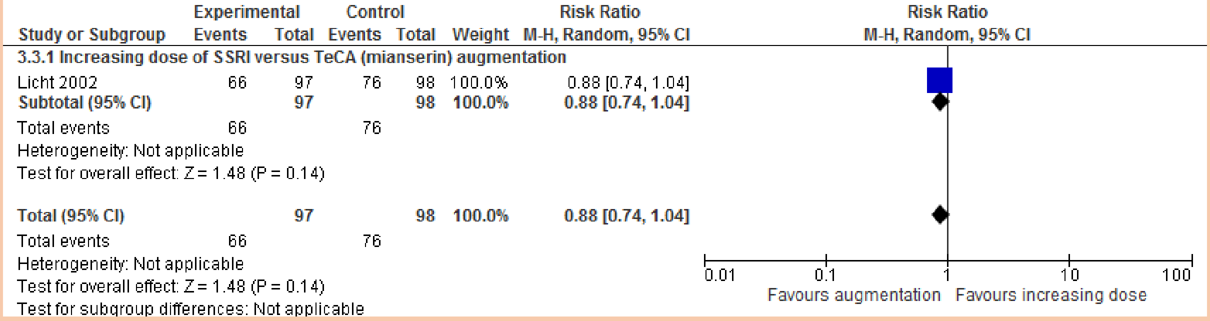
Test for subgroup differences: Chi² = 12.25, df = 3 (P = 0.007), I² = 75.5%

Response (≥50% improvement on HAMD)



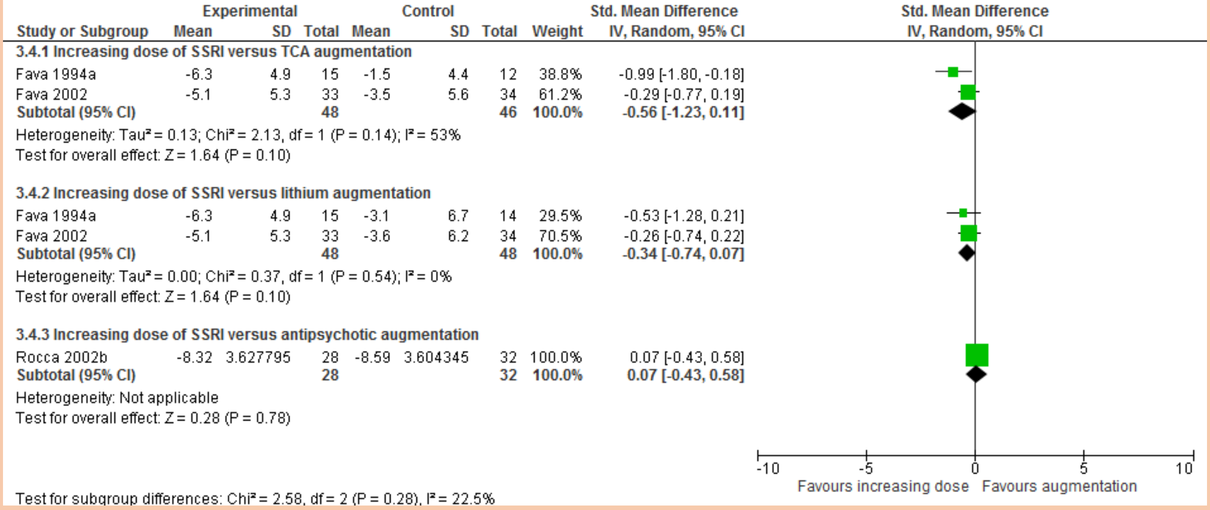
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Increasing dose of SSRI versus TeCA (mianserin) augmentation						
Licht 2002	54	97	66	98	80.8%	0.83 [0.66, 1.03]
Subtotal (95% CI)		**97**		**98**	**80.8%**	**0.83 [0.66, 1.03]**
Total events	54		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
3.2.2 Increasing dose of SSRI versus antipsychotic augmentation						
Rocca 2002b	15	28	18	32	19.2%	0.95 [0.60, 1.51]
Subtotal (95% CI)		**28**		**32**	**19.2%**	**0.95 [0.60, 1.51]**
Total events	15		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
Total (95% CI)		**125**		**130**	**100.0%**	**0.85 [0.69, 1.04]**
Total events	69		84			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						

Response (much/very much improved on CGI-I)



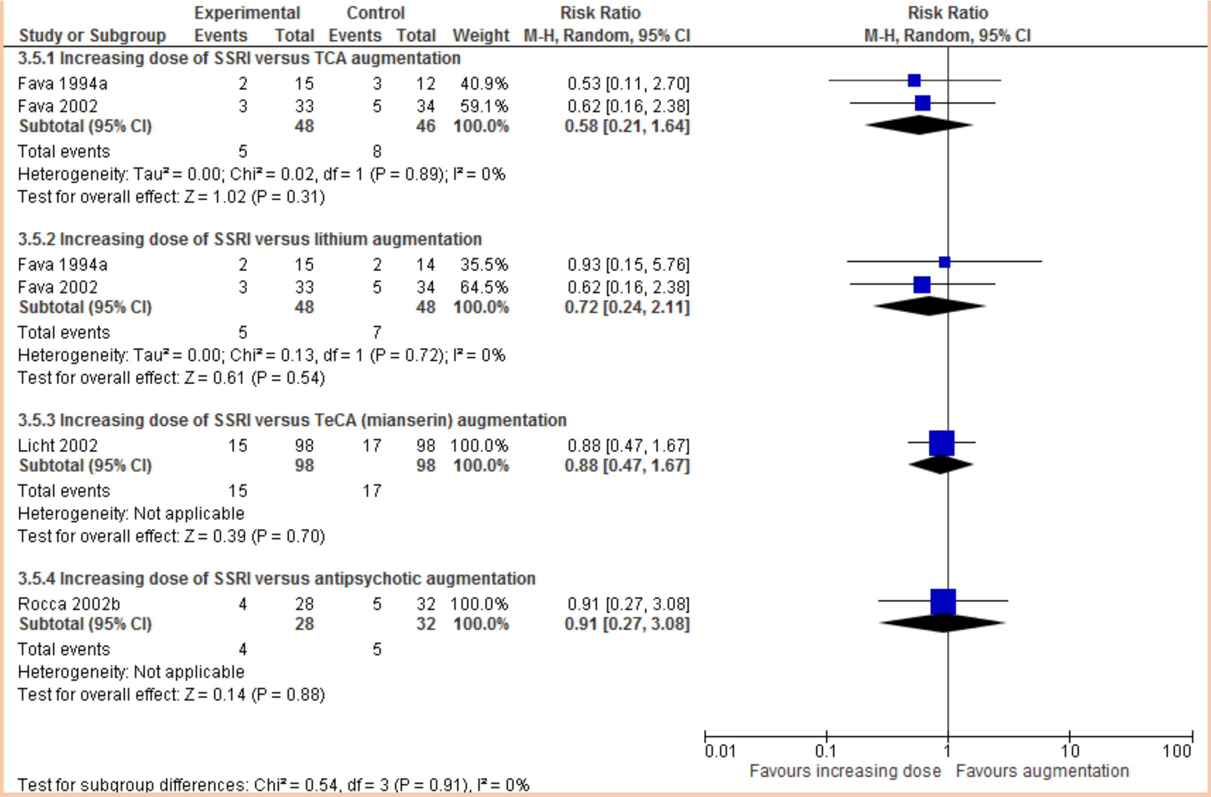
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Increasing dose of SSRI versus TeCA (mianserin) augmentation						
Licht 2002	66	97	76	98	100.0%	0.88 [0.74, 1.04]
Subtotal (95% CI)		**97**		**98**	**100.0%**	**0.88 [0.74, 1.04]**
Total events	66		76			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Total (95% CI)		**97**		**98**	**100.0%**	**0.88 [0.74, 1.04]**
Total events	66		76			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Not applicable						

Depression symptomatology (HAMD change score)



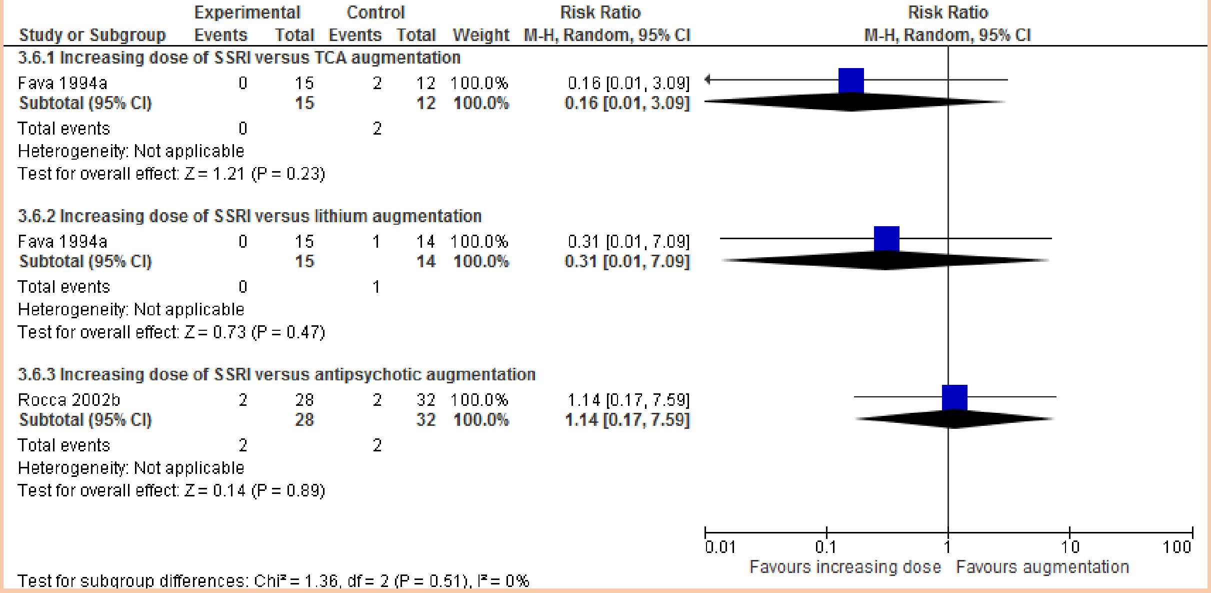
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.4.1 Increasing dose of SSRI versus TCA augmentation								
Fava 1994a	-6.3	4.9	15	-1.5	4.4	12	38.8%	-0.99 [-1.80, -0.18]
Fava 2002	-5.1	5.3	33	-3.5	5.6	34	61.2%	-0.29 [-0.77, 0.19]
Subtotal (95% CI)			**48**			**46**	**100.0%**	**-0.56 [-1.23, 0.11]**
Heterogeneity: Tau² = 0.13; Chi² = 2.13, df = 1 (P = 0.14); I² = 53%								
Test for overall effect: Z = 1.64 (P = 0.10)								
3.4.2 Increasing dose of SSRI versus lithium augmentation								
Fava 1994a	-6.3	4.9	15	-3.1	6.7	14	29.5%	-0.53 [-1.28, 0.21]
Fava 2002	-5.1	5.3	33	-3.6	6.2	34	70.5%	-0.26 [-0.74, 0.22]
Subtotal (95% CI)			**48**			**48**	**100.0%**	**-0.34 [-0.74, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%								
Test for overall effect: Z = 1.64 (P = 0.10)								
3.4.3 Increasing dose of SSRI versus antipsychotic augmentation								
Rocca 2002b	-8.32	3.627795	28	-8.59	3.604345	32	100.0%	0.07 [-0.43, 0.58]
Subtotal (95% CI)			**28**			**32**	**100.0%**	**0.07 [-0.43, 0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								
Test for subgroup differences: Chi² = 2.58, df = 2 (P = 0.28), I² = 22.5%								

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Increasing dose of SSRI versus TCA augmentation						
Fava 1994a	2	15	3	12	40.9%	0.53 [0.11, 2.70]
Fava 2002	3	33	5	34	59.1%	0.62 [0.16, 2.38]
Subtotal (95% CI)		**48**		**46**	**100.0%**	**0.58 [0.21, 1.64]**
Total events	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
3.5.2 Increasing dose of SSRI versus lithium augmentation						
Fava 1994a	2	15	2	14	35.5%	0.93 [0.15, 5.76]
Fava 2002	3	33	5	34	64.5%	0.62 [0.16, 2.38]
Subtotal (95% CI)		**48**		**48**	**100.0%**	**0.72 [0.24, 2.11]**
Total events	5		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
3.5.3 Increasing dose of SSRI versus TeCA (mianserin) augmentation						
Licht 2002	15	98	17	98	100.0%	0.88 [0.47, 1.67]
Subtotal (95% CI)		**98**		**98**	**100.0%**	**0.88 [0.47, 1.67]**
Total events	15		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
3.5.4 Increasing dose of SSRI versus antipsychotic augmentation						
Rocca 2002b	4	28	5	32	100.0%	0.91 [0.27, 3.08]
Subtotal (95% CI)		**28**		**32**	**100.0%**	**0.91 [0.27, 3.08]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.88)						
Test for subgroup differences: Chi² = 0.54, df = 3 (P = 0.91), I² = 0%						

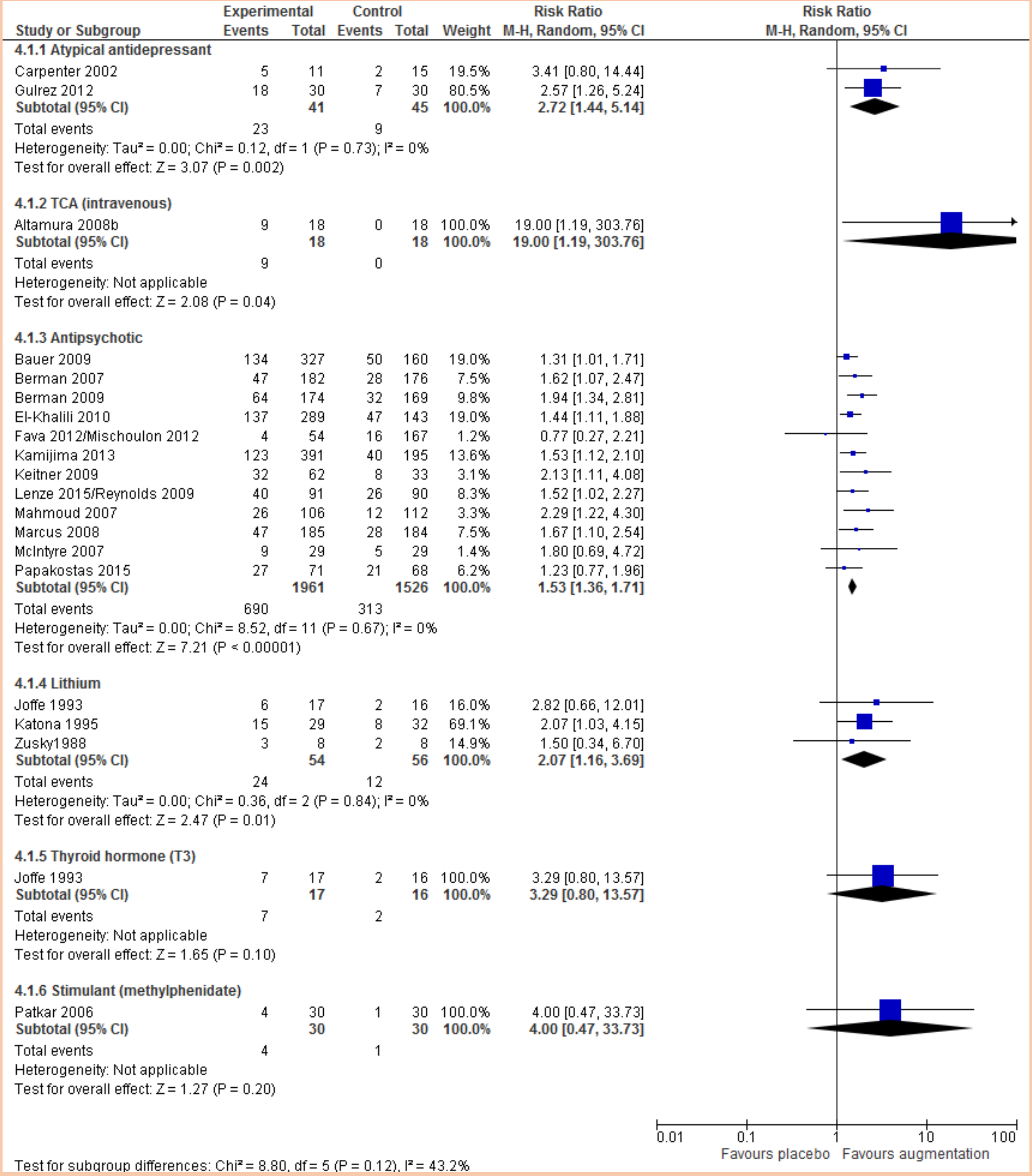
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Increasing dose of SSRI versus TCA augmentation						
Fava 1994a	0	15	2	12	100.0%	0.16 [0.01, 3.09]
Subtotal (95% CI)		**15**		**12**	**100.0%**	**0.16 [0.01, 3.09]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
3.6.2 Increasing dose of SSRI versus lithium augmentation						
Fava 1994a	0	15	1	14	100.0%	0.31 [0.01, 7.09]
Subtotal (95% CI)		**15**		**14**	**100.0%**	**0.31 [0.01, 7.09]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
3.6.3 Increasing dose of SSRI versus antipsychotic augmentation						
Rocca 2002b	2	28	2	32	100.0%	1.14 [0.17, 7.59]
Subtotal (95% CI)		**28**		**32**	**100.0%**	**1.14 [0.17, 7.59]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi² = 1.36, df = 2 (P = 0.51), I² = 0%						

Augmenting the antidepressant with another antidepressant or a non-antidepressant agent versus placebo

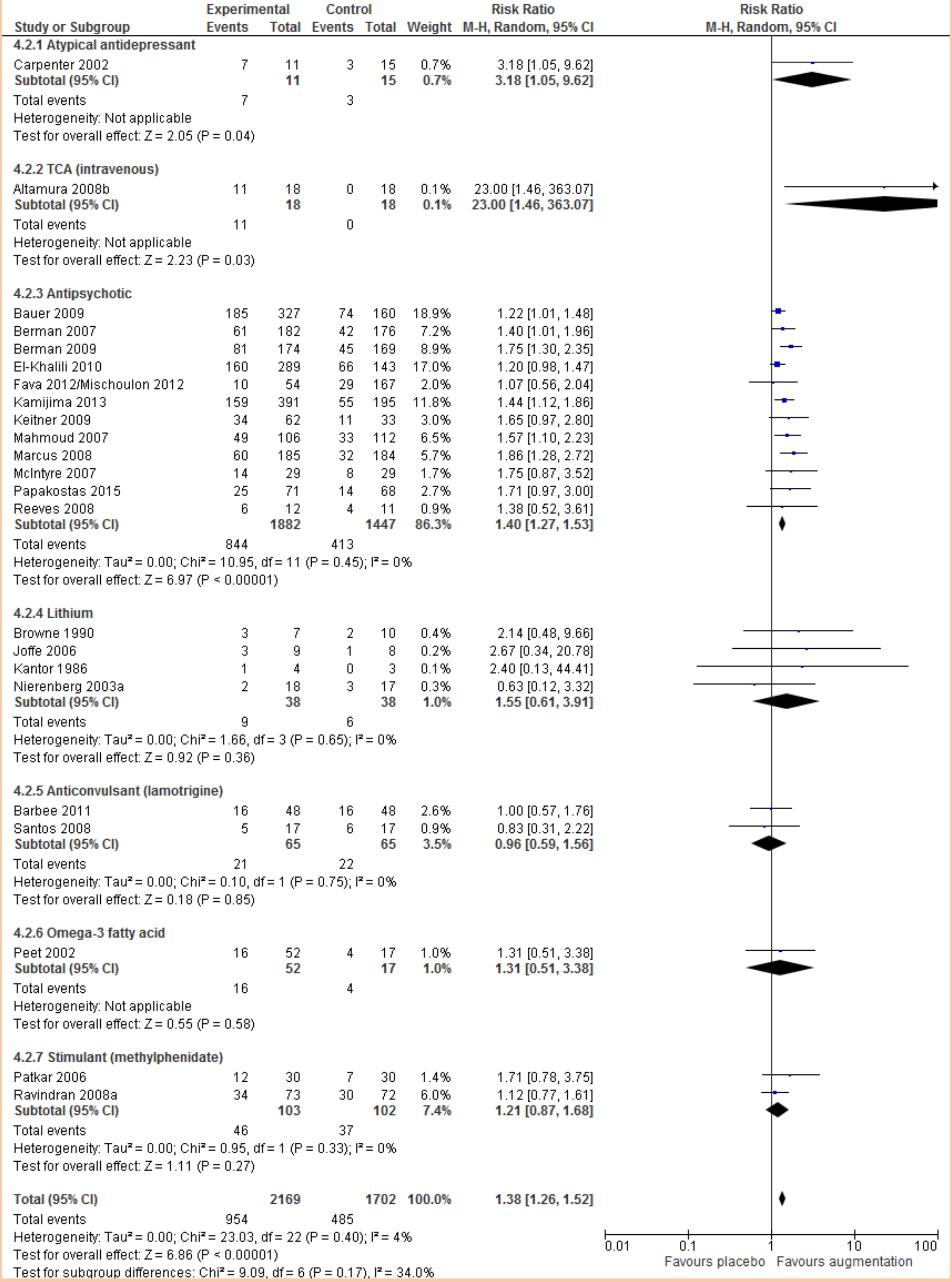
Remission (<10/11 on MADRS/<7/8/10 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Atypical antidepressant						
Carpenter 2002	5	11	2	15	19.5%	3.41 [0.80, 14.44]
Gulrez 2012	18	30	7	30	80.5%	2.57 [1.26, 5.24]
Subtotal (95% CI)		**41**		**45**	**100.0%**	**2.72 [1.44, 5.14]**
Total events	23		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 3.07 (P = 0.002)						
4.1.2 TCA (intravenous)						
Altamura 2008b	9	18	0	18	100.0%	19.00 [1.19, 303.76]
Subtotal (95% CI)		**18**		**18**	**100.0%**	**19.00 [1.19, 303.76]**
Total events	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
4.1.3 Antipsychotic						
Bauer 2009	134	327	50	160	19.0%	1.31 [1.01, 1.71]
Berman 2007	47	182	28	176	7.5%	1.62 [1.07, 2.47]
Berman 2009	64	174	32	169	9.8%	1.94 [1.34, 2.81]
El-Khalili 2010	137	289	47	143	19.0%	1.44 [1.11, 1.88]
Fava 2012/Mischoulon 2012	4	54	16	167	1.2%	0.77 [0.27, 2.21]
Kamijima 2013	123	391	40	195	13.6%	1.53 [1.12, 2.10]
Keitner 2009	32	62	8	33	3.1%	2.13 [1.11, 4.08]
Lenze 2015/Reynolds 2009	40	91	26	90	8.3%	1.52 [1.02, 2.27]
Mahmoud 2007	26	106	12	112	3.3%	2.29 [1.22, 4.30]
Marcus 2008	47	185	28	184	7.5%	1.67 [1.10, 2.54]
McIntyre 2007	9	29	5	29	1.4%	1.80 [0.69, 4.72]
Papakostas 2015	27	71	21	68	6.2%	1.23 [0.77, 1.96]
Subtotal (95% CI)		**1961**		**1526**	**100.0%**	**1.53 [1.36, 1.71]**
Total events	690		313			
Heterogeneity: Tau² = 0.00; Chi² = 8.52, df = 11 (P = 0.67); I² = 0%						
Test for overall effect: Z = 7.21 (P < 0.00001)						
4.1.4 Lithium						
Joffe 1993	6	17	2	16	16.0%	2.82 [0.66, 12.01]
Katona 1995	15	29	8	32	69.1%	2.07 [1.03, 4.15]
Zusky1988	3	8	2	8	14.9%	1.50 [0.34, 6.70]
Subtotal (95% CI)		**54**		**56**	**100.0%**	**2.07 [1.16, 3.69]**
Total events	24		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.47 (P = 0.01)						
4.1.5 Thyroid hormone (T3)						
Joffe 1993	7	17	2	16	100.0%	3.29 [0.80, 13.57]
Subtotal (95% CI)		**17**		**16**	**100.0%**	**3.29 [0.80, 13.57]**
Total events	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
4.1.6 Stimulant (methylphenidate)						
Patkar 2006	4	30	1	30	100.0%	4.00 [0.47, 33.73]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**4.00 [0.47, 33.73]**
Total events	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						

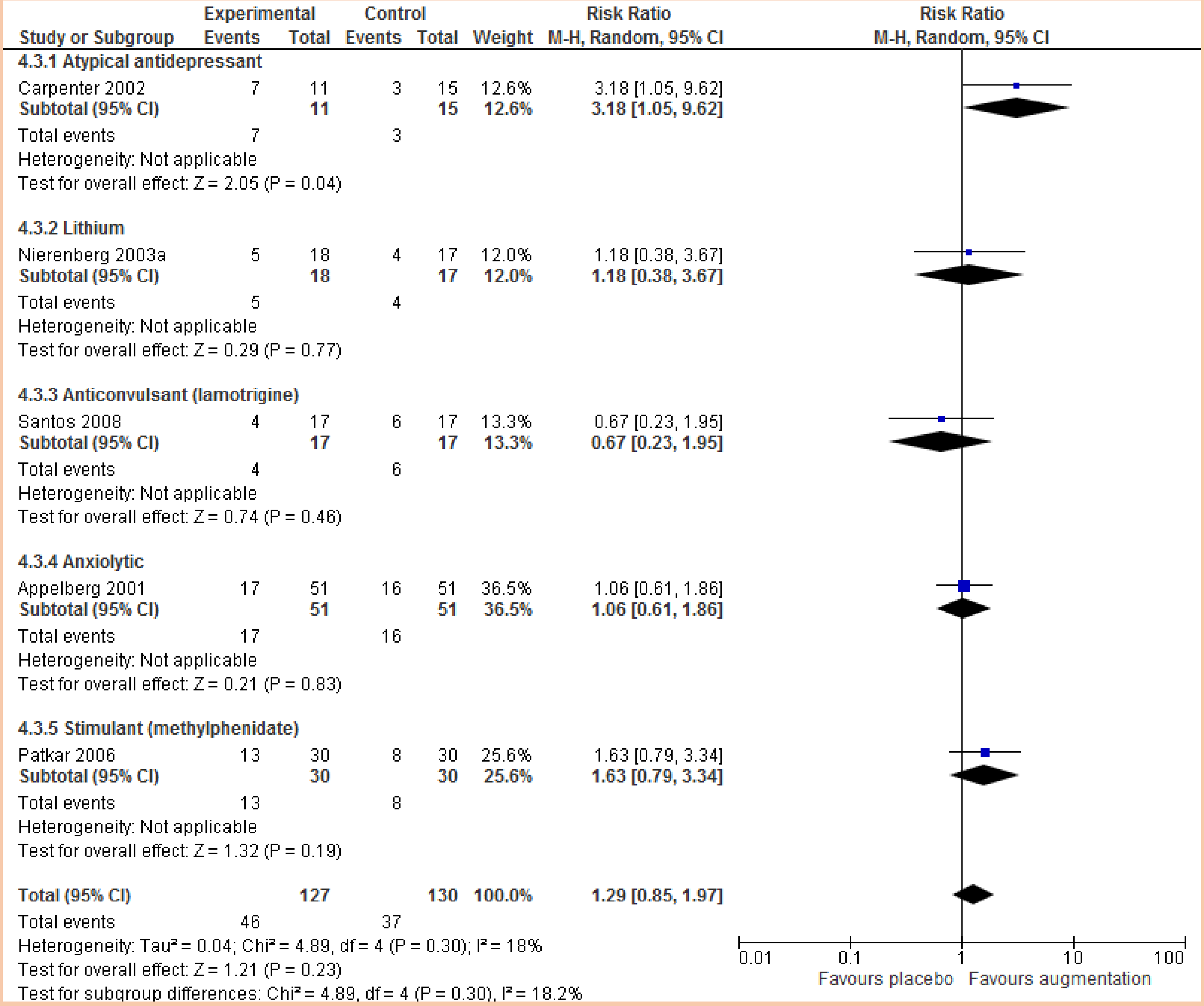
Test for subgroup differences: Chi² = 8.80, df = 5 (P = 0.12), I² = 43.2%

Response (≥50% improvement on MADRS/HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Atypical antidepressant						
Carpenter 2002	7	11	3	15	0.7%	3.18 [1.05, 9.62]
Subtotal (95% CI)		**11**		**15**	**0.7%**	**3.18 [1.05, 9.62]**
Total events	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
4.2.2 TCA (intravenous)						
Altamura 2008b	11	18	0	18	0.1%	23.00 [1.46, 363.07]
Subtotal (95% CI)		**18**		**18**	**0.1%**	**23.00 [1.46, 363.07]**
Total events	11		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.23 (P = 0.03)						
4.2.3 Antipsychotic						
Bauer 2009	185	327	74	160	18.9%	1.22 [1.01, 1.48]
Berman 2007	61	182	42	176	7.2%	1.40 [1.01, 1.96]
Berman 2009	81	174	45	169	8.9%	1.75 [1.30, 2.35]
El-Khalili 2010	160	289	66	143	17.0%	1.20 [0.98, 1.47]
Fava 2012/Mischoulon 2012	10	54	29	167	2.0%	1.07 [0.56, 2.04]
Kamijima 2013	159	391	55	195	11.8%	1.44 [1.12, 1.86]
Keitner 2009	34	62	11	33	3.0%	1.65 [0.97, 2.80]
Mahmoud 2007	49	106	33	112	6.5%	1.57 [1.10, 2.23]
Marcus 2008	60	185	32	184	5.7%	1.86 [1.28, 2.72]
McIntyre 2007	14	29	8	29	1.7%	1.75 [0.87, 3.52]
Papakostas 2015	25	71	14	68	2.7%	1.71 [0.97, 3.00]
Reeves 2008	6	12	4	11	0.9%	1.38 [0.52, 3.61]
Subtotal (95% CI)		**1882**		**1447**	**86.3%**	**1.40 [1.27, 1.53]**
Total events	844		413			
Heterogeneity: Tau² = 0.00; Chi² = 10.95, df = 11 (P = 0.45); I² = 0%						
Test for overall effect: Z = 6.97 (P < 0.00001)						
4.2.4 Lithium						
Browne 1990	3	7	2	10	0.4%	2.14 [0.48, 9.66]
Joffe 2006	3	9	1	8	0.2%	2.67 [0.34, 20.78]
Kantor 1986	1	4	0	3	0.1%	2.40 [0.13, 44.41]
Nierenberg 2003a	2	18	3	17	0.3%	0.63 [0.12, 3.32]
Subtotal (95% CI)		**38**		**38**	**1.0%**	**1.55 [0.61, 3.91]**
Total events	9		6			
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 3 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
4.2.5 Anticonvulsant (lamotrigine)						
Barbee 2011	16	48	16	48	2.6%	1.00 [0.57, 1.76]
Santos 2008	5	17	6	17	0.9%	0.83 [0.31, 2.22]
Subtotal (95% CI)		**65**		**65**	**3.5%**	**0.96 [0.59, 1.56]**
Total events	21		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.85)						
4.2.6 Omega-3 fatty acid						
Peet 2002	16	52	4	17	1.0%	1.31 [0.51, 3.38]
Subtotal (95% CI)		**52**		**17**	**1.0%**	**1.31 [0.51, 3.38]**
Total events	16		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
4.2.7 Stimulant (methylphenidate)						
Patkar 2006	12	30	7	30	1.4%	1.71 [0.78, 3.75]
Ravindran 2008a	34	73	30	72	6.0%	1.12 [0.77, 1.61]
Subtotal (95% CI)		**103**		**102**	**7.4%**	**1.21 [0.87, 1.68]**
Total events	46		37			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**2169**		**1702**	**100.0%**	**1.38 [1.26, 1.52]**
Total events	954		485			
Heterogeneity: Tau² = 0.00; Chi² = 23.03, df = 22 (P = 0.40); I² = 4%						
Test for overall effect: Z = 6.86 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.09, df = 6 (P = 0.17), I² = 34.0%						

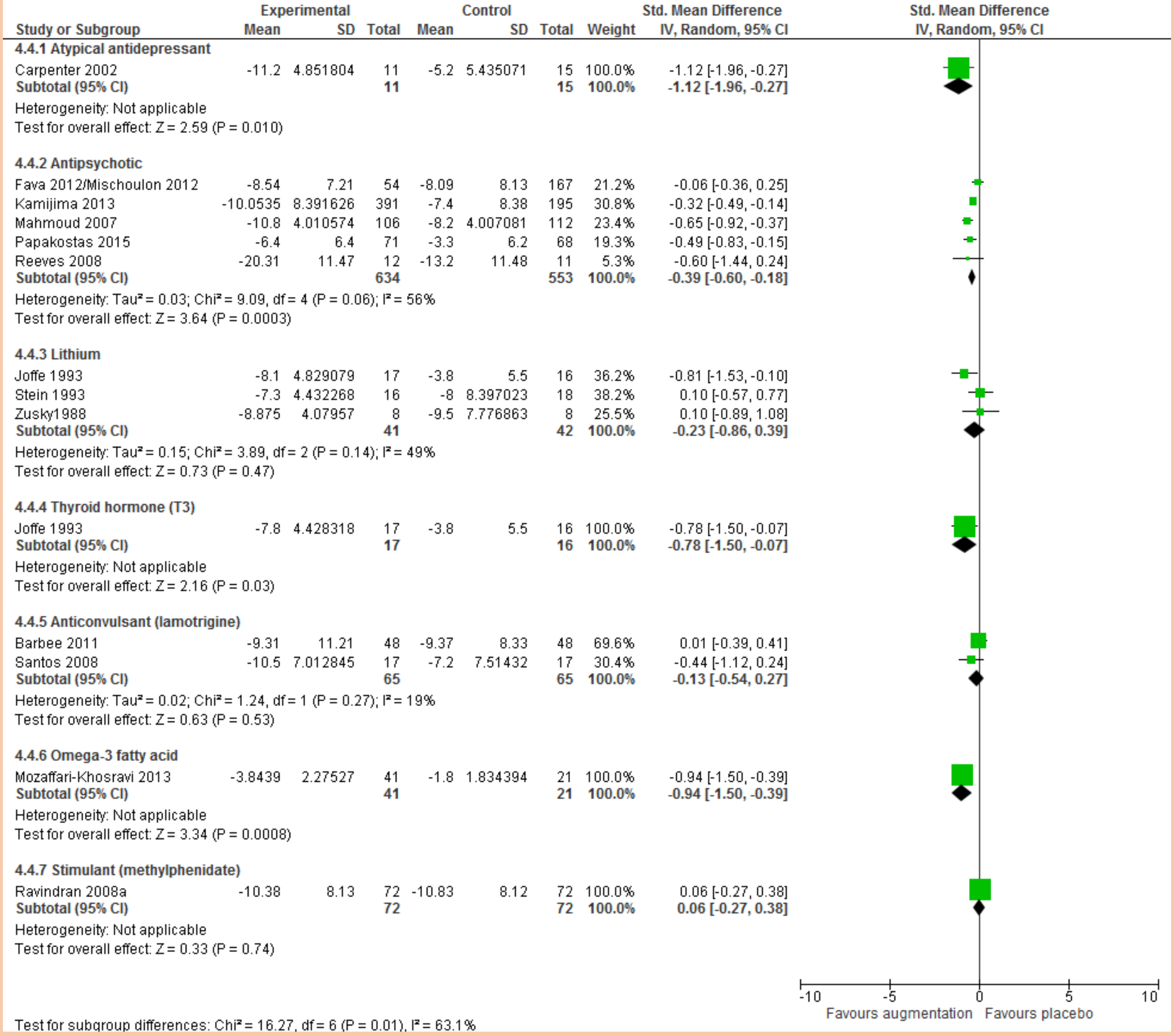
Response (much/very much improved on CGI-I)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Atypical antidepressant						
Carpenter 2002	7	11	3	15	12.6%	3.18 [1.05, 9.62]
Subtotal (95% CI)		**11**		**15**	**12.6%**	**3.18 [1.05, 9.62]**
Total events	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
4.3.2 Lithium						
Nierenberg 2003a	5	18	4	17	12.0%	1.18 [0.38, 3.67]
Subtotal (95% CI)		**18**		**17**	**12.0%**	**1.18 [0.38, 3.67]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
4.3.3 Anticonvulsant (lamotrigine)						
Santos 2008	4	17	6	17	13.3%	0.67 [0.23, 1.95]
Subtotal (95% CI)		**17**		**17**	**13.3%**	**0.67 [0.23, 1.95]**
Total events	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
4.3.4 Anxiolytic						
Appelberg 2001	17	51	16	51	36.5%	1.06 [0.61, 1.86]
Subtotal (95% CI)		**51**		**51**	**36.5%**	**1.06 [0.61, 1.86]**
Total events	17		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
4.3.5 Stimulant (methylphenidate)						
Patkar 2006	13	30	8	30	25.6%	1.63 [0.79, 3.34]
Subtotal (95% CI)		**30**		**30**	**25.6%**	**1.63 [0.79, 3.34]**
Total events	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**127**		**130**	**100.0%**	**1.29 [0.85, 1.97]**
Total events	46		37			

Heterogeneity: Tau² = 0.04; Chi² = 4.89, df = 4 (P = 0.30); I² = 18%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Chi² = 4.89, df = 4 (P = 0.30), I² = 18.2%

Depression symptomatology (MADRS/HAMD change score)

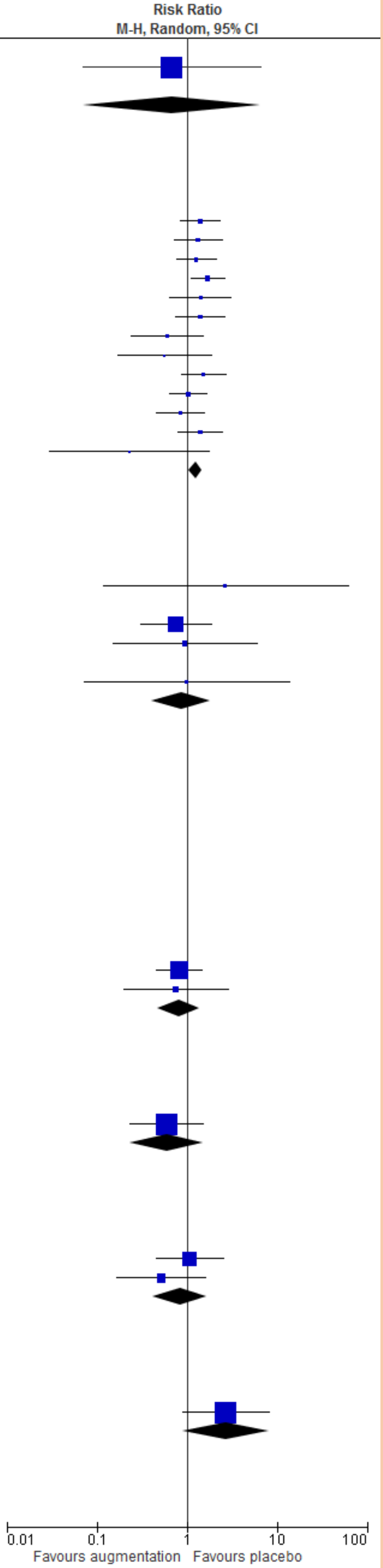


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.4.1 Atypical antidepressant								
Carpenter 2002	-11.2	4.851804	11	-5.2	5.435071	15	100.0%	-1.12 [-1.96, -0.27]
Subtotal (95% CI)			**11**			**15**	**100.0%**	**-1.12 [-1.96, -0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.59 (P = 0.010)								
4.4.2 Antipsychotic								
Fava 2012/Mischoulon 2012	-8.54	7.21	54	-8.09	8.13	167	21.2%	-0.06 [-0.36, 0.25]
Kamijima 2013	-10.0535	8.391626	391	-7.4	8.38	195	30.8%	-0.32 [-0.49, -0.14]
Mahmoud 2007	-10.8	4.010574	106	-8.2	4.007081	112	23.4%	-0.65 [-0.92, -0.37]
Papakostas 2015	-6.4	6.4	71	-3.3	6.2	68	19.3%	-0.49 [-0.83, -0.15]
Reeves 2008	-20.31	11.47	12	-13.2	11.48	11	5.3%	-0.60 [-1.44, 0.24]
Subtotal (95% CI)			**634**			**553**	**100.0%**	**-0.39 [-0.60, -0.18]**
Heterogeneity: Tau² = 0.03; Chi² = 9.09, df = 4 (P = 0.06); I² = 56%								
Test for overall effect: Z = 3.64 (P = 0.0003)								
4.4.3 Lithium								
Joffe 1993	-8.1	4.829079	17	-3.8	5.5	16	36.2%	-0.81 [-1.53, -0.10]
Stein 1993	-7.3	4.432268	16	-8	8.397023	18	38.2%	0.10 [-0.57, 0.77]
Zusky1988	-8.875	4.07957	8	-9.5	7.776863	8	25.5%	0.10 [-0.89, 1.08]
Subtotal (95% CI)			**41**			**42**	**100.0%**	**-0.23 [-0.86, 0.39]**
Heterogeneity: Tau² = 0.15; Chi² = 3.89, df = 2 (P = 0.14); I² = 49%								
Test for overall effect: Z = 0.73 (P = 0.47)								
4.4.4 Thyroid hormone (T3)								
Joffe 1993	-7.8	4.428318	17	-3.8	5.5	16	100.0%	-0.78 [-1.50, -0.07]
Subtotal (95% CI)			**17**			**16**	**100.0%**	**-0.78 [-1.50, -0.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.16 (P = 0.03)								
4.4.5 Anticonvulsant (lamotrigine)								
Barbee 2011	-9.31	11.21	48	-9.37	8.33	48	69.6%	0.01 [-0.39, 0.41]
Santos 2008	-10.5	7.012845	17	-7.2	7.51432	17	30.4%	-0.44 [-1.12, 0.24]
Subtotal (95% CI)			**65**			**65**	**100.0%**	**-0.13 [-0.54, 0.27]**
Heterogeneity: Tau² = 0.02; Chi² = 1.24, df = 1 (P = 0.27); I² = 19%								
Test for overall effect: Z = 0.63 (P = 0.53)								
4.4.6 Omega-3 fatty acid								
Mozaffari-Khosravi 2013	-3.8439	2.27527	41	-1.8	1.834394	21	100.0%	-0.94 [-1.50, -0.39]
Subtotal (95% CI)			**41**			**21**	**100.0%**	**-0.94 [-1.50, -0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.34 (P = 0.0008)								
4.4.7 Stimulant (methylphenidate)								
Ravindran 2008a	-10.38	8.13	72	-10.83	8.12	72	100.0%	0.06 [-0.27, 0.38]
Subtotal (95% CI)			**72**			**72**	**100.0%**	**0.06 [-0.27, 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								

Test for subgroup differences: Chi² = 16.27, df = 6 (P = 0.01), I² = 63.1%

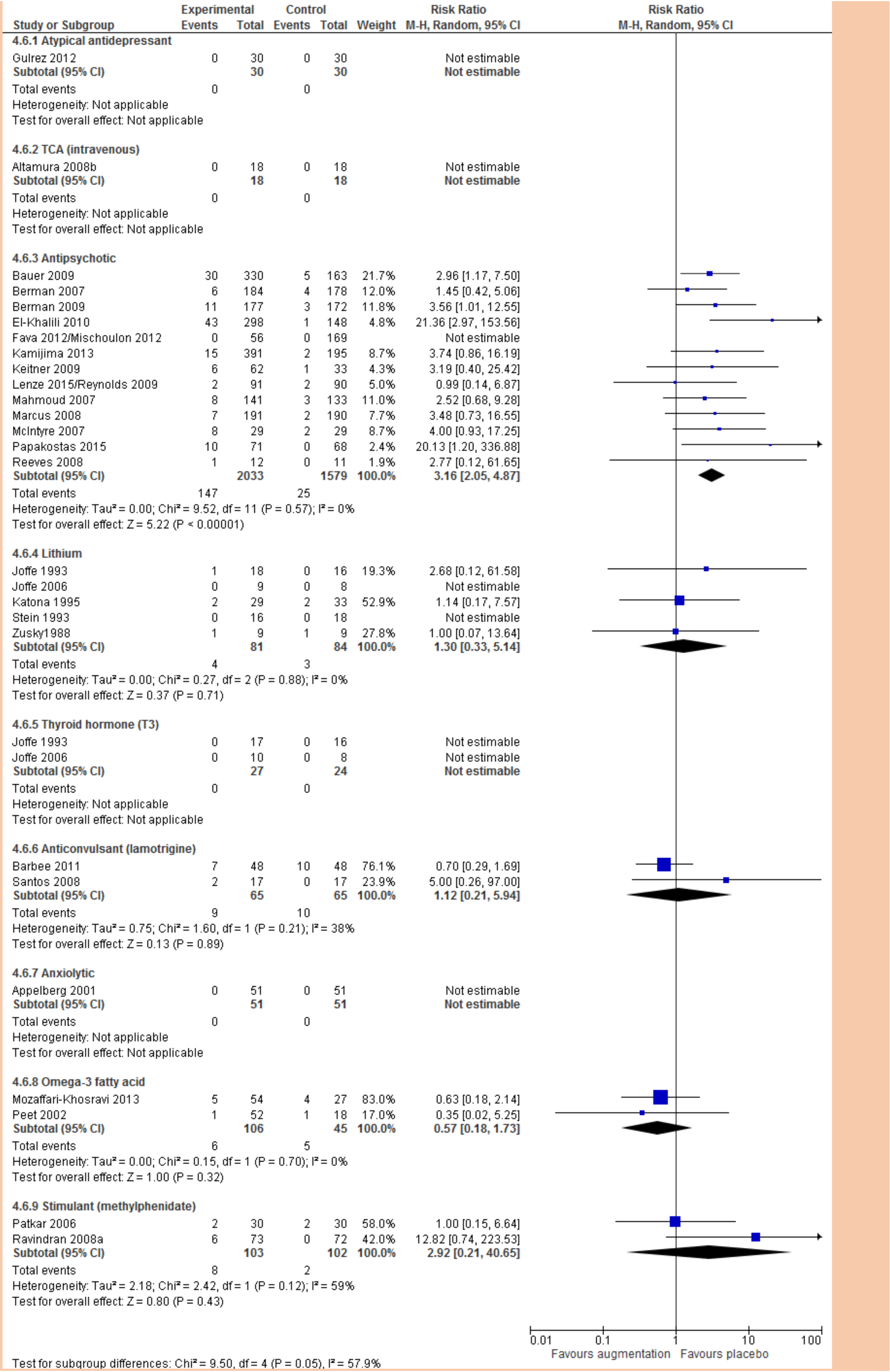
Discontinuation for any reason (including adverse events)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 Atypical antidepressant						
Carpenter 2002	1	11	2	15	100.0%	0.68 [0.07, 6.61]
Gulrez 2012	0	30	0	30		Not estimable
Subtotal (95% CI)		**41**		**45**	**100.0%**	**0.68 [0.07, 6.61]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
4.5.2 Antipsychotic						
Bauer 2009	51	330	18	163	11.1%	1.40 [0.85, 2.32]
Berman 2007	22	184	16	178	7.6%	1.33 [0.72, 2.45]
Berman 2009	30	177	23	172	11.2%	1.27 [0.77, 2.09]
El-Khalili 2010	79	298	23	148	15.8%	1.71 [1.12, 2.60]
Fava 2012/Mischoulon 2012	8	56	17	169	4.6%	1.42 [0.65, 3.11]
Kamijima 2013	34	391	12	195	7.0%	1.41 [0.75, 2.67]
Keitner 2009	8	62	7	33	3.3%	0.61 [0.24, 1.53]
Lenze 2015/Reynolds 2009	4	91	7	90	2.0%	0.57 [0.17, 1.86]
Mahmoud 2007	26	141	16	133	8.5%	1.53 [0.86, 2.73]
Marcus 2008	29	191	28	190	12.2%	1.03 [0.64, 1.66]
McIntyre 2007	11	29	13	29	7.4%	0.85 [0.46, 1.57]
Papakostas 2015	22	71	15	68	8.8%	1.40 [0.80, 2.47]
Reeves 2008	1	12	4	11	0.7%	0.23 [0.03, 1.75]
Subtotal (95% CI)		**2033**		**1579**	**100.0%**	**1.26 [1.06, 1.49]**
Total events	325		199			
Heterogeneity: Tau² = 0.00; Chi² = 12.11, df = 12 (P = 0.44); I² = 1%						
Test for overall effect: Z = 2.66 (P = 0.008)						
4.5.3 Lithium						
Joffe 1993	1	18	0	16	5.8%	2.68 [0.12, 61.58]
Joffe 2006	0	9	0	8		Not estimable
Katona 1995	6	29	9	33	69.3%	0.76 [0.31, 1.87]
Nierenberg 2003a	2	18	2	17	16.7%	0.94 [0.15, 5.97]
Stein 1993	0	16	0	18		Not estimable
Zusky1988	1	9	1	9	8.3%	1.00 [0.07, 13.64]
Subtotal (95% CI)		**99**		**101**	**100.0%**	**0.87 [0.41, 1.84]**
Total events	10		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.5.4 Thyroid hormone (T3)						
Joffe 1993	0	17	0	16		Not estimable
Joffe 2006	0	10	0	8		Not estimable
Subtotal (95% CI)		**27**		**24**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.5 Anticonvulsant (lamotrigine)						
Barbee 2011	14	48	17	48	84.0%	0.82 [0.46, 1.48]
Santos 2008	3	17	4	17	16.0%	0.75 [0.20, 2.86]
Subtotal (95% CI)		**65**		**65**	**100.0%**	**0.81 [0.48, 1.38]**
Total events	17		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
4.5.6 Anxiolytic						
Appelberg 2001	6	51	10	51	100.0%	0.60 [0.24, 1.53]
Subtotal (95% CI)		**51**		**51**	**100.0%**	**0.60 [0.24, 1.53]**
Total events	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
4.5.7 Omega-3 fatty acid						
Mozaffari-Khosravi 2013	13	54	6	27	64.2%	1.08 [0.46, 2.53]
Peet 2002	6	52	4	18	35.8%	0.52 [0.17, 1.63]
Subtotal (95% CI)		**106**		**45**	**100.0%**	**0.83 [0.42, 1.66]**
Total events	19		10			
Heterogeneity: Tau² = 0.01; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%						
Test for overall effect: Z = 0.52 (P = 0.60)						
4.5.8 Stimulant (methylphenidate)						
Ravindran 2008a	11	73	4	72	100.0%	2.71 [0.91, 8.12]
Subtotal (95% CI)		**73**		**72**	**100.0%**	**2.71 [0.91, 8.12]**
Total events	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.07)						



Test for subgroup differences: Chi² = 8.48, df = 6 (P = 0.21), I² = 29.2%

Discontinuation due to adverse events

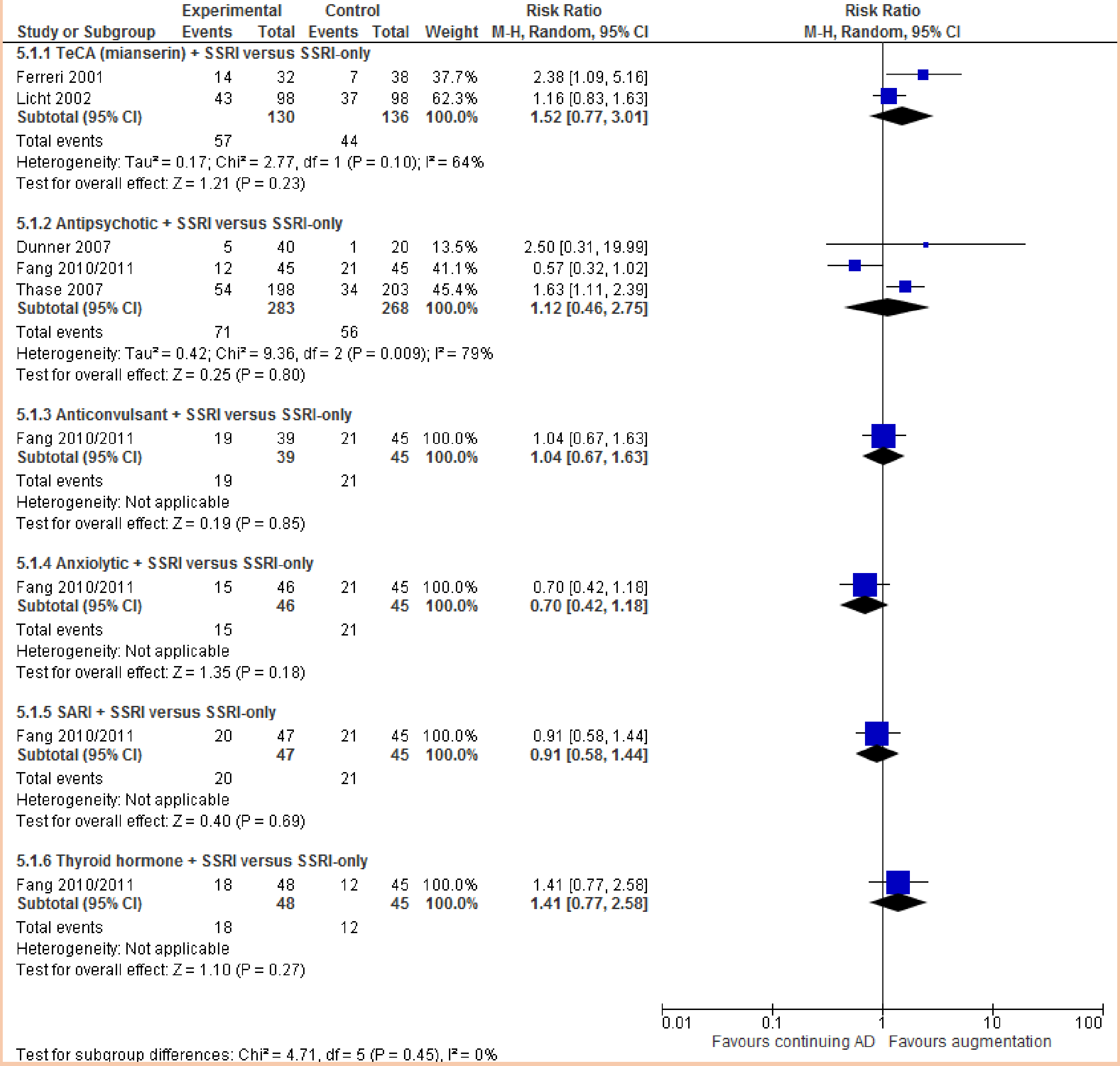


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Atypical antidepressant						
Gulrez 2012	0	30	0	30		Not estimable
Subtotal (95% CI)		**30**		**30**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.6.2 TCA (intravenous)						
Altamura 2008b	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.6.3 Antipsychotic						
Bauer 2009	30	330	5	163	21.7%	2.96 [1.17, 7.50]
Berman 2007	6	184	4	178	12.0%	1.45 [0.42, 5.06]
Berman 2009	11	177	3	172	11.8%	3.56 [1.01, 12.55]
El-Khalili 2010	43	298	1	148	4.8%	21.36 [2.97, 153.56]
Fava 2012/Mischoulon 2012	0	56	0	169		Not estimable
Kamijima 2013	15	391	2	195	8.7%	3.74 [0.86, 16.19]
Keitner 2009	6	62	1	33	4.3%	3.19 [0.40, 25.42]
Lenze 2015/Reynolds 2009	2	91	2	90	5.0%	0.99 [0.14, 6.87]
Mahmoud 2007	8	141	3	133	11.0%	2.52 [0.68, 9.28]
Marcus 2008	7	191	2	190	7.7%	3.48 [0.73, 16.55]
McIntyre 2007	8	29	2	29	8.7%	4.00 [0.93, 17.25]
Papakostas 2015	10	71	0	68	2.4%	20.13 [1.20, 336.88]
Reeves 2008	1	12	0	11	1.9%	2.77 [0.12, 61.65]
Subtotal (95% CI)		**2033**		**1579**	**100.0%**	**3.16 [2.05, 4.87]**
Total events	147		25			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.52, df = 11 (P = 0.57); I^2 = 0%						
Test for overall effect: Z = 5.22 (P < 0.00001)						
4.6.4 Lithium						
Joffe 1993	1	18	0	16	19.3%	2.68 [0.12, 61.58]
Joffe 2006	0	9	0	8		Not estimable
Katona 1995	2	29	2	33	52.9%	1.14 [0.17, 7.57]
Stein 1993	0	16	0	18		Not estimable
Zusky1988	1	9	1	9	27.8%	1.00 [0.07, 13.64]
Subtotal (95% CI)		**81**		**84**	**100.0%**	**1.30 [0.33, 5.14]**
Total events	4		3			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.27, df = 2 (P = 0.88); I^2 = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.6.5 Thyroid hormone (T3)						
Joffe 1993	0	17	0	16		Not estimable
Joffe 2006	0	10	0	8		Not estimable
Subtotal (95% CI)		**27**		**24**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.6.6 Anticonvulsant (lamotrigine)						
Barbee 2011	7	48	10	48	76.1%	0.70 [0.29, 1.69]
Santos 2008	2	17	0	17	23.9%	5.00 [0.26, 97.00]
Subtotal (95% CI)		**65**		**65**	**100.0%**	**1.12 [0.21, 5.94]**
Total events	9		10			
Heterogeneity: Tau^2 = 0.75; Chi^2 = 1.60, df = 1 (P = 0.21); I^2 = 38%						
Test for overall effect: Z = 0.13 (P = 0.89)						
4.6.7 Anxiolytic						
Appelberg 2001	0	51	0	51		Not estimable
Subtotal (95% CI)		**51**		**51**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.6.8 Omega-3 fatty acid						
Mozaffari-Khosravi 2013	5	54	4	27	83.0%	0.63 [0.18, 2.14]
Peet 2002	1	52	1	18	17.0%	0.35 [0.02, 5.25]
Subtotal (95% CI)		**106**		**45**	**100.0%**	**0.57 [0.18, 1.73]**
Total events	6		5			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.15, df = 1 (P = 0.70); I^2 = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
4.6.9 Stimulant (methylphenidate)						
Patkar 2006	2	30	2	30	58.0%	1.00 [0.15, 6.64]
Ravindran 2008a	6	73	0	72	42.0%	12.82 [0.74, 223.53]
Subtotal (95% CI)		**103**		**102**	**100.0%**	**2.92 [0.21, 40.65]**
Total events	8		2			
Heterogeneity: Tau^2 = 2.18; Chi^2 = 2.42, df = 1 (P = 0.12); I^2 = 59%						
Test for overall effect: Z = 0.80 (P = 0.43)						

Test for subgroup differences: Chi^2 = 9.50, df = 4 (P = 0.05), I^2 = 57.9%

Augmenting the antidepressant with another antidepressant/non-antidepressant agent versus continuing with the antidepressant-only

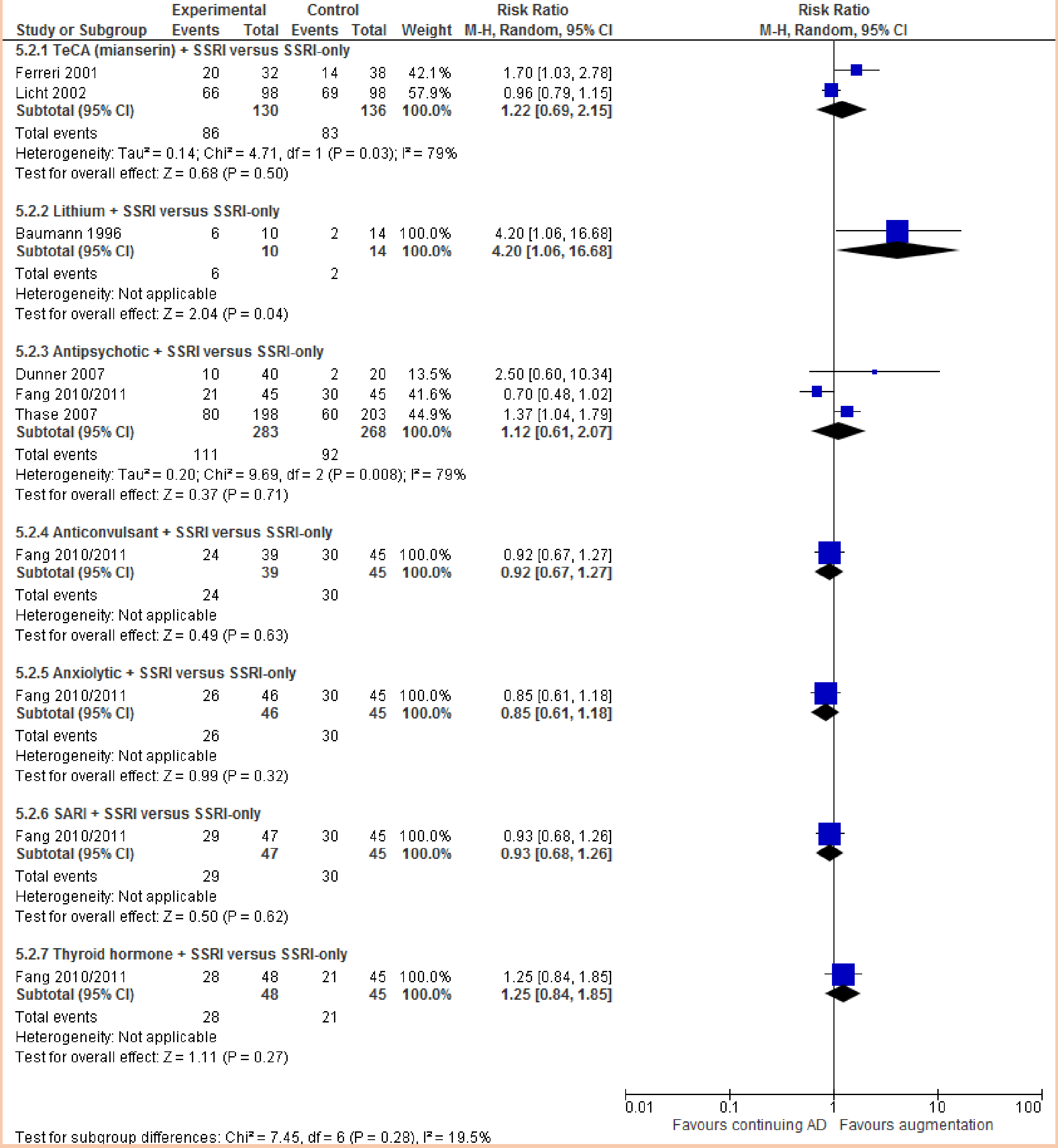
Remission (MADRS≤10/HAMD≤7/8)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 TeCA (mianserin) + SSRI versus SSRI-only						
Ferreri 2001	14	32	7	38	37.7%	2.38 [1.09, 5.16]
Licht 2002	43	98	37	98	62.3%	1.16 [0.83, 1.63]
Subtotal (95% CI)		**130**		**136**	**100.0%**	**1.52 [0.77, 3.01]**
Total events	57		44			
Heterogeneity: Tau^2 = 0.17; Chi^2 = 2.77, df = 1 (P = 0.10); I^2 = 64%						
Test for overall effect: Z = 1.21 (P = 0.23)						
5.1.2 Antipsychotic + SSRI versus SSRI-only						
Dunner 2007	5	40	1	20	13.5%	2.50 [0.31, 19.99]
Fang 2010/2011	12	45	21	45	41.1%	0.57 [0.32, 1.02]
Thase 2007	54	198	34	203	45.4%	1.63 [1.11, 2.39]
Subtotal (95% CI)		**283**		**268**	**100.0%**	**1.12 [0.46, 2.75]**
Total events	71		56			
Heterogeneity: Tau^2 = 0.42; Chi^2 = 9.36, df = 2 (P = 0.009); I^2 = 79%						
Test for overall effect: Z = 0.25 (P = 0.80)						
5.1.3 Anticonvulsant + SSRI versus SSRI-only						
Fang 2010/2011	19	39	21	45	100.0%	1.04 [0.67, 1.63]
Subtotal (95% CI)		**39**		**45**	**100.0%**	**1.04 [0.67, 1.63]**
Total events	19		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
5.1.4 Anxiolytic + SSRI versus SSRI-only						
Fang 2010/2011	15	46	21	45	100.0%	0.70 [0.42, 1.18]
Subtotal (95% CI)		**46**		**45**	**100.0%**	**0.70 [0.42, 1.18]**
Total events	15		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
5.1.5 SARI + SSRI versus SSRI-only						
Fang 2010/2011	20	47	21	45	100.0%	0.91 [0.58, 1.44]
Subtotal (95% CI)		**47**		**45**	**100.0%**	**0.91 [0.58, 1.44]**
Total events	20		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
5.1.6 Thyroid hormone + SSRI versus SSRI-only						
Fang 2010/2011	18	48	12	45	100.0%	1.41 [0.77, 2.58]
Subtotal (95% CI)		**48**		**45**	**100.0%**	**1.41 [0.77, 2.58]**
Total events	18		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						

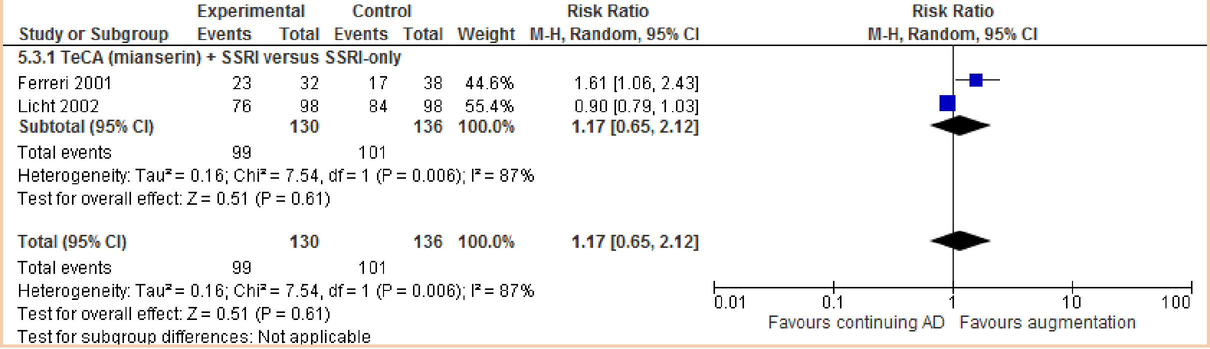
Test for subgroup differences: Chi^2 = 4.71, df = 5 (P = 0.45), I^2 = 0%

Response (≥50% improvement on MADRS/HAMD)



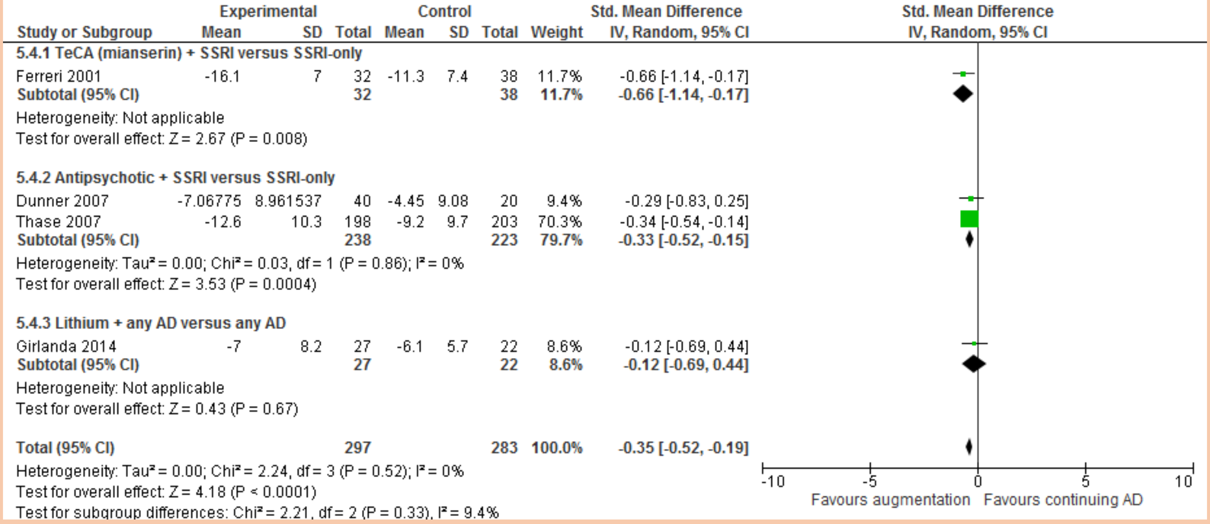
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 TeCA (mianserin) + SSRI versus SSRI-only						
Ferreri 2001	20	32	14	38	42.1%	1.70 [1.03, 2.78]
Licht 2002	66	98	69	98	57.9%	0.96 [0.79, 1.15]
Subtotal (95% CI)		**130**		**136**	**100.0%**	**1.22 [0.69, 2.15]**
Total events	86		83			
Heterogeneity: Tau² = 0.14; Chi² = 4.71, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.68 (P = 0.50)						
5.2.2 Lithium + SSRI versus SSRI-only						
Baumann 1996	6	10	2	14	100.0%	4.20 [1.06, 16.68]
Subtotal (95% CI)		**10**		**14**	**100.0%**	**4.20 [1.06, 16.68]**
Total events	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
5.2.3 Antipsychotic + SSRI versus SSRI-only						
Dunner 2007	10	40	2	20	13.5%	2.50 [0.60, 10.34]
Fang 2010/2011	21	45	30	45	41.6%	0.70 [0.48, 1.02]
Thase 2007	80	198	60	203	44.9%	1.37 [1.04, 1.79]
Subtotal (95% CI)		**283**		**268**	**100.0%**	**1.12 [0.61, 2.07]**
Total events	111		92			
Heterogeneity: Tau² = 0.20; Chi² = 9.69, df = 2 (P = 0.008); I² = 79%						
Test for overall effect: Z = 0.37 (P = 0.71)						
5.2.4 Anticonvulsant + SSRI versus SSRI-only						
Fang 2010/2011	24	39	30	45	100.0%	0.92 [0.67, 1.27]
Subtotal (95% CI)		**39**		**45**	**100.0%**	**0.92 [0.67, 1.27]**
Total events	24		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
5.2.5 Anxiolytic + SSRI versus SSRI-only						
Fang 2010/2011	26	46	30	45	100.0%	0.85 [0.61, 1.18]
Subtotal (95% CI)		**46**		**45**	**100.0%**	**0.85 [0.61, 1.18]**
Total events	26		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
5.2.6 SARI + SSRI versus SSRI-only						
Fang 2010/2011	29	47	30	45	100.0%	0.93 [0.68, 1.26]
Subtotal (95% CI)		**47**		**45**	**100.0%**	**0.93 [0.68, 1.26]**
Total events	29		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
5.2.7 Thyroid hormone + SSRI versus SSRI-only						
Fang 2010/2011	28	48	21	45	100.0%	1.25 [0.84, 1.85]
Subtotal (95% CI)		**48**		**45**	**100.0%**	**1.25 [0.84, 1.85]**
Total events	28		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Test for subgroup differences: Chi² = 7.45, df = 6 (P = 0.28), I² = 19.5%						

Response (much/very much improved on CGI-I)



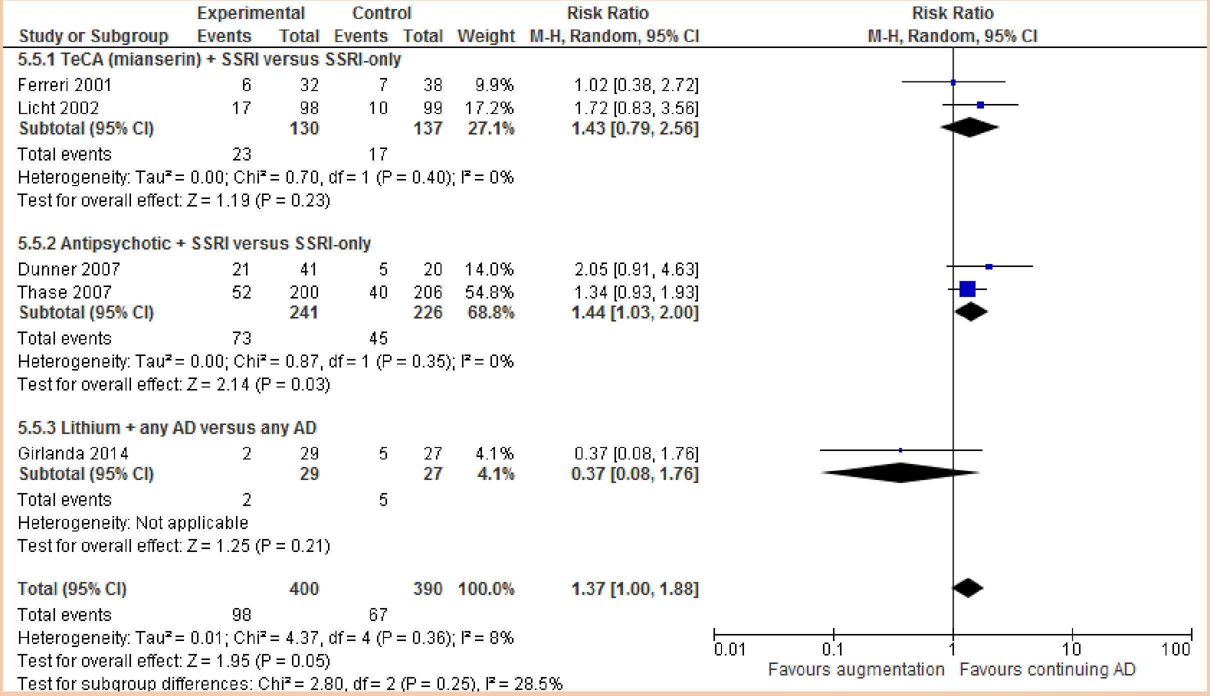
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 TeCA (mianserin) + SSRI versus SSRI-only						
Ferreri 2001	23	32	17	38	44.6%	1.61 [1.06, 2.43]
Licht 2002	76	98	84	98	55.4%	0.90 [0.79, 1.03]
Subtotal (95% CI)		**130**		**136**	**100.0%**	**1.17 [0.65, 2.12]**
Total events	99		101			
Heterogeneity: Tau² = 0.16; Chi² = 7.54, df = 1 (P = 0.006); I² = 87%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**130**		**136**	**100.0%**	**1.17 [0.65, 2.12]**
Total events	99		101			
Heterogeneity: Tau² = 0.16; Chi² = 7.54, df = 1 (P = 0.006); I² = 87%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Not applicable						

Depression symptomatology (MADRS/HAMD change score)



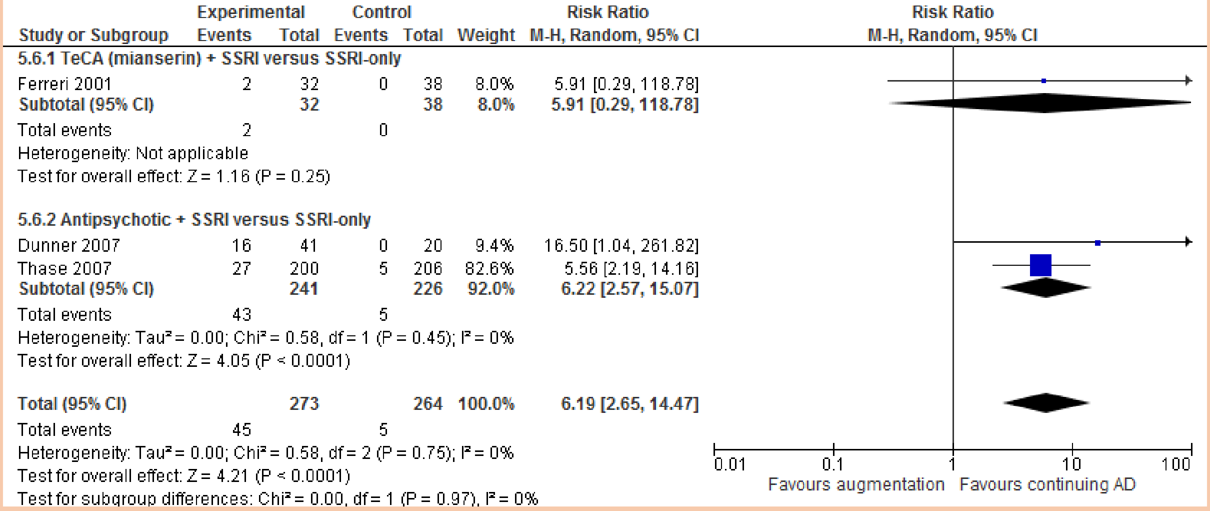
	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
5.4.1 TeCA (mianserin) + SSRI versus SSRI-only								
Ferreri 2001	-16.1	7	32	-11.3	7.4	38	11.7%	-0.66 [-1.14, -0.17]
Subtotal (95% CI)			**32**			**38**	**11.7%**	**-0.66 [-1.14, -0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.67 (P = 0.008)								
5.4.2 Antipsychotic + SSRI versus SSRI-only								
Dunner 2007	-7.06775	8.961537	40	-4.45	9.08	20	9.4%	-0.29 [-0.83, 0.25]
Thase 2007	-12.6	10.3	198	-9.2	9.7	203	70.3%	-0.34 [-0.54, -0.14]
Subtotal (95% CI)			**238**			**223**	**79.7%**	**-0.33 [-0.52, -0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
5.4.3 Lithium + any AD versus any AD								
Girlanda 2014	-7	8.2	27	-6.1	5.7	22	8.6%	-0.12 [-0.69, 0.44]
Subtotal (95% CI)			**27**			**22**	**8.6%**	**-0.12 [-0.69, 0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								
Total (95% CI)			**297**			**283**	**100.0%**	**-0.35 [-0.52, -0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 3 (P = 0.52); I² = 0%								
Test for overall effect: Z = 4.18 (P < 0.0001)								
Test for subgroup differences: Chi² = 2.21, df = 2 (P = 0.33), I² = 9.4%								

Discontinuation for any reason (including adverse events)



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
5.5.1 TeCA (mianserin) + SSRI versus SSRI-only						
Ferreri 2001	6	32	7	38	9.9%	1.02 [0.38, 2.72]
Licht 2002	17	98	10	99	17.2%	1.72 [0.83, 3.56]
Subtotal (95% CI)		**130**		**137**	**27.1%**	**1.43 [0.79, 2.56]**
Total events	23		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
5.5.2 Antipsychotic + SSRI versus SSRI-only						
Dunner 2007	21	41	5	20	14.0%	2.05 [0.91, 4.63]
Thase 2007	52	200	40	206	54.8%	1.34 [0.93, 1.93]
Subtotal (95% CI)		**241**		**226**	**68.8%**	**1.44 [1.03, 2.00]**
Total events	73		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 2.14 (P = 0.03)						
5.5.3 Lithium + any AD versus any AD						
Girlanda 2014	2	29	5	27	4.1%	0.37 [0.08, 1.76]
Subtotal (95% CI)		**29**		**27**	**4.1%**	**0.37 [0.08, 1.76]**
Total events	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**400**		**390**	**100.0%**	**1.37 [1.00, 1.88]**
Total events	98		67			
Heterogeneity: Tau² = 0.01; Chi² = 4.37, df = 4 (P = 0.36); I² = 8%						
Test for overall effect: Z = 1.95 (P = 0.05)						
Test for subgroup differences: Chi² = 2.80, df = 2 (P = 0.25), I² = 28.5%						

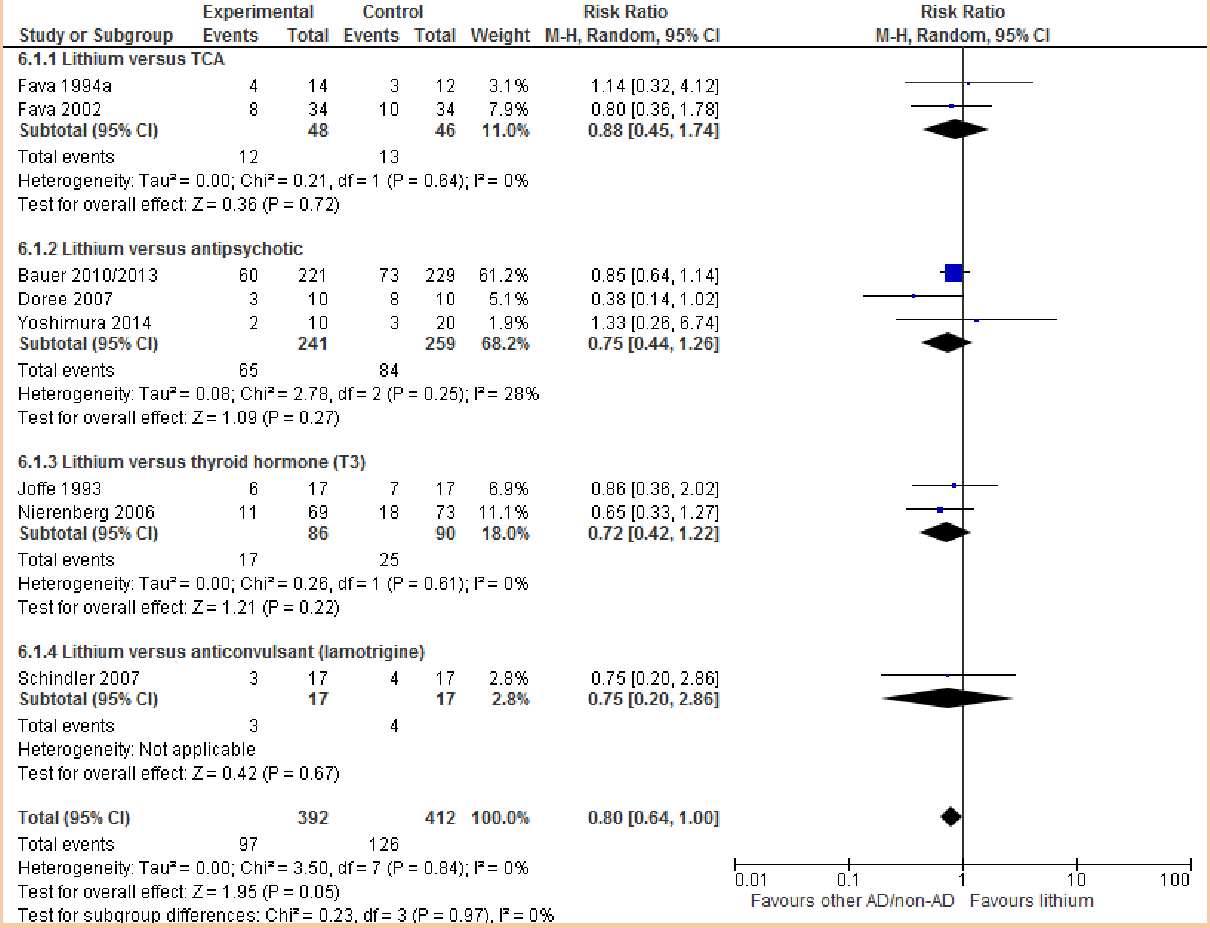
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.6.1 TeCA (mianserin) + SSRI versus SSRI-only						
Ferreri 2001	2	32	0	38	8.0%	5.91 [0.29, 118.78]
Subtotal (95% CI)		**32**		**38**	**8.0%**	**5.91 [0.29, 118.78]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.16 (P = 0.25)						
5.6.2 Antipsychotic + SSRI versus SSRI-only						
Dunner 2007	16	41	0	20	9.4%	16.50 [1.04, 261.82]
Thase 2007	27	200	5	206	82.6%	5.56 [2.19, 14.16]
Subtotal (95% CI)		**241**		**226**	**92.0%**	**6.22 [2.57, 15.07]**
Total events	43		5			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.58, df = 1 (P = 0.45); I^2 = 0%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
Total (95% CI)		**273**		**264**	**100.0%**	**6.19 [2.65, 14.47]**
Total events	45		5			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.58, df = 2 (P = 0.75); I^2 = 0%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 = 0%						

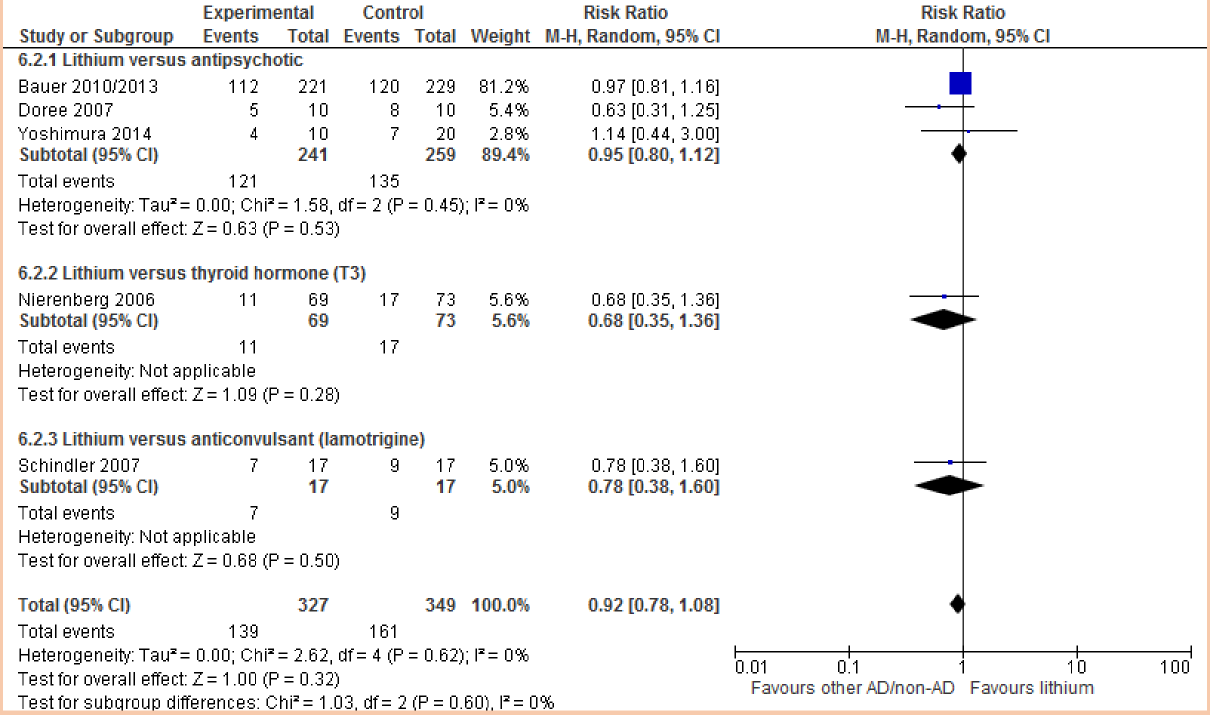
Augmenting the antidepressant with lithium compared to 'other' augmentation agents (head-to-head comparisons)

Remission (<8/10 on MADRS/HAMD)



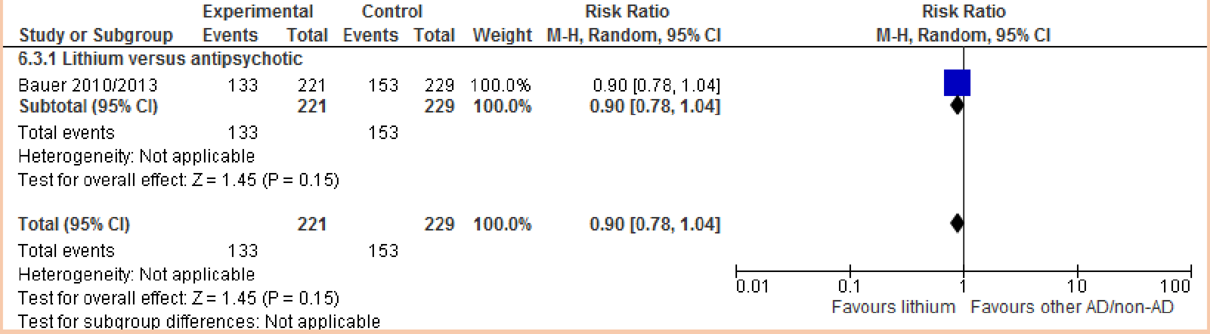
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Lithium versus TCA						
Fava 1994a	4	14	3	12	3.1%	1.14 [0.32, 4.12]
Fava 2002	8	34	10	34	7.9%	0.80 [0.36, 1.78]
Subtotal (95% CI)		**48**		**46**	**11.0%**	**0.88 [0.45, 1.74]**
Total events	12		13			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.21, df = 1 (P = 0.64); I^2 = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
6.1.2 Lithium versus antipsychotic						
Bauer 2010/2013	60	221	73	229	61.2%	0.85 [0.64, 1.14]
Doree 2007	3	10	8	10	5.1%	0.38 [0.14, 1.02]
Yoshimura 2014	2	10	3	20	1.9%	1.33 [0.26, 6.74]
Subtotal (95% CI)		**241**		**259**	**68.2%**	**0.75 [0.44, 1.26]**
Total events	65		84			
Heterogeneity: Tau^2 = 0.08; Chi^2 = 2.78, df = 2 (P = 0.25); I^2 = 28%						
Test for overall effect: Z = 1.09 (P = 0.27)						
6.1.3 Lithium versus thyroid hormone (T3)						
Joffe 1993	6	17	7	17	6.9%	0.86 [0.36, 2.02]
Nierenberg 2006	11	69	18	73	11.1%	0.65 [0.33, 1.27]
Subtotal (95% CI)		**86**		**90**	**18.0%**	**0.72 [0.42, 1.22]**
Total events	17		25			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 = 0%						
Test for overall effect: Z = 1.21 (P = 0.22)						
6.1.4 Lithium versus anticonvulsant (lamotrigine)						
Schindler 2007	3	17	4	17	2.8%	0.75 [0.20, 2.86]
Subtotal (95% CI)		**17**		**17**	**2.8%**	**0.75 [0.20, 2.86]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
Total (95% CI)		**392**		**412**	**100.0%**	**0.80 [0.64, 1.00]**
Total events	97		126			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.50, df = 7 (P = 0.84); I^2 = 0%						
Test for overall effect: Z = 1.95 (P = 0.05)						
Test for subgroup differences: Chi^2 = 0.23, df = 3 (P = 0.97), I^2 = 0%						

Response (≥50% improvement on HAMD/MADRS/QIDS)



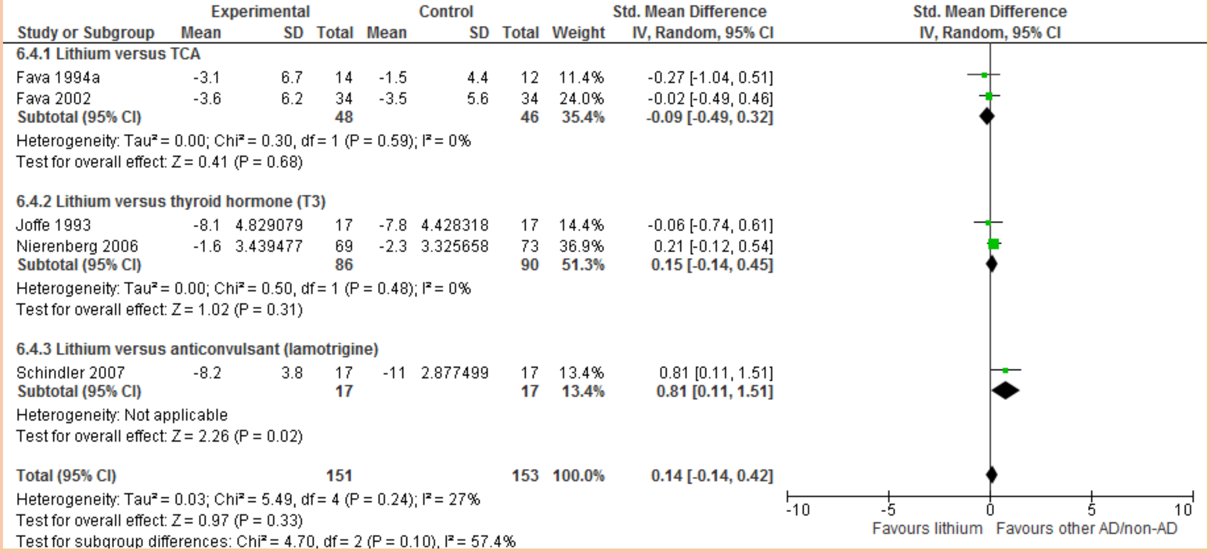
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Lithium versus antipsychotic						
Bauer 2010/2013	112	221	120	229	81.2%	0.97 [0.81, 1.16]
Doree 2007	5	10	8	10	5.4%	0.63 [0.31, 1.25]
Yoshimura 2014	4	10	7	20	2.8%	1.14 [0.44, 3.00]
Subtotal (95% CI)		**241**		**259**	**89.4%**	**0.95 [0.80, 1.12]**
Total events	121		135			
Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
6.2.2 Lithium versus thyroid hormone (T3)						
Nierenberg 2006	11	69	17	73	5.6%	0.68 [0.35, 1.36]
Subtotal (95% CI)		**69**		**73**	**5.6%**	**0.68 [0.35, 1.36]**
Total events	11		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
6.2.3 Lithium versus anticonvulsant (lamotrigine)						
Schindler 2007	7	17	9	17	5.0%	0.78 [0.38, 1.60]
Subtotal (95% CI)		**17**		**17**	**5.0%**	**0.78 [0.38, 1.60]**
Total events	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**327**		**349**	**100.0%**	**0.92 [0.78, 1.08]**
Total events	139		161			
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 4 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Chi² = 1.03, df = 2 (P = 0.60), I² = 0%						

Response (much/very much improved on CGI-I)

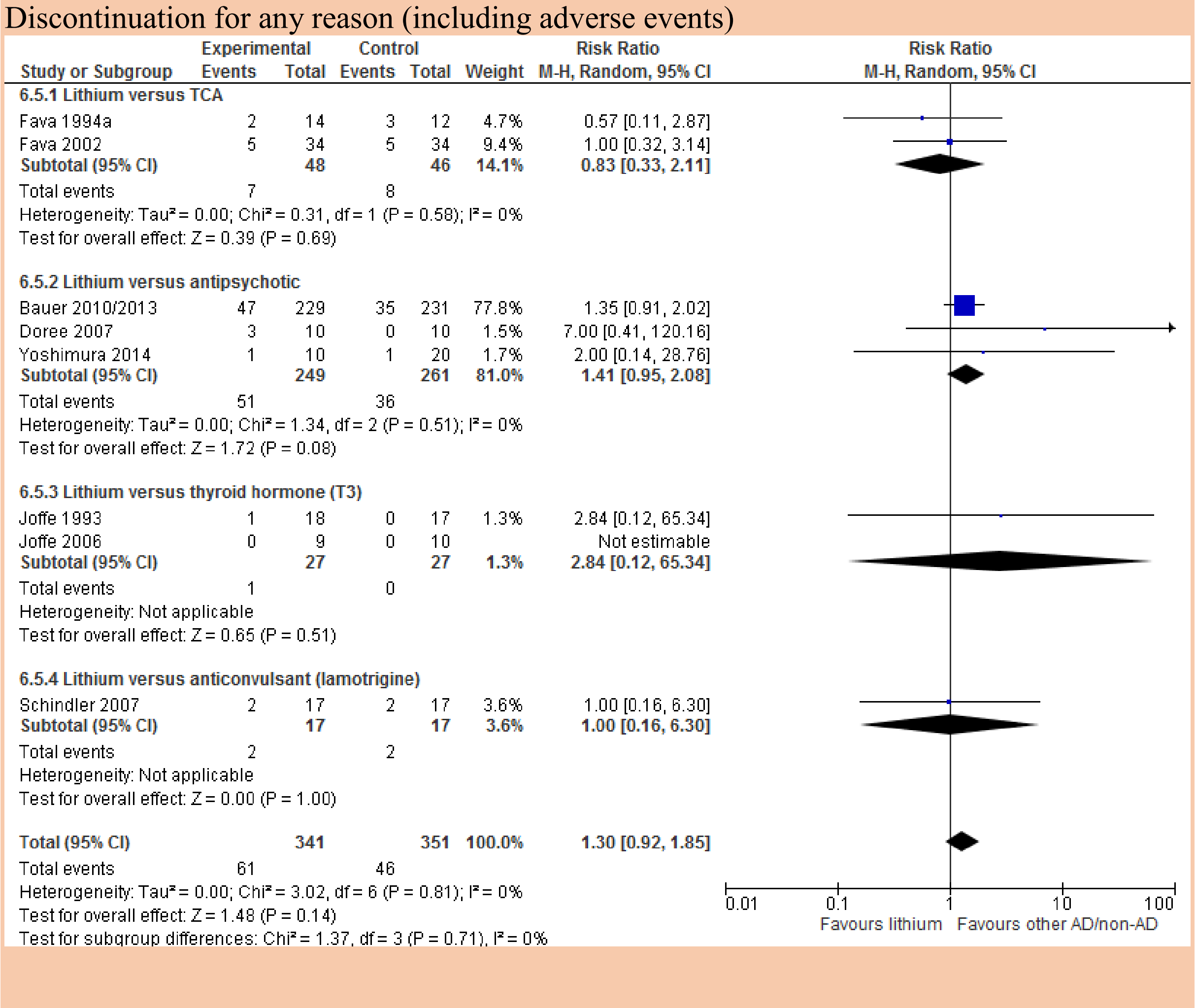


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Lithium versus antipsychotic						
Bauer 2010/2013	133	221	153	229	100.0%	0.90 [0.78, 1.04]
Subtotal (95% CI)		**221**		**229**	**100.0%**	**0.90 [0.78, 1.04]**
Total events	133		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**221**		**229**	**100.0%**	**0.90 [0.78, 1.04]**
Total events	133		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Not applicable						

Depression symptomatology (HAMD/QIDS change score)

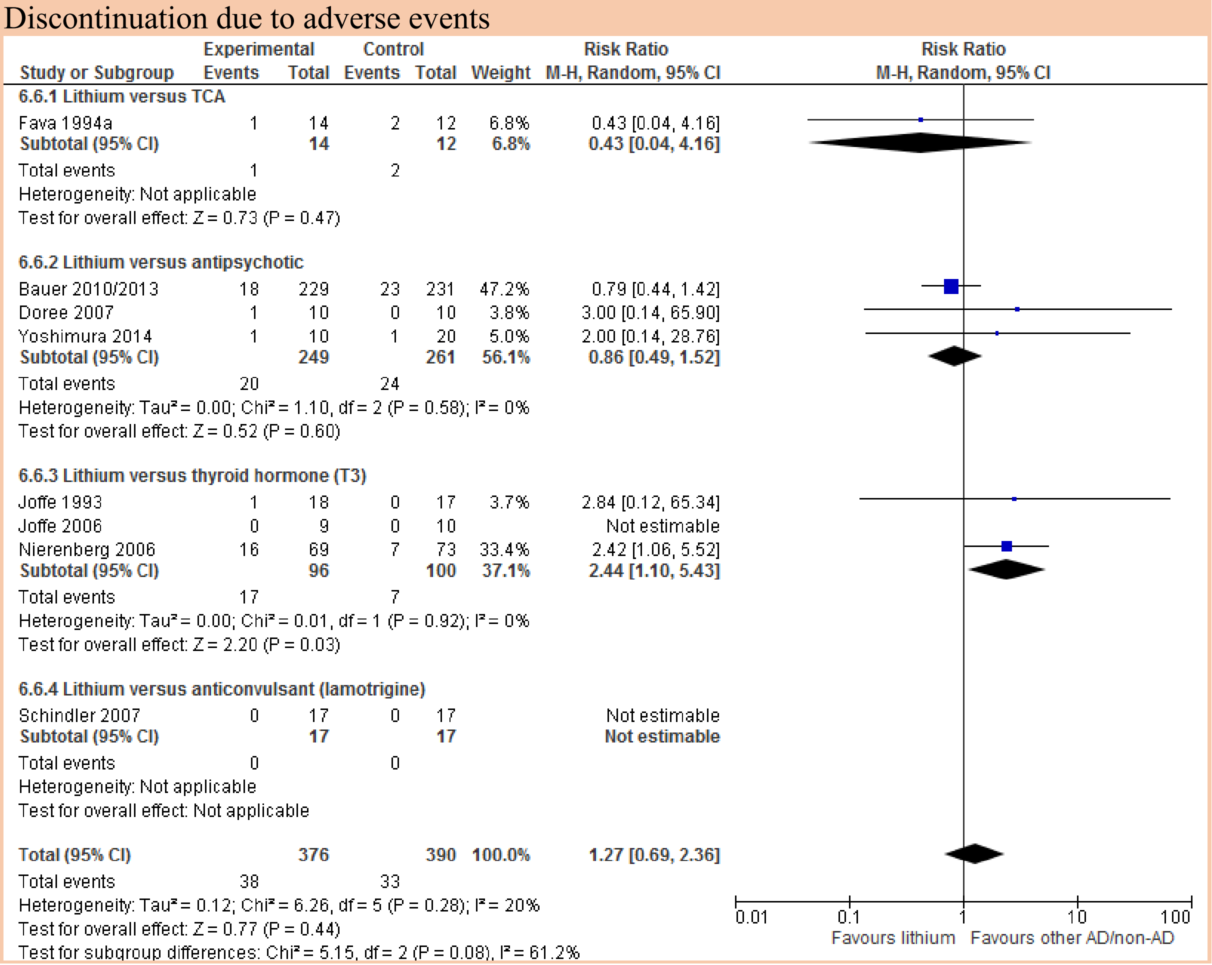


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
6.4.1 Lithium versus TCA								
Fava 1994a	-3.1	6.7	14	-1.5	4.4	12	11.4%	-0.27 [-1.04, 0.51]
Fava 2002	-3.6	6.2	34	-3.5	5.6	34	24.0%	-0.02 [-0.49, 0.46]
Subtotal (95% CI)			**48**			**46**	**35.4%**	**-0.09 [-0.49, 0.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.59); I² = 0%								
Test for overall effect: Z = 0.41 (P = 0.68)								
6.4.2 Lithium versus thyroid hormone (T3)								
Joffe 1993	-8.1	4.829079	17	-7.8	4.428318	17	14.4%	-0.06 [-0.74, 0.61]
Nierenberg 2006	-1.6	3.439477	69	-2.3	3.325658	73	36.9%	0.21 [-0.12, 0.54]
Subtotal (95% CI)			**86**			**90**	**51.3%**	**0.15 [-0.14, 0.45]**
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 1.02 (P = 0.31)								
6.4.3 Lithium versus anticonvulsant (lamotrigine)								
Schindler 2007	-8.2	3.8	17	-11	2.877499	17	13.4%	0.81 [0.11, 1.51]
Subtotal (95% CI)			**17**			**17**	**13.4%**	**0.81 [0.11, 1.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.26 (P = 0.02)								
Total (95% CI)			**151**			**153**	**100.0%**	**0.14 [-0.14, 0.42]**
Heterogeneity: Tau² = 0.03; Chi² = 5.49, df = 4 (P = 0.24); I² = 27%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Test for subgroup differences: Chi² = 4.70, df = 2 (P = 0.10), I² = 57.4%								



Discontinuation for any reason (including adverse events)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Lithium versus TCA						
Fava 1994a	2	14	3	12	4.7%	0.57 [0.11, 2.87]
Fava 2002	5	34	5	34	9.4%	1.00 [0.32, 3.14]
Subtotal (95% CI)		**48**		**46**	**14.1%**	**0.83 [0.33, 2.11]**
Total events	7		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.69)						
6.5.2 Lithium versus antipsychotic						
Bauer 2010/2013	47	229	35	231	77.8%	1.35 [0.91, 2.02]
Doree 2007	3	10	0	10	1.5%	7.00 [0.41, 120.16]
Yoshimura 2014	1	10	1	20	1.7%	2.00 [0.14, 28.76]
Subtotal (95% CI)		**249**		**261**	**81.0%**	**1.41 [0.95, 2.08]**
Total events	51		36			
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.08)						
6.5.3 Lithium versus thyroid hormone (T3)						
Joffe 1993	1	18	0	17	1.3%	2.84 [0.12, 65.34]
Joffe 2006	0	9	0	10		Not estimable
Subtotal (95% CI)		**27**		**27**	**1.3%**	**2.84 [0.12, 65.34]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
6.5.4 Lithium versus anticonvulsant (lamotrigine)						
Schindler 2007	2	17	2	17	3.6%	1.00 [0.16, 6.30]
Subtotal (95% CI)		**17**		**17**	**3.6%**	**1.00 [0.16, 6.30]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**341**		**351**	**100.0%**	**1.30 [0.92, 1.85]**
Total events	61		46			
Heterogeneity: Tau² = 0.00; Chi² = 3.02, df = 6 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 1.37, df = 3 (P = 0.71), I² = 0%						

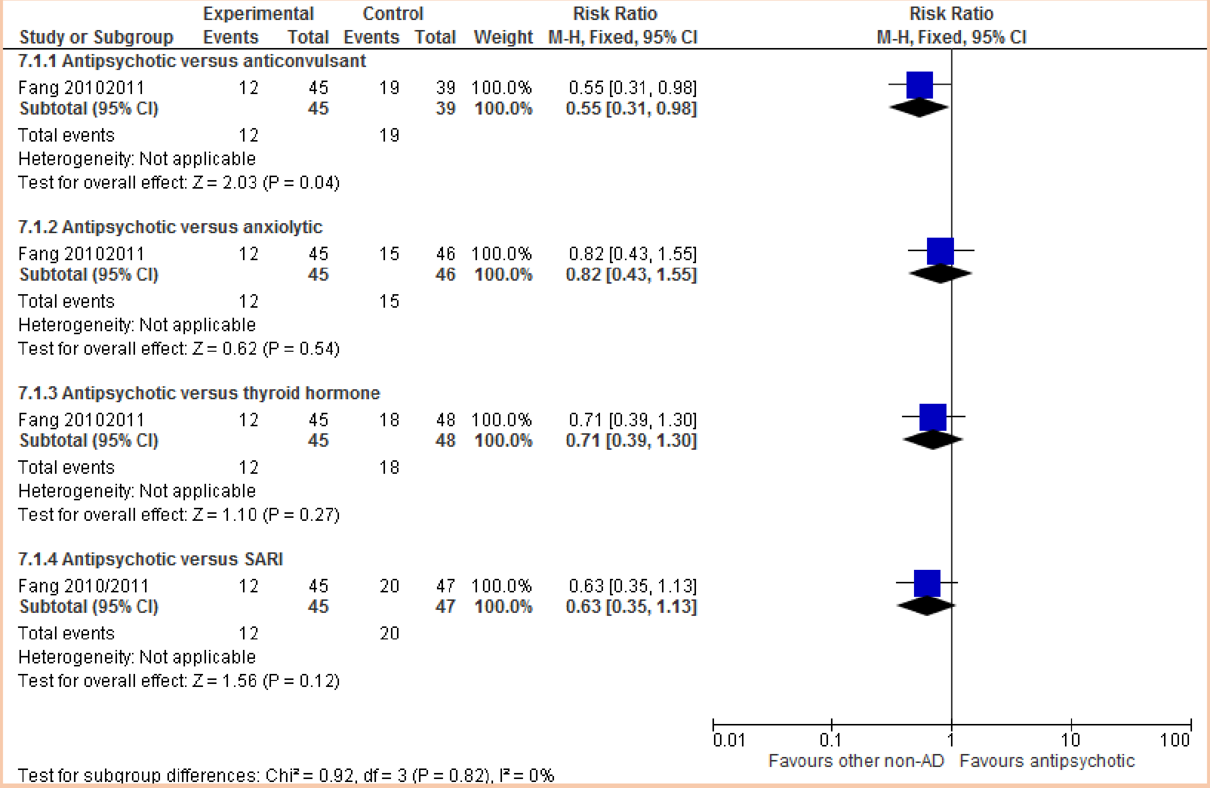


Discontinuation due to adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.6.1 Lithium versus TCA						
Fava 1994a	1	14	2	12	6.8%	0.43 [0.04, 4.16]
Subtotal (95% CI)		**14**		**12**	**6.8%**	**0.43 [0.04, 4.16]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
6.6.2 Lithium versus antipsychotic						
Bauer 2010/2013	18	229	23	231	47.2%	0.79 [0.44, 1.42]
Doree 2007	1	10	0	10	3.8%	3.00 [0.14, 65.90]
Yoshimura 2014	1	10	1	20	5.0%	2.00 [0.14, 28.76]
Subtotal (95% CI)		**249**		**261**	**56.1%**	**0.86 [0.49, 1.52]**
Total events	20		24			
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.60)						
6.6.3 Lithium versus thyroid hormone (T3)						
Joffe 1993	1	18	0	17	3.7%	2.84 [0.12, 65.34]
Joffe 2006	0	9	0	10		Not estimable
Nierenberg 2006	16	69	7	73	33.4%	2.42 [1.06, 5.52]
Subtotal (95% CI)		**96**		**100**	**37.1%**	**2.44 [1.10, 5.43]**
Total events	17		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
6.6.4 Lithium versus anticonvulsant (lamotrigine)						
Schindler 2007	0	17	0	17		Not estimable
Subtotal (95% CI)		**17**		**17**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**376**		**390**	**100.0%**	**1.27 [0.69, 2.36]**
Total events	38		33			
Heterogeneity: Tau² = 0.12; Chi² = 6.26, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 5.15, df = 2 (P = 0.08), I² = 61.2%						

Augmenting the antidepressant with an antipsychotic compared to 'other' augmentation agents (head-to-head comparisons)

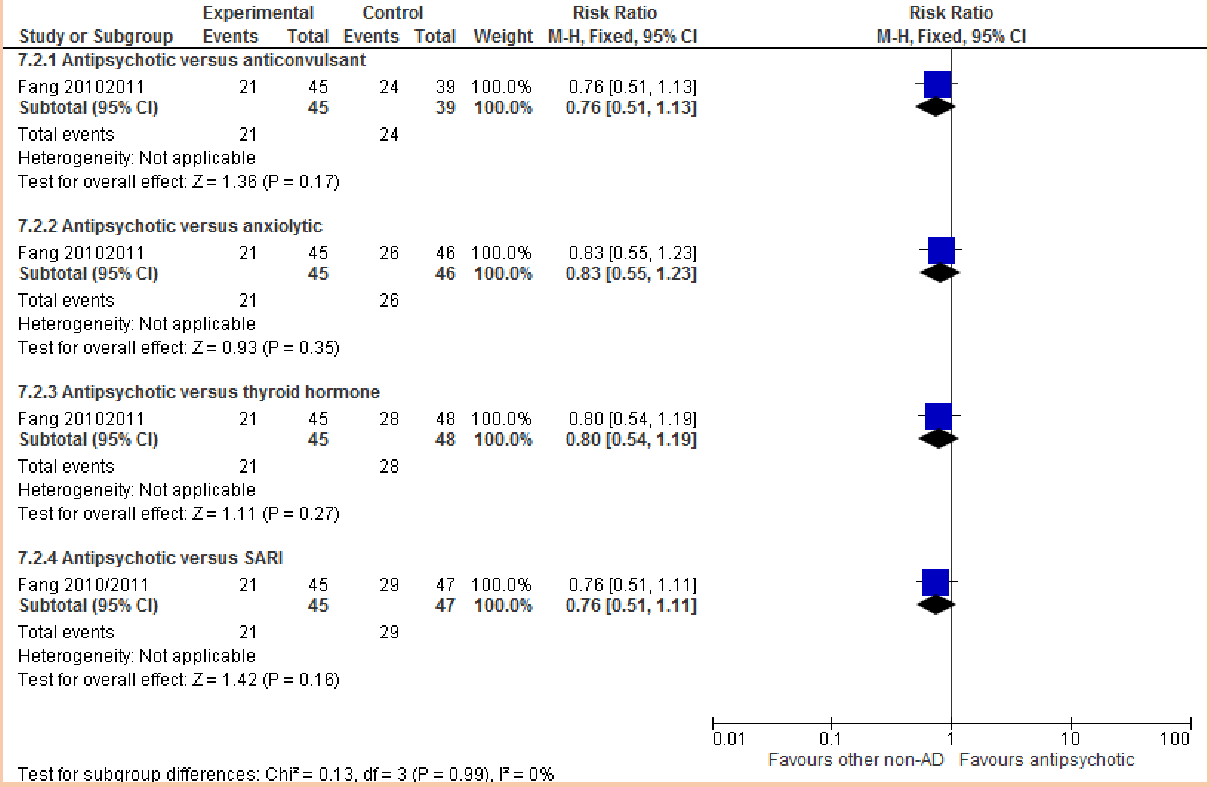
Remission ($\leq$7 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 Antipsychotic versus anticonvulsant						
Fang 20102011	12	45	19	39	100.0%	0.55 [0.31, 0.98]
Subtotal (95% CI)		**45**		**39**	**100.0%**	**0.55 [0.31, 0.98]**
Total events	12		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.03 (P = 0.04)						
7.1.2 Antipsychotic versus anxiolytic						
Fang 20102011	12	45	15	46	100.0%	0.82 [0.43, 1.55]
Subtotal (95% CI)		**45**		**46**	**100.0%**	**0.82 [0.43, 1.55]**
Total events	12		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
7.1.3 Antipsychotic versus thyroid hormone						
Fang 20102011	12	45	18	48	100.0%	0.71 [0.39, 1.30]
Subtotal (95% CI)		**45**		**48**	**100.0%**	**0.71 [0.39, 1.30]**
Total events	12		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
7.1.4 Antipsychotic versus SARI						
Fang 2010/2011	12	45	20	47	100.0%	0.63 [0.35, 1.13]
Subtotal (95% CI)		**45**		**47**	**100.0%**	**0.63 [0.35, 1.13]**
Total events	12		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						

Test for subgroup differences: Chi² = 0.92, df = 3 (P = 0.82), I² = 0%

Response (≥50% improvement on HAMD)

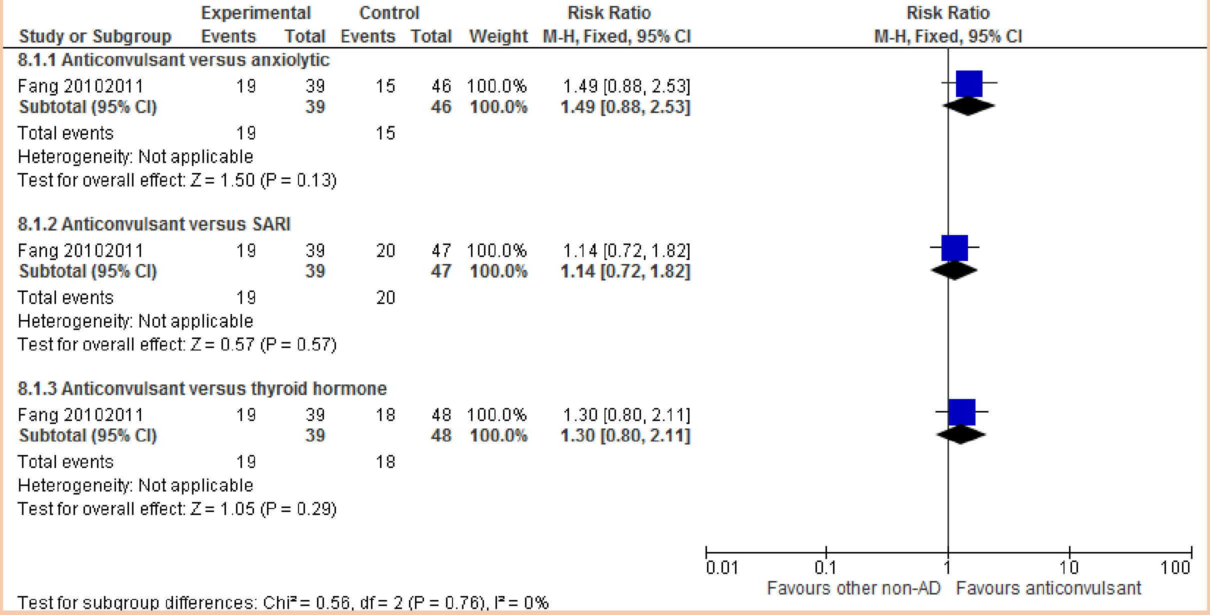


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Antipsychotic versus anticonvulsant						
Fang 20102011	21	45	24	39	100.0%	0.76 [0.51, 1.13]
Subtotal (95% CI)		**45**		**39**	**100.0%**	**0.76 [0.51, 1.13]**
Total events	21		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
7.2.2 Antipsychotic versus anxiolytic						
Fang 20102011	21	45	26	46	100.0%	0.83 [0.55, 1.23]
Subtotal (95% CI)		**45**		**46**	**100.0%**	**0.83 [0.55, 1.23]**
Total events	21		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
7.2.3 Antipsychotic versus thyroid hormone						
Fang 20102011	21	45	28	48	100.0%	0.80 [0.54, 1.19]
Subtotal (95% CI)		**45**		**48**	**100.0%**	**0.80 [0.54, 1.19]**
Total events	21		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
7.2.4 Antipsychotic versus SARI						
Fang 2010/2011	21	45	29	47	100.0%	0.76 [0.51, 1.11]
Subtotal (95% CI)		**45**		**47**	**100.0%**	**0.76 [0.51, 1.11]**
Total events	21		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						

Test for subgroup differences: Chi² = 0.13, df = 3 (P = 0.99), I² = 0%

Augmenting the antidepressant with an anticonvulsant compared to 'other' augmentation agents (head-to-head comparisons)

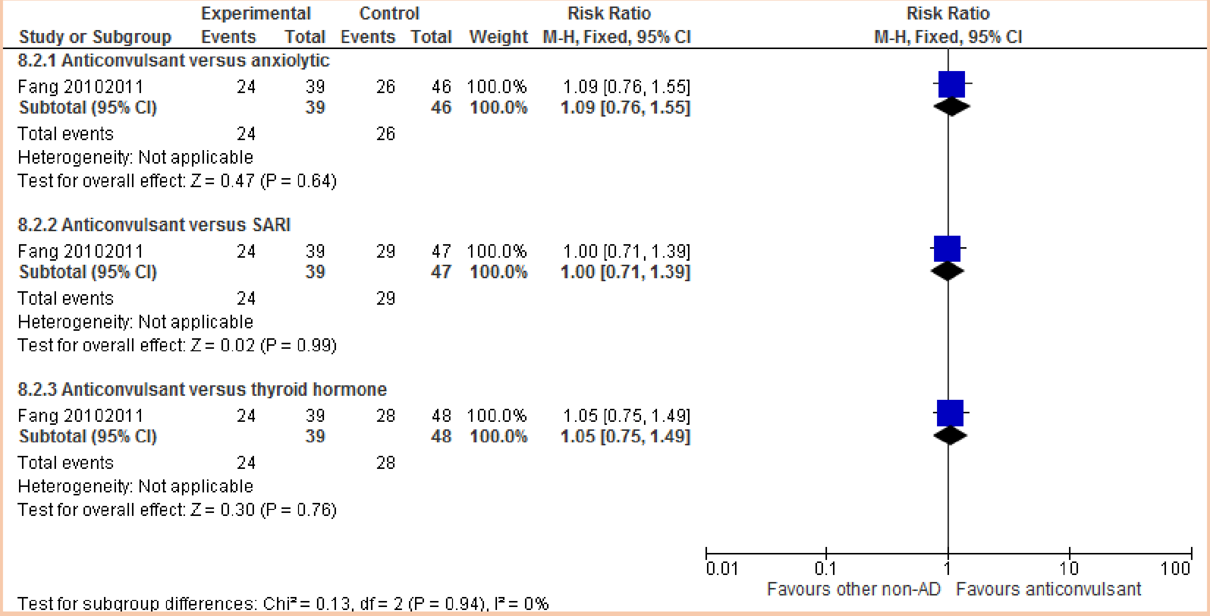
Remission (≤7 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 Anticonvulsant versus anxiolytic						
Fang 20102011	19	39	15	46	100.0%	1.49 [0.88, 2.53]
Subtotal (95% CI)		**39**		**46**	**100.0%**	**1.49 [0.88, 2.53]**
Total events	19		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
8.1.2 Anticonvulsant versus SARI						
Fang 20102011	19	39	20	47	100.0%	1.14 [0.72, 1.82]
Subtotal (95% CI)		**39**		**47**	**100.0%**	**1.14 [0.72, 1.82]**
Total events	19		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
8.1.3 Anticonvulsant versus thyroid hormone						
Fang 20102011	19	39	18	48	100.0%	1.30 [0.80, 2.11]
Subtotal (95% CI)		**39**		**48**	**100.0%**	**1.30 [0.80, 2.11]**
Total events	19		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						

Test for subgroup differences: Chi² = 0.56, df = 2 (P = 0.76), I² = 0%

Response (≥50% improvement on HAMD)

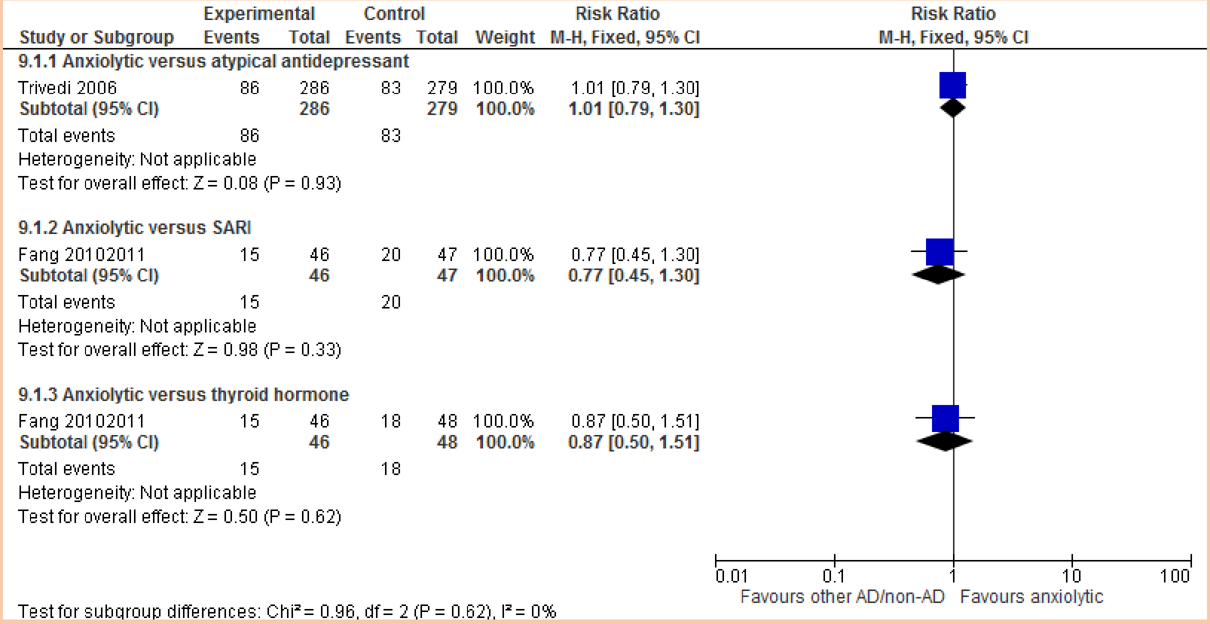


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 Anticonvulsant versus anxiolytic						
Fang 20102011	24	39	26	46	100.0%	1.09 [0.76, 1.55]
Subtotal (95% CI)		**39**		**46**	**100.0%**	**1.09 [0.76, 1.55]**
Total events	24		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
8.2.2 Anticonvulsant versus SARI						
Fang 20102011	24	39	29	47	100.0%	1.00 [0.71, 1.39]
Subtotal (95% CI)		**39**		**47**	**100.0%**	**1.00 [0.71, 1.39]**
Total events	24		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
8.2.3 Anticonvulsant versus thyroid hormone						
Fang 20102011	24	39	28	48	100.0%	1.05 [0.75, 1.49]
Subtotal (95% CI)		**39**		**48**	**100.0%**	**1.05 [0.75, 1.49]**
Total events	24		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						

Test for subgroup differences: Chi² = 0.13, df = 2 (P = 0.94), I² = 0%

Augmenting the antidepressant with an anxiolytic compared to 'other' augmentation agents (head-to-head comparisons)

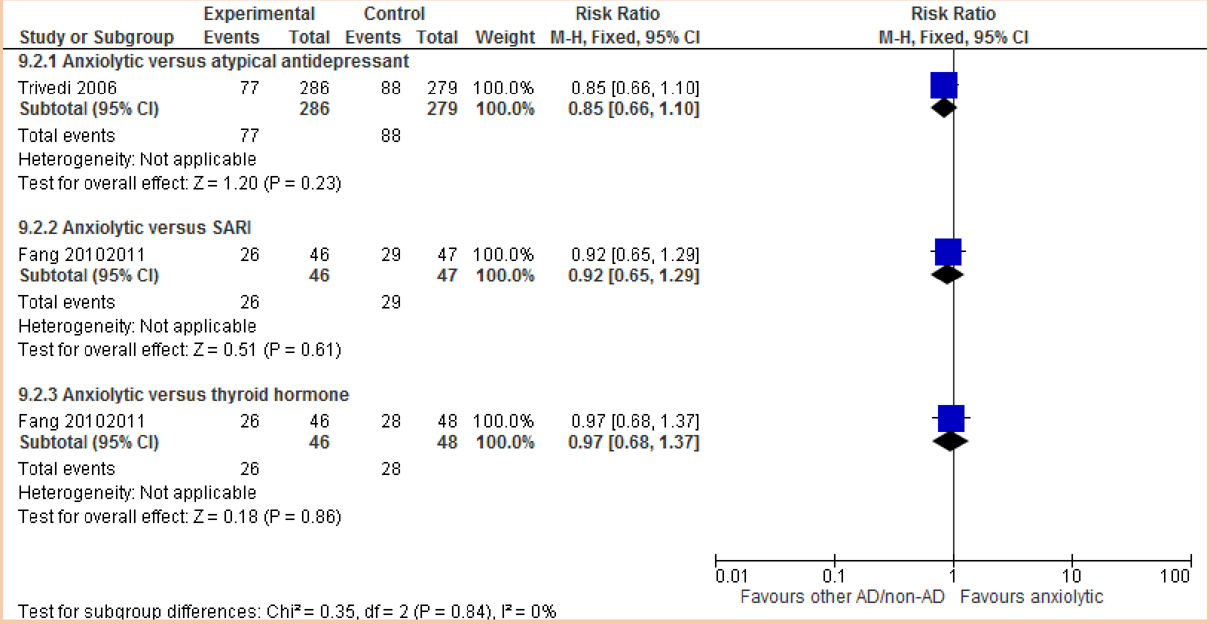
Remission (≤7 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 Anxiolytic versus atypical antidepressant						
Trivedi 2006	86	286	83	279	100.0%	1.01 [0.79, 1.30]
Subtotal (95% CI)		**286**		**279**	**100.0%**	**1.01 [0.79, 1.30]**
Total events	86		83			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
9.1.2 Anxiolytic versus SARI						
Fang 20102011	15	46	20	47	100.0%	0.77 [0.45, 1.30]
Subtotal (95% CI)		**46**		**47**	**100.0%**	**0.77 [0.45, 1.30]**
Total events	15		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
9.1.3 Anxiolytic versus thyroid hormone						
Fang 20102011	15	46	18	48	100.0%	0.87 [0.50, 1.51]
Subtotal (95% CI)		**46**		**48**	**100.0%**	**0.87 [0.50, 1.51]**
Total events	15		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						

Test for subgroup differences: Chi² = 0.96, df = 2 (P = 0.62), I² = 0%

Response (≥50% improvement on HAMD/QIDS)

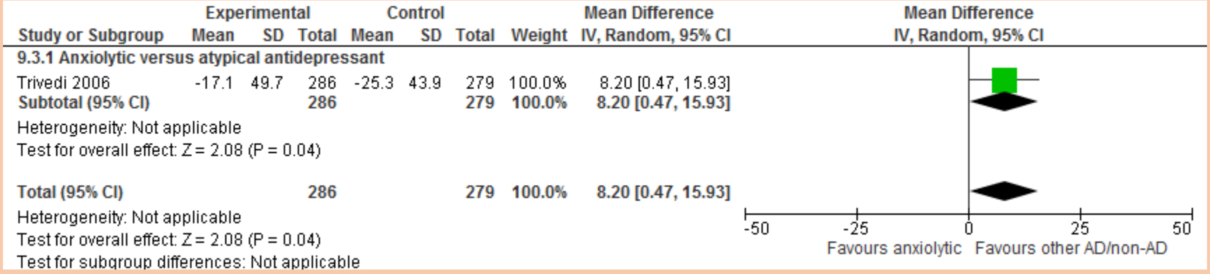


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.2.1 Anxiolytic versus atypical antidepressant						
Trivedi 2006	77	286	88	279	100.0%	0.85 [0.66, 1.10]
Subtotal (95% CI)		**286**		**279**	**100.0%**	**0.85 [0.66, 1.10]**
Total events	77		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
9.2.2 Anxiolytic versus SARI						
Fang 20102011	26	46	29	47	100.0%	0.92 [0.65, 1.29]
Subtotal (95% CI)		**46**		**47**	**100.0%**	**0.92 [0.65, 1.29]**
Total events	26		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
9.2.3 Anxiolytic versus thyroid hormone						
Fang 20102011	26	46	28	48	100.0%	0.97 [0.68, 1.37]
Subtotal (95% CI)		**46**		**48**	**100.0%**	**0.97 [0.68, 1.37]**
Total events	26		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						

Test for subgroup differences: Chi² = 0.35, df = 2 (P = 0.84), I² = 0%

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours other AD/non-AD
Favours anxiolytic

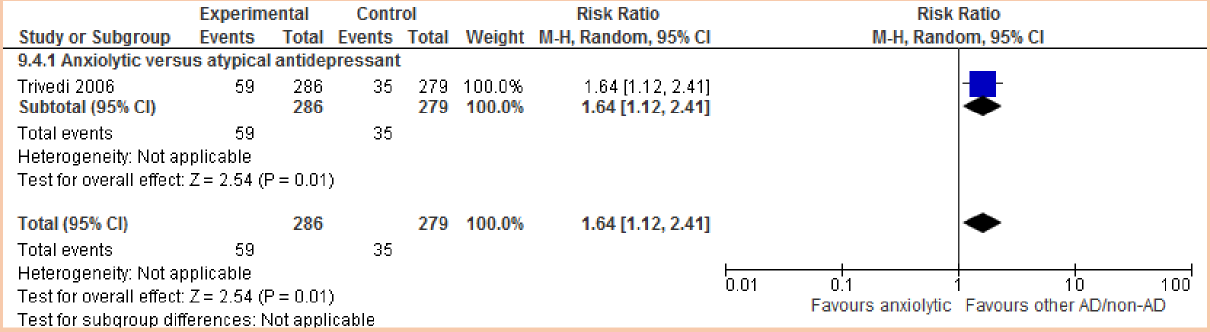
Depression symptomatology (QIDS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
9.3.1 Anxiolytic versus atypical antidepressant								
Trivedi 2006	-17.1	49.7	286	-25.3	43.9	279	100.0%	8.20 [0.47, 15.93]
Subtotal (95% CI)			**286**			**279**	**100.0%**	**8.20 [0.47, 15.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								
Total (95% CI)			**286**			**279**	**100.0%**	**8.20 [0.47, 15.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Random, 95% CI
-50
-25
0
25
50
Favours anxiolytic
Favours other AD/non-AD

Discontinuation due to adverse events

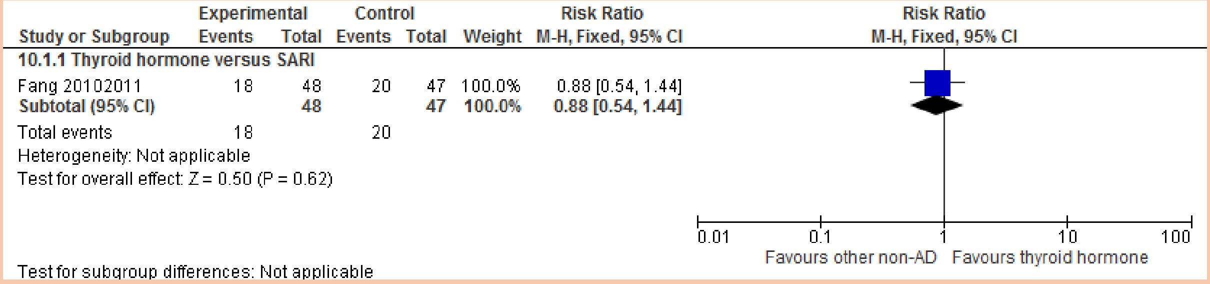


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.4.1 Anxiolytic versus atypical antidepressant						
Trivedi 2006	59	286	35	279	100.0%	1.64 [1.12, 2.41]
Subtotal (95% CI)		**286**		**279**	**100.0%**	**1.64 [1.12, 2.41]**
Total events	59		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.54 (P = 0.01)						
Total (95% CI)		**286**		**279**	**100.0%**	**1.64 [1.12, 2.41]**
Total events	59		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.54 (P = 0.01)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours anxiolytic
Favours other AD/non-AD

Augmenting the antidepressant with a thyroid hormone compared to 'other' augmentation agents (head-to-head comparisons)

Remission (≤7 on HAMD)

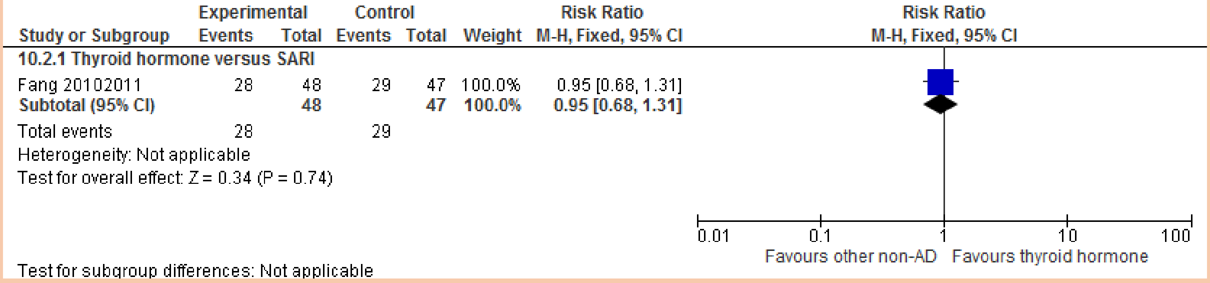


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 Thyroid hormone versus SARI						
Fang 20102011	18	48	20	47	100.0%	0.88 [0.54, 1.44]
Subtotal (95% CI)		**48**		**47**	**100.0%**	**0.88 [0.54, 1.44]**
Total events	18		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

Response (≥50% improvement on HAMD)



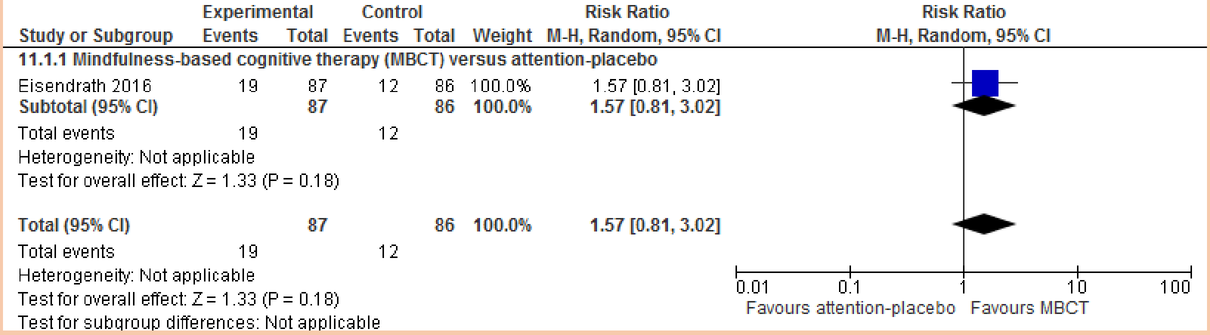
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.2.1 Thyroid hormone versus SARI						
Fang 20102011	28	48	29	47	100.0%	0.95 [0.68, 1.31]
Subtotal (95% CI)		**48**		**47**	**100.0%**	**0.95 [0.68, 1.31]**
Total events	28		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)

Test for subgroup differences: Not applicable

Augmenting the antidepressant with a psychological intervention compared to attention-placebo

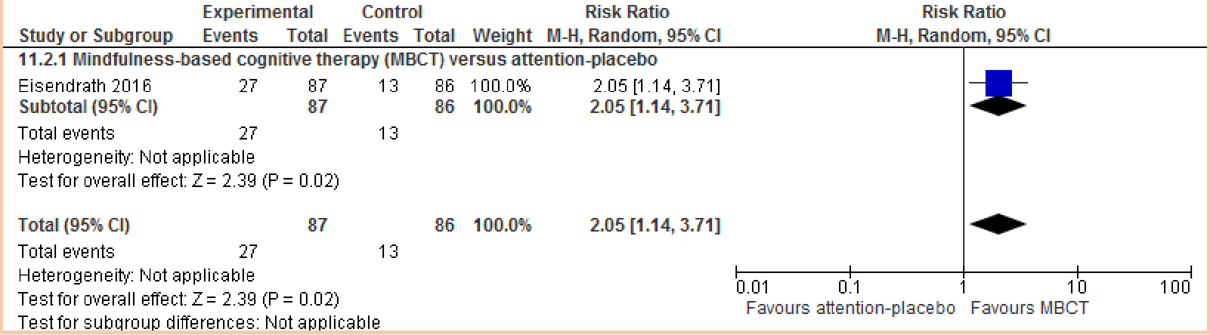
Remission (≤7 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Mindfulness-based cognitive therapy (MBCT) versus attention-placebo						
Eisendrath 2016	19	87	12	86	100.0%	1.57 [0.81, 3.02]
Subtotal (95% CI)		**87**		**86**	**100.0%**	**1.57 [0.81, 3.02]**
Total events	19		12			
Total (95% CI)		**87**		**86**	**100.0%**	**1.57 [0.81, 3.02]**
Total events	19		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable

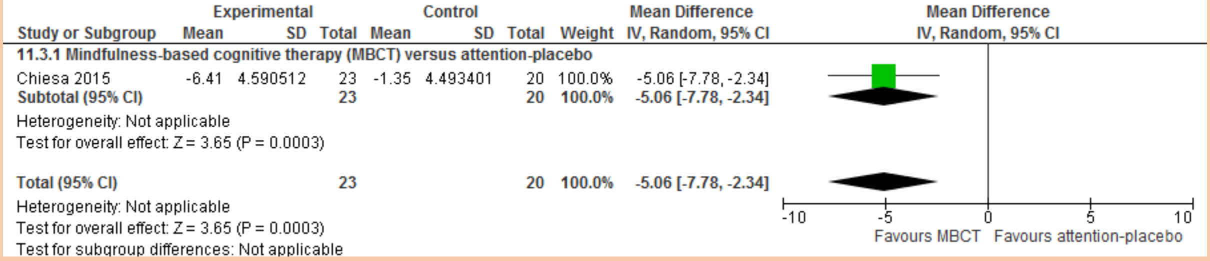
Response (≥50% improvement on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.2.1 Mindfulness-based cognitive therapy (MBCT) versus attention-placebo						
Eisendrath 2016	27	87	13	86	100.0%	2.05 [1.14, 3.71]
Subtotal (95% CI)		**87**		**86**	**100.0%**	**2.05 [1.14, 3.71]**
Total events	27		13			
Total (95% CI)		**87**		**86**	**100.0%**	**2.05 [1.14, 3.71]**
Total events	27		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable

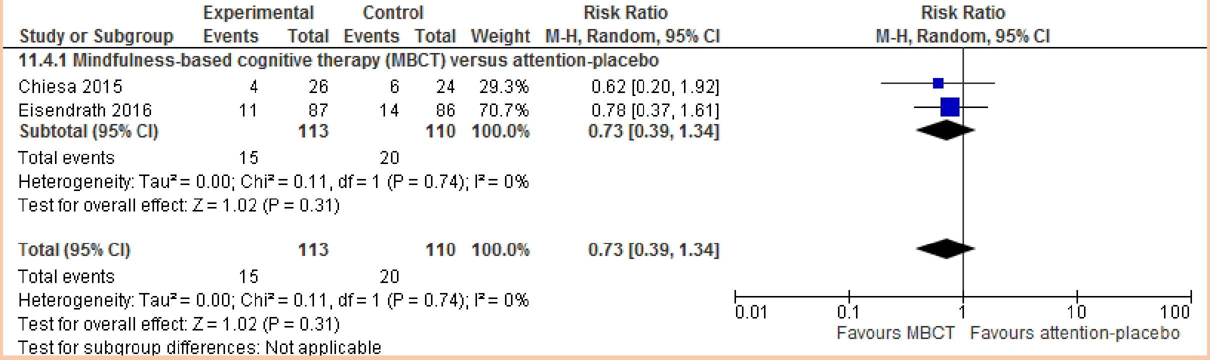
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
11.3.1 Mindfulness-based cognitive therapy (MBCT) versus attention-placebo								
Chiesa 2015	-6.41	4.590512	23	-1.35	4.493401	20	100.0%	-5.06 [-7.78, -2.34]
Subtotal (95% CI)			**23**			**20**	**100.0%**	**-5.06 [-7.78, -2.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.65 (P = 0.0003)								
Total (95% CI)			**23**			**20**	**100.0%**	**-5.06 [-7.78, -2.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.65 (P = 0.0003)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours MBCT
Favours attention-placebo

Discontinuation for any reason (including adverse events)

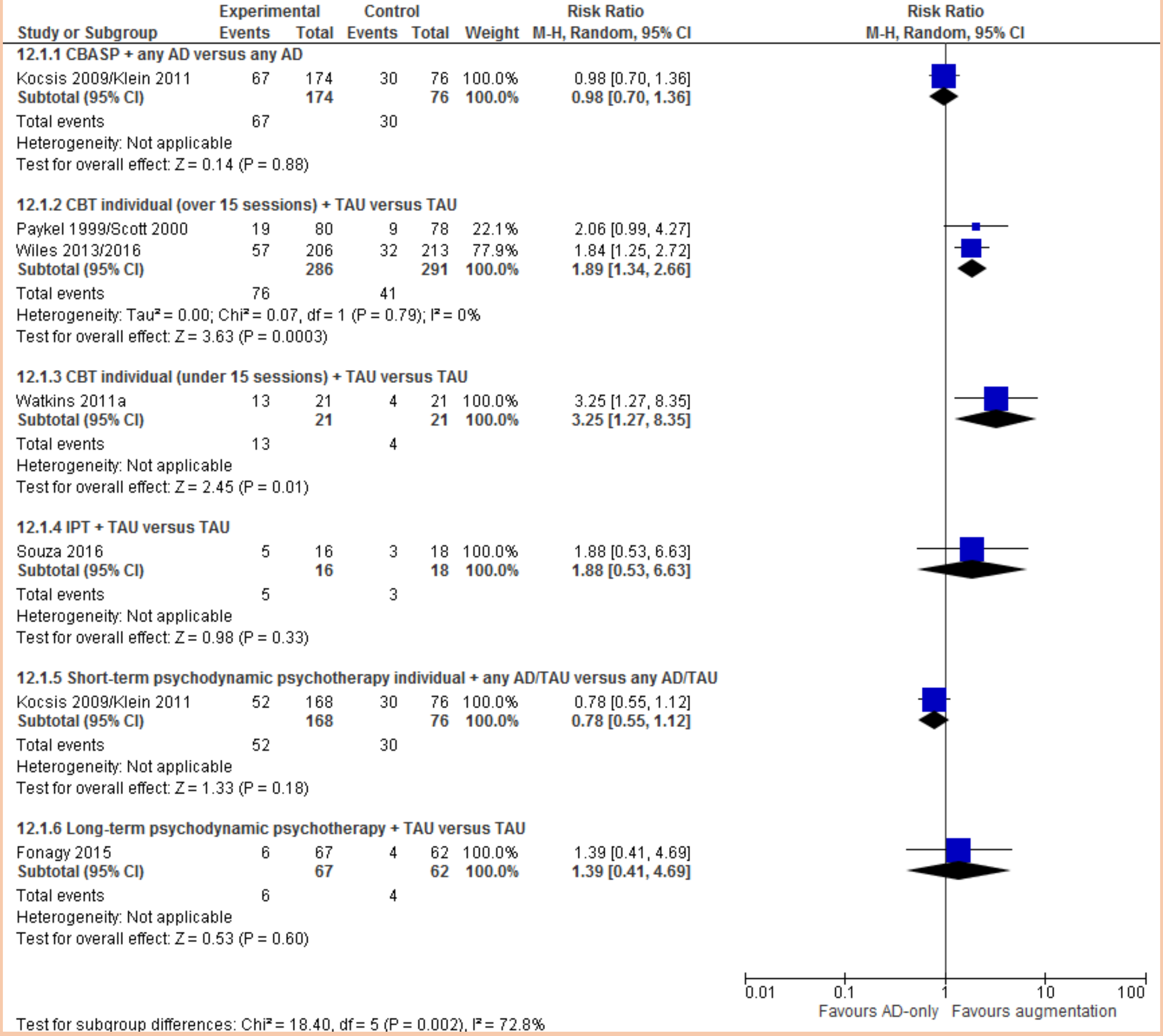


Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.4.1 Mindfulness-based cognitive therapy (MBCT) versus attention-placebo						
Chiesa 2015	4	26	6	24	29.3%	0.62 [0.20, 1.92]
Eisendrath 2016	11	87	14	86	70.7%	0.78 [0.37, 1.61]
Subtotal (95% CI)		**113**		**110**	**100.0%**	**0.73 [0.39, 1.34]**
Total events	15		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**113**		**110**	**100.0%**	**0.73 [0.39, 1.34]**
Total events	15		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours MBCT
Favours attention-placebo

Augmenting the antidepressant with a psychological intervention compared to continuing with the antidepressant-only

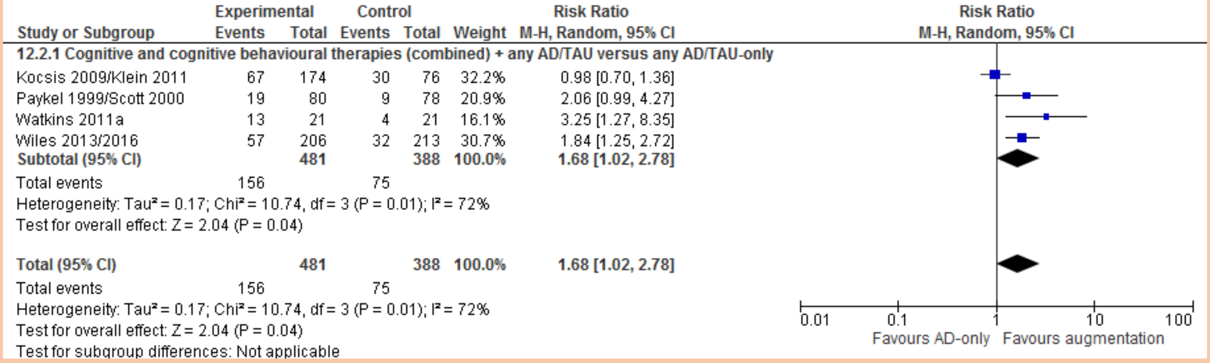
Remission (≤7/8 on HAMD/<10 on BDI)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.1.1 CBASP + any AD versus any AD						
Kocsis 2009/Klein 2011	67	174	30	76	100.0%	0.98 [0.70, 1.36]
Subtotal (95% CI)		**174**		**76**	**100.0%**	**0.98 [0.70, 1.36]**
Total events	67		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.88)						
12.1.2 CBT individual (over 15 sessions) + TAU versus TAU						
Paykel 1999/Scott 2000	19	80	9	78	22.1%	2.06 [0.99, 4.27]
Wiles 2013/2016	57	206	32	213	77.9%	1.84 [1.25, 2.72]
Subtotal (95% CI)		**286**		**291**	**100.0%**	**1.89 [1.34, 2.66]**
Total events	76		41			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 3.63 (P = 0.0003)						
12.1.3 CBT individual (under 15 sessions) + TAU versus TAU						
Watkins 2011a	13	21	4	21	100.0%	3.25 [1.27, 8.35]
Subtotal (95% CI)		**21**		**21**	**100.0%**	**3.25 [1.27, 8.35]**
Total events	13		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.45 (P = 0.01)						
12.1.4 IPT + TAU versus TAU						
Souza 2016	5	16	3	18	100.0%	1.88 [0.53, 6.63]
Subtotal (95% CI)		**16**		**18**	**100.0%**	**1.88 [0.53, 6.63]**
Total events	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
12.1.5 Short-term psychodynamic psychotherapy individual + any AD/TAU versus any AD/TAU						
Kocsis 2009/Klein 2011	52	168	30	76	100.0%	0.78 [0.55, 1.12]
Subtotal (95% CI)		**168**		**76**	**100.0%**	**0.78 [0.55, 1.12]**
Total events	52		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
12.1.6 Long-term psychodynamic psychotherapy + TAU versus TAU						
Fonagy 2015	6	67	4	62	100.0%	1.39 [0.41, 4.69]
Subtotal (95% CI)		**67**		**62**	**100.0%**	**1.39 [0.41, 4.69]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						

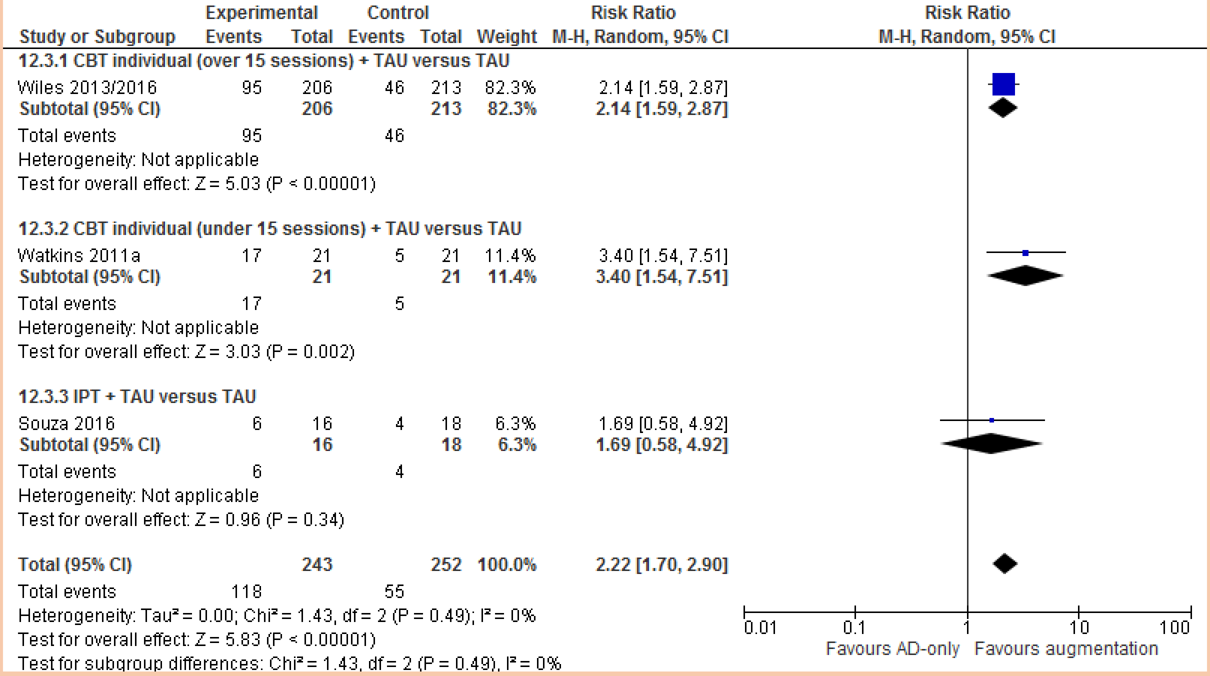
Test for subgroup differences: Chi² = 18.40, df = 5 (P = 0.002), I² = 72.8%

Remission (≤7/8 on HAMD/<10 on BDI)



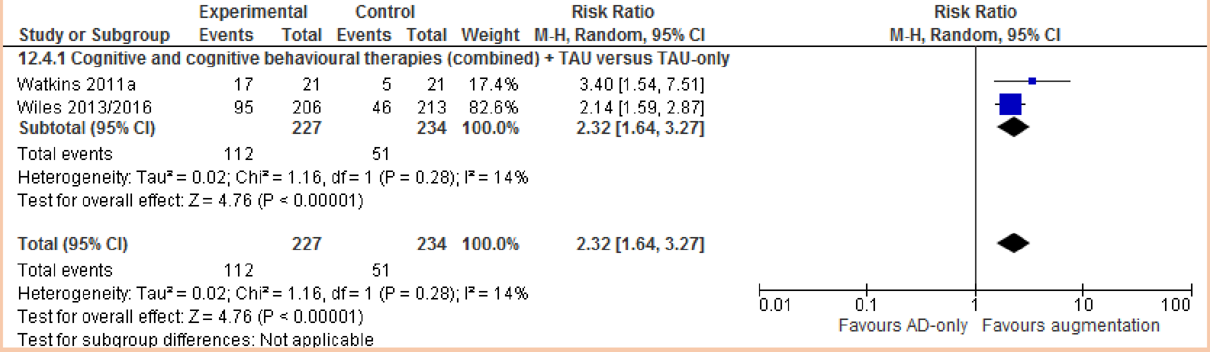
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.2.1 Cognitive and cognitive behavioural therapies (combined) + any AD/TAU versus any AD/TAU-only						
Kocsis 2009/Klein 2011	67	174	30	76	32.2%	0.98 [0.70, 1.36]
Paykel 1999/Scott 2000	19	80	9	78	20.9%	2.06 [0.99, 4.27]
Watkins 2011a	13	21	4	21	16.1%	3.25 [1.27, 8.35]
Wiles 2013/2016	57	206	32	213	30.7%	1.84 [1.25, 2.72]
Subtotal (95% CI)		**481**		**388**	**100.0%**	**1.68 [1.02, 2.78]**
Total events	156		75			
Heterogeneity: Tau² = 0.17; Chi² = 10.74, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Total (95% CI)		**481**		**388**	**100.0%**	**1.68 [1.02, 2.78]**
Total events	156		75			
Heterogeneity: Tau² = 0.17; Chi² = 10.74, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Not applicable						

Response (≥50% improvement on HAMD/BDI)



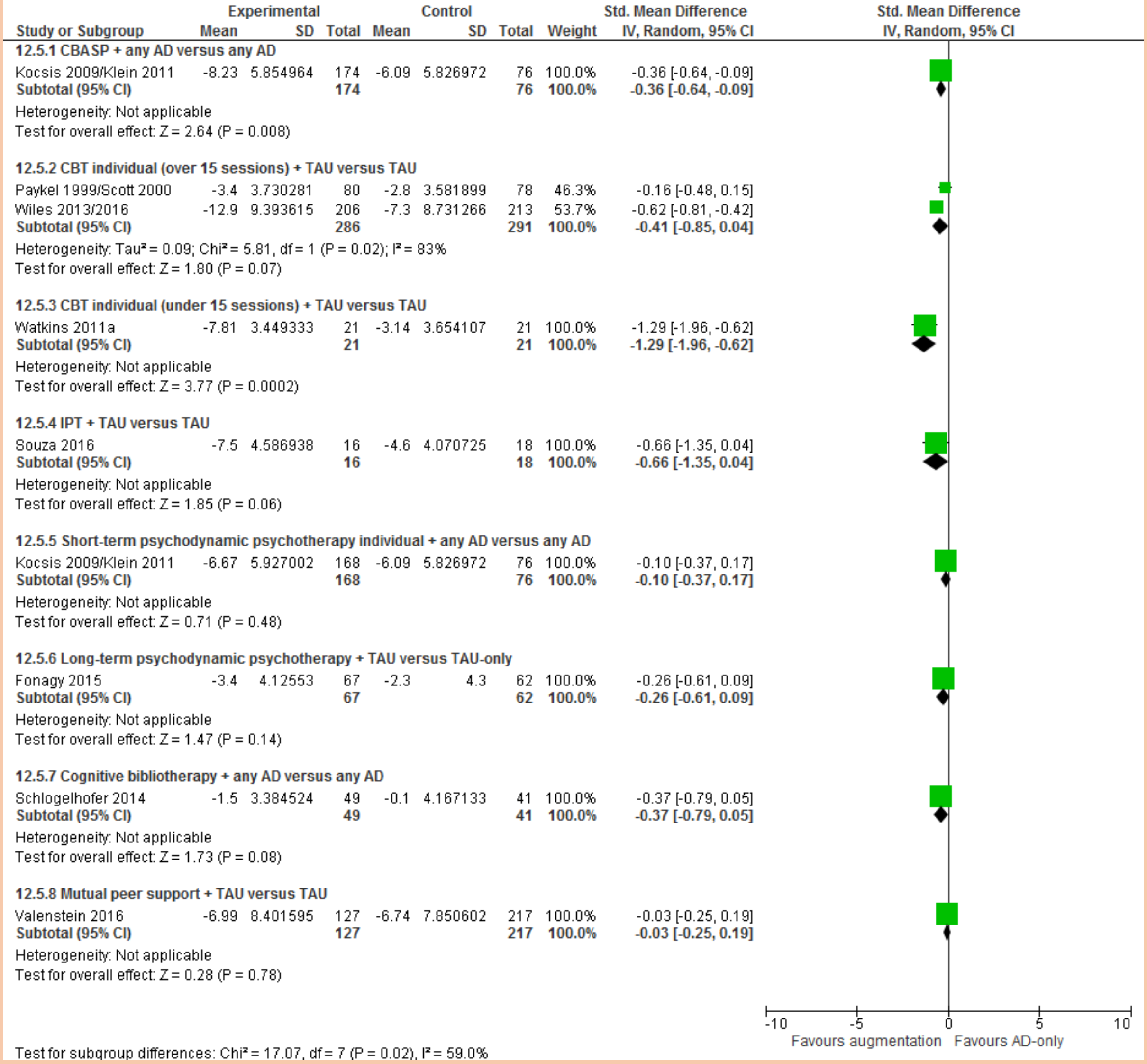
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 CBT individual (over 15 sessions) + TAU versus TAU						
Wiles 2013/2016	95	206	46	213	82.3%	2.14 [1.59, 2.87]
Subtotal (95% CI)		**206**		**213**	**82.3%**	**2.14 [1.59, 2.87]**
Total events	95		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.03 (P < 0.00001)						
12.3.2 CBT individual (under 15 sessions) + TAU versus TAU						
Watkins 2011a	17	21	5	21	11.4%	3.40 [1.54, 7.51]
Subtotal (95% CI)		**21**		**21**	**11.4%**	**3.40 [1.54, 7.51]**
Total events	17		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.03 (P = 0.002)						
12.3.3 IPT + TAU versus TAU						
Souza 2016	6	16	4	18	6.3%	1.69 [0.58, 4.92]
Subtotal (95% CI)		**16**		**18**	**6.3%**	**1.69 [0.58, 4.92]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Total (95% CI)		**243**		**252**	**100.0%**	**2.22 [1.70, 2.90]**
Total events	118		55			
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 5.83 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.43, df = 2 (P = 0.49), I² = 0%						

Response (≥50% improvement on HAMD/BDI)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.4.1 Cognitive and cognitive behavioural therapies (combined) + TAU versus TAU-only						
Watkins 2011a	17	21	5	21	17.4%	3.40 [1.54, 7.51]
Wiles 2013/2016	95	206	46	213	82.6%	2.14 [1.59, 2.87]
Subtotal (95% CI)		**227**		**234**	**100.0%**	**2.32 [1.64, 3.27]**
Total events	112		51			
Heterogeneity: Tau² = 0.02; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 4.76 (P < 0.00001)						
Total (95% CI)		**227**		**234**	**100.0%**	**2.32 [1.64, 3.27]**
Total events	112		51			
Heterogeneity: Tau² = 0.02; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 4.76 (P < 0.00001)						
Test for subgroup differences: Not applicable						

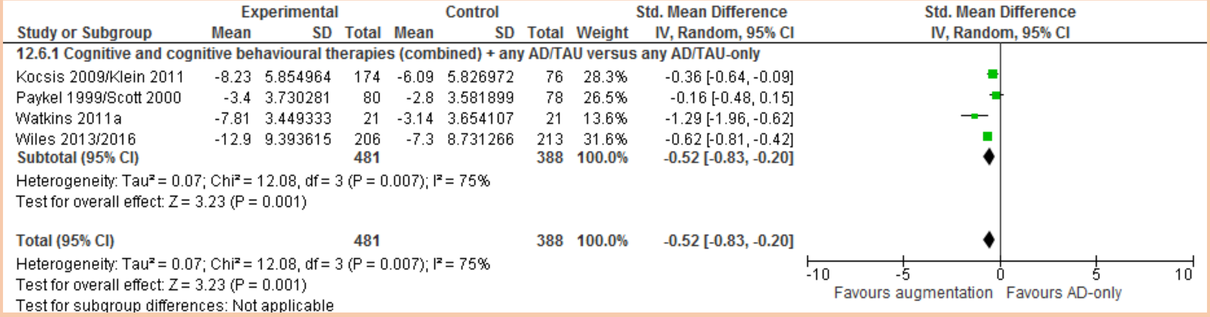
Depression symptomatology (HAMD/BDI change score)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
12.5.1 CBASP + any AD versus any AD								
Kocsis 2009/Klein 2011	-8.23	5.854964	174	-6.09	5.826972	76	100.0%	-0.36 [-0.64, -0.09]
Subtotal (95% CI)			**174**			**76**	**100.0%**	**-0.36 [-0.64, -0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.64 (P = 0.008)								
12.5.2 CBT individual (over 15 sessions) + TAU versus TAU								
Paykel 1999/Scott 2000	-3.4	3.730281	80	-2.8	3.581899	78	46.3%	-0.16 [-0.48, 0.15]
Wiles 2013/2016	-12.9	9.393615	206	-7.3	8.731266	213	53.7%	-0.62 [-0.81, -0.42]
Subtotal (95% CI)			**286**			**291**	**100.0%**	**-0.41 [-0.85, 0.04]**
Heterogeneity: Tau² = 0.09; Chi² = 5.81, df = 1 (P = 0.02); I² = 83%								
Test for overall effect: Z = 1.80 (P = 0.07)								
12.5.3 CBT individual (under 15 sessions) + TAU versus TAU								
Watkins 2011a	-7.81	3.449333	21	-3.14	3.654107	21	100.0%	-1.29 [-1.96, -0.62]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**-1.29 [-1.96, -0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.77 (P = 0.0002)								
12.5.4 IPT + TAU versus TAU								
Souza 2016	-7.5	4.586938	16	-4.6	4.070725	18	100.0%	-0.66 [-1.35, 0.04]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**-0.66 [-1.35, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.85 (P = 0.06)								
12.5.5 Short-term psychodynamic psychotherapy individual + any AD versus any AD								
Kocsis 2009/Klein 2011	-6.67	5.927002	168	-6.09	5.826972	76	100.0%	-0.10 [-0.37, 0.17]
Subtotal (95% CI)			**168**			**76**	**100.0%**	**-0.10 [-0.37, 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
12.5.6 Long-term psychodynamic psychotherapy + TAU versus TAU-only								
Fonagy 2015	-3.4	4.12553	67	-2.3	4.3	62	100.0%	-0.26 [-0.61, 0.09]
Subtotal (95% CI)			**67**			**62**	**100.0%**	**-0.26 [-0.61, 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.47 (P = 0.14)								
12.5.7 Cognitive bibliotherapy + any AD versus any AD								
Schlogelhofer 2014	-1.5	3.384524	49	-0.1	4.167133	41	100.0%	-0.37 [-0.79, 0.05]
Subtotal (95% CI)			**49**			**41**	**100.0%**	**-0.37 [-0.79, 0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.73 (P = 0.08)								
12.5.8 Mutual peer support + TAU versus TAU								
Valenstein 2016	-6.99	8.401595	127	-6.74	7.850602	217	100.0%	-0.03 [-0.25, 0.19]
Subtotal (95% CI)			**127**			**217**	**100.0%**	**-0.03 [-0.25, 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								

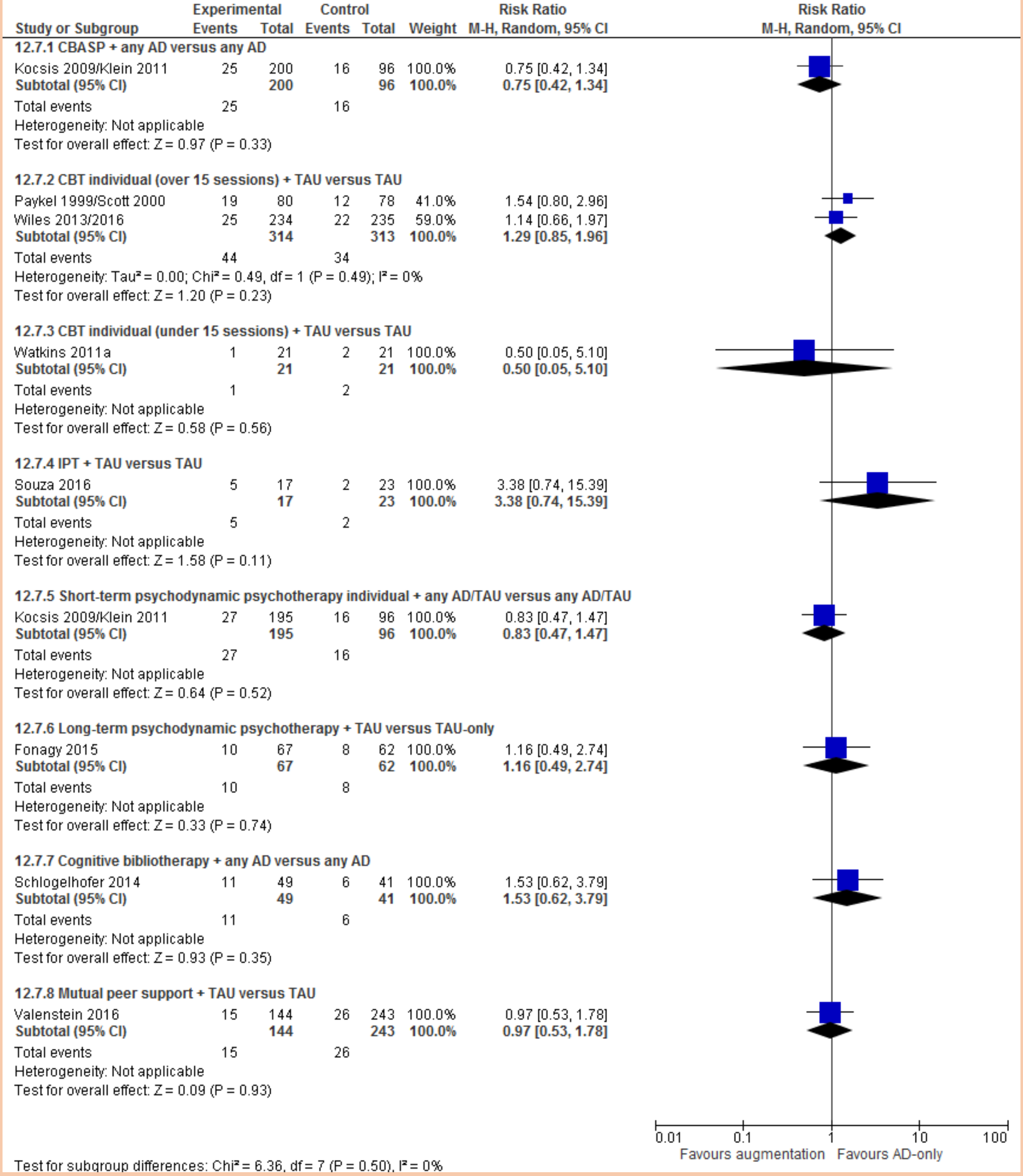
Test for subgroup differences: Chi² = 17.07, df = 7 (P = 0.02), I² = 59.0%

Depression symptomatology (HAMD/BDI change score)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
12.6.1 Cognitive and cognitive behavioural therapies (combined) + any AD/TAU versus any AD/TAU-only								
Kocsis 2009/Klein 2011	-8.23	5.854964	174	-6.09	5.826972	76	28.3%	-0.36 [-0.64, -0.09]
Paykel 1999/Scott 2000	-3.4	3.730281	80	-2.8	3.581899	78	26.5%	-0.16 [-0.48, 0.15]
Watkins 2011a	-7.81	3.449333	21	-3.14	3.654107	21	13.6%	-1.29 [-1.96, -0.62]
Wiles 2013/2016	-12.9	9.393615	206	-7.3	8.731266	213	31.6%	-0.62 [-0.81, -0.42]
Subtotal (95% CI)			**481**			**388**	**100.0%**	**-0.52 [-0.83, -0.20]**
Heterogeneity: Tau² = 0.07; Chi² = 12.08, df = 3 (P = 0.007); I² = 75%								
Test for overall effect: Z = 3.23 (P = 0.001)								
Total (95% CI)			**481**			**388**	**100.0%**	**-0.52 [-0.83, -0.20]**
Heterogeneity: Tau² = 0.07; Chi² = 12.08, df = 3 (P = 0.007); I² = 75%								
Test for overall effect: Z = 3.23 (P = 0.001)								
Test for subgroup differences: Not applicable								

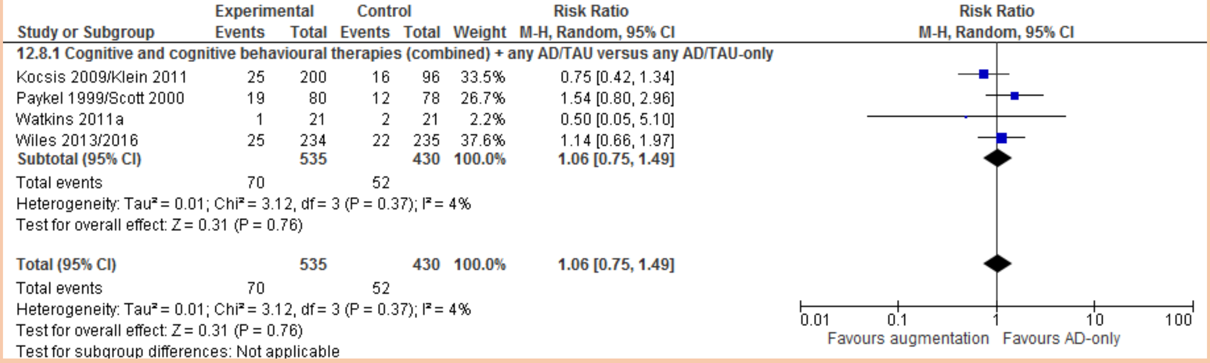
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.7.1 CBASP + any AD versus any AD						
Kocsis 2009/Klein 2011	25	200	16	96	100.0%	0.75 [0.42, 1.34]
Subtotal (95% CI)		**200**		**96**	**100.0%**	**0.75 [0.42, 1.34]**
Total events	25		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
12.7.2 CBT individual (over 15 sessions) + TAU versus TAU						
Paykel 1999/Scott 2000	19	80	12	78	41.0%	1.54 [0.80, 2.96]
Wiles 2013/2016	25	234	22	235	59.0%	1.14 [0.66, 1.97]
Subtotal (95% CI)		**314**		**313**	**100.0%**	**1.29 [0.85, 1.96]**
Total events	44		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
12.7.3 CBT individual (under 15 sessions) + TAU versus TAU						
Watkins 2011a	1	21	2	21	100.0%	0.50 [0.05, 5.10]
Subtotal (95% CI)		**21**		**21**	**100.0%**	**0.50 [0.05, 5.10]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
12.7.4 IPT + TAU versus TAU						
Souza 2016	5	17	2	23	100.0%	3.38 [0.74, 15.39]
Subtotal (95% CI)		**17**		**23**	**100.0%**	**3.38 [0.74, 15.39]**
Total events	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
12.7.5 Short-term psychodynamic psychotherapy individual + any AD/TAU versus any AD/TAU						
Kocsis 2009/Klein 2011	27	195	16	96	100.0%	0.83 [0.47, 1.47]
Subtotal (95% CI)		**195**		**96**	**100.0%**	**0.83 [0.47, 1.47]**
Total events	27		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
12.7.6 Long-term psychodynamic psychotherapy + TAU versus TAU-only						
Fonagy 2015	10	67	8	62	100.0%	1.16 [0.49, 2.74]
Subtotal (95% CI)		**67**		**62**	**100.0%**	**1.16 [0.49, 2.74]**
Total events	10		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
12.7.7 Cognitive bibliotherapy + any AD versus any AD						
Schlogelhofer 2014	11	49	6	41	100.0%	1.53 [0.62, 3.79]
Subtotal (95% CI)		**49**		**41**	**100.0%**	**1.53 [0.62, 3.79]**
Total events	11		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
12.7.8 Mutual peer support + TAU versus TAU						
Valenstein 2016	15	144	26	243	100.0%	0.97 [0.53, 1.78]
Subtotal (95% CI)		**144**		**243**	**100.0%**	**0.97 [0.53, 1.78]**
Total events	15		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						

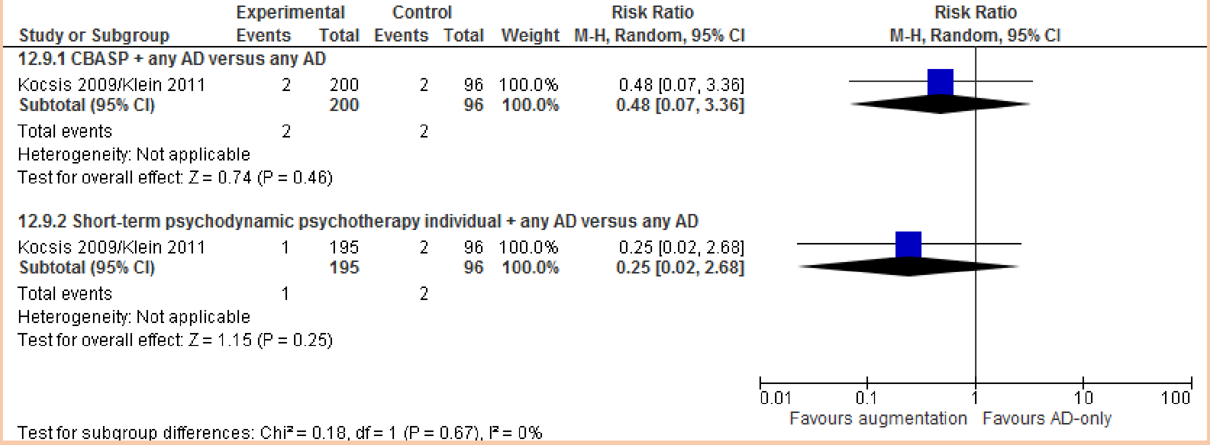
Test for subgroup differences: Chi² = 6.36, df = 7 (P = 0.50), I² = 0%

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.8.1 Cognitive and cognitive behavioural therapies (combined) + any AD/TAU versus any AD/TAU-only						
Kocsis 2009/Klein 2011	25	200	16	96	33.5%	0.75 [0.42, 1.34]
Paykel 1999/Scott 2000	19	80	12	78	26.7%	1.54 [0.80, 2.96]
Watkins 2011a	1	21	2	21	2.2%	0.50 [0.05, 5.10]
Wiles 2013/2016	25	234	22	235	37.6%	1.14 [0.66, 1.97]
Subtotal (95% CI)		**535**		**430**	**100.0%**	**1.06 [0.75, 1.49]**
Total events	70		52			
Heterogeneity: Tau² = 0.01; Chi² = 3.12, df = 3 (P = 0.37); I² = 4%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**535**		**430**	**100.0%**	**1.06 [0.75, 1.49]**
Total events	70		52			
Heterogeneity: Tau² = 0.01; Chi² = 3.12, df = 3 (P = 0.37); I² = 4%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Not applicable						

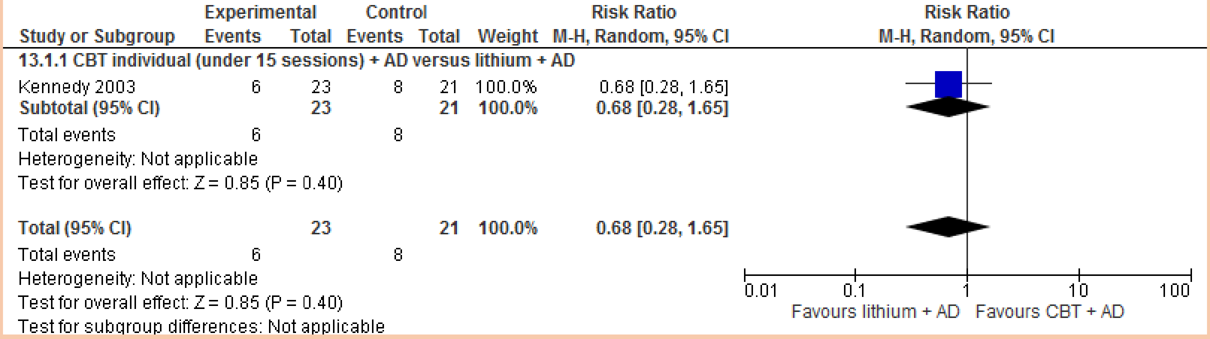
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.9.1 CBASP + any AD versus any AD						
Kocsis 2009/Klein 2011	2	200	2	96	100.0%	0.48 [0.07, 3.36]
Subtotal (95% CI)		**200**		**96**	**100.0%**	**0.48 [0.07, 3.36]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
12.9.2 Short-term psychodynamic psychotherapy individual + any AD versus any AD						
Kocsis 2009/Klein 2011	1	195	2	96	100.0%	0.25 [0.02, 2.68]
Subtotal (95% CI)		**195**		**96**	**100.0%**	**0.25 [0.02, 2.68]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						

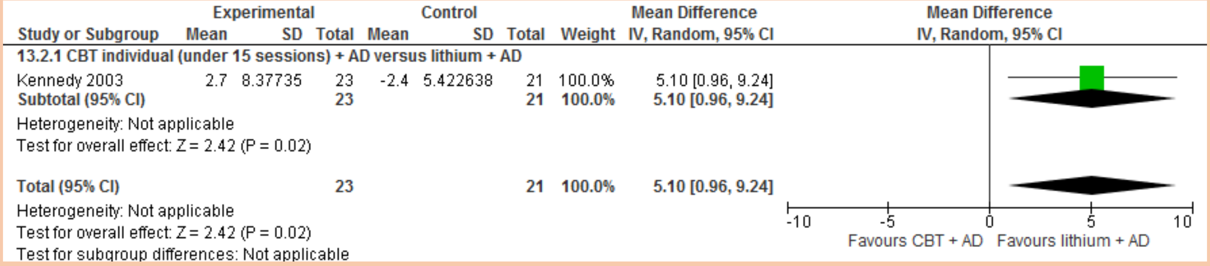
Augmenting the antidepressant with a psychological intervention compared to augmenting with a non-antidepressant agent

Remission (HAMD ≤7)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 CBT individual (under 15 sessions) + AD versus lithium + AD						
Kennedy 2003	6	23	8	21	100.0%	0.68 [0.28, 1.65]
Subtotal (95% CI)		**23**		**21**	**100.0%**	**0.68 [0.28, 1.65]**
Total events	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**23**		**21**	**100.0%**	**0.68 [0.28, 1.65]**
Total events	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Not applicable						

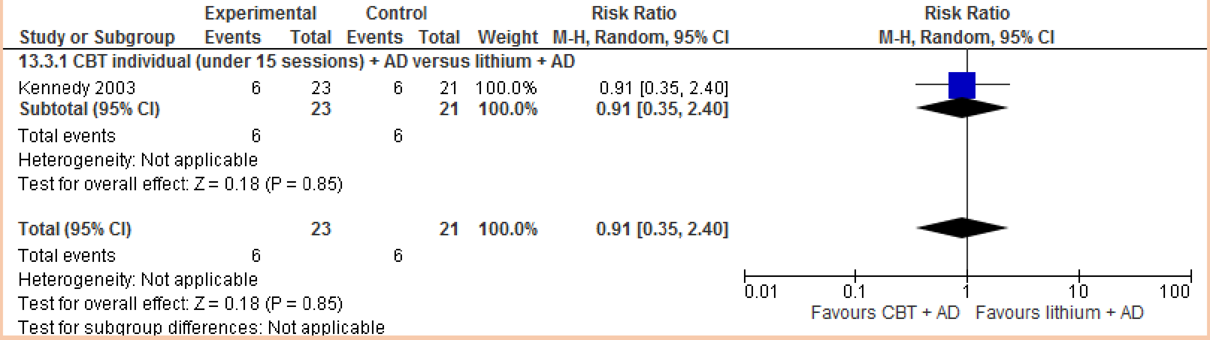
Depression symptomatology (HAMD change score)



	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
13.2.1 CBT individual (under 15 sessions) + AD versus lithium + AD								
Kennedy 2003	2.7	8.37735	23	-2.4	5.422638	21	100.0%	5.10 [0.96, 9.24]
Subtotal (95% CI)			**23**			**21**	**100.0%**	**5.10 [0.96, 9.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.42 (P = 0.02)								
Total (95% CI)			**23**			**21**	**100.0%**	**5.10 [0.96, 9.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.42 (P = 0.02)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours CBT + AD
Favours lithium + AD

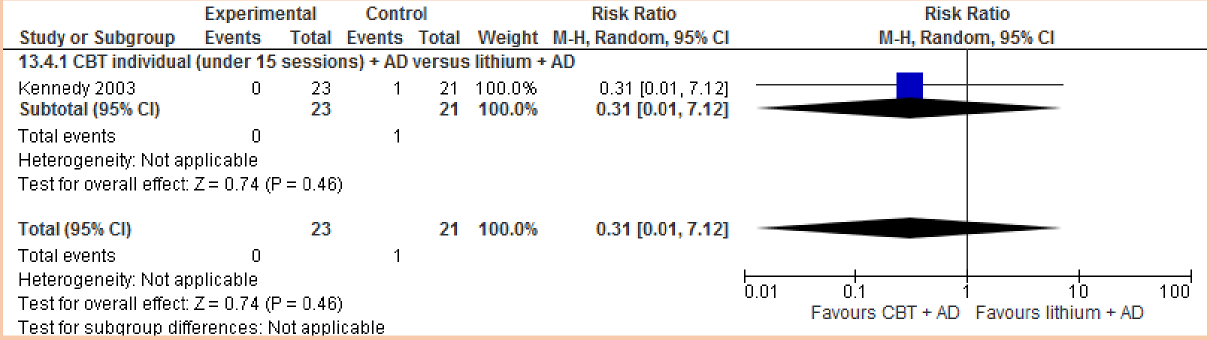
Discontinuation for any reason



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
13.3.1 CBT individual (under 15 sessions) + AD versus lithium + AD						
Kennedy 2003	6	23	6	21	100.0%	0.91 [0.35, 2.40]
Subtotal (95% CI)		**23**		**21**	**100.0%**	**0.91 [0.35, 2.40]**
Total events	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.85)						
Total (95% CI)		**23**		**21**	**100.0%**	**0.91 [0.35, 2.40]**
Total events	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.85)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CBT + AD
Favours lithium + AD

Discontinuation due to adverse events

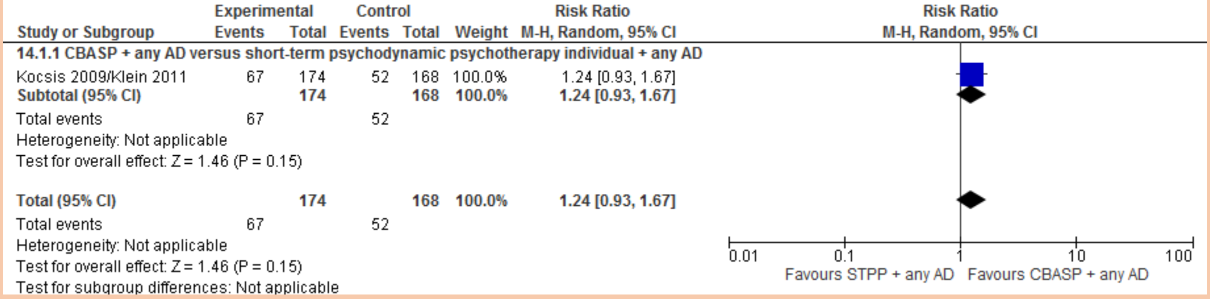


	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
13.4.1 CBT individual (under 15 sessions) + AD versus lithium + AD						
Kennedy 2003	0	23	1	21	100.0%	0.31 [0.01, 7.12]
Subtotal (95% CI)		**23**		**21**	**100.0%**	**0.31 [0.01, 7.12]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**23**		**21**	**100.0%**	**0.31 [0.01, 7.12]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CBT + AD
Favours lithium + AD

Augmenting the antidepressant with a psychological intervention compared to ‘other’ psychological intervention (head-to-head comparisons)

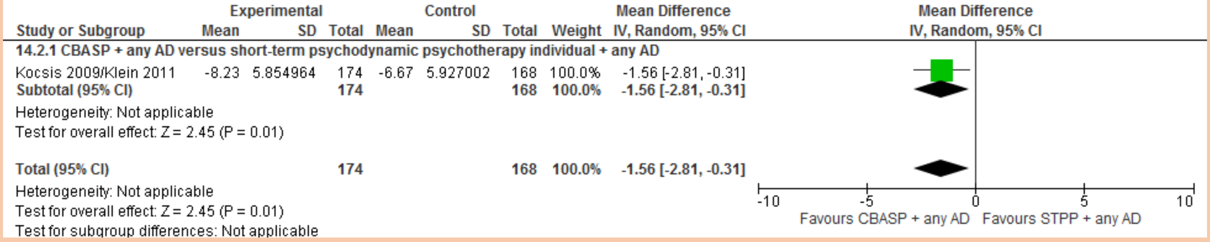
Remission (<8 on HAMD)



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
14.1.1 CBASP + any AD versus short-term psychodynamic psychotherapy individual + any AD						
Kocsis 2009/Klein 2011	67	174	52	168	100.0%	1.24 [0.93, 1.67]
Subtotal (95% CI)		**174**		**168**	**100.0%**	**1.24 [0.93, 1.67]**
Total events	67		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.15)						
Total (95% CI)		**174**		**168**	**100.0%**	**1.24 [0.93, 1.67]**
Total events	67		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.15)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours STPP + any AD
Favours CBASP + any AD

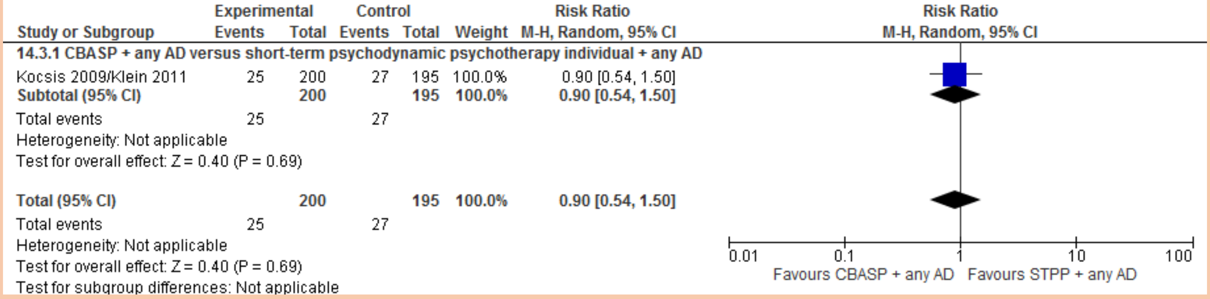
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
14.2.1 CBASP + any AD versus short-term psychodynamic psychotherapy individual + any AD								
Kocsis 2009/Klein 2011	-8.23	5.854964	174	-6.67	5.927002	168	100.0%	-1.56 [-2.81, -0.31]
Subtotal (95% CI)			**174**			**168**	**100.0%**	**-1.56 [-2.81, -0.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.45 (P = 0.01)								
Total (95% CI)			**174**			**168**	**100.0%**	**-1.56 [-2.81, -0.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.45 (P = 0.01)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours CBASP + any AD
Favours STPP + any AD

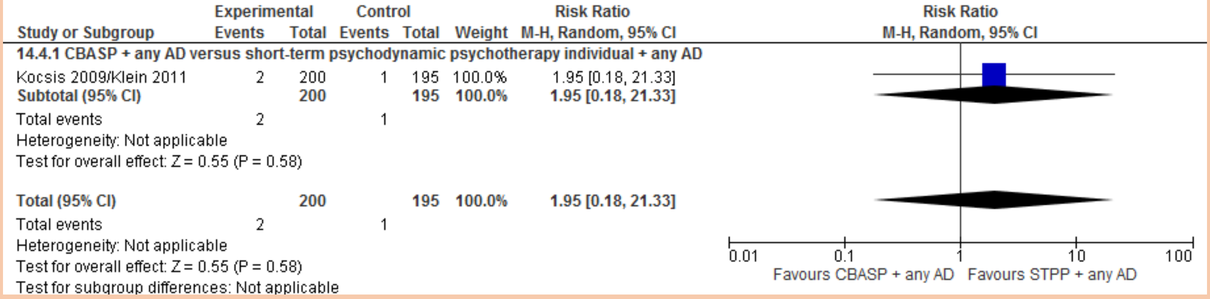
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
14.3.1 CBASP + any AD versus short-term psychodynamic psychotherapy individual + any AD						
Kocsis 2009/Klein 2011	25	200	27	195	100.0%	0.90 [0.54, 1.50]
Subtotal (95% CI)		**200**		**195**	**100.0%**	**0.90 [0.54, 1.50]**
Total events	25		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Total (95% CI)		**200**		**195**	**100.0%**	**0.90 [0.54, 1.50]**
Total events	25		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CBASP + any AD
Favours STPP + any AD

Discontinuation due to adverse events

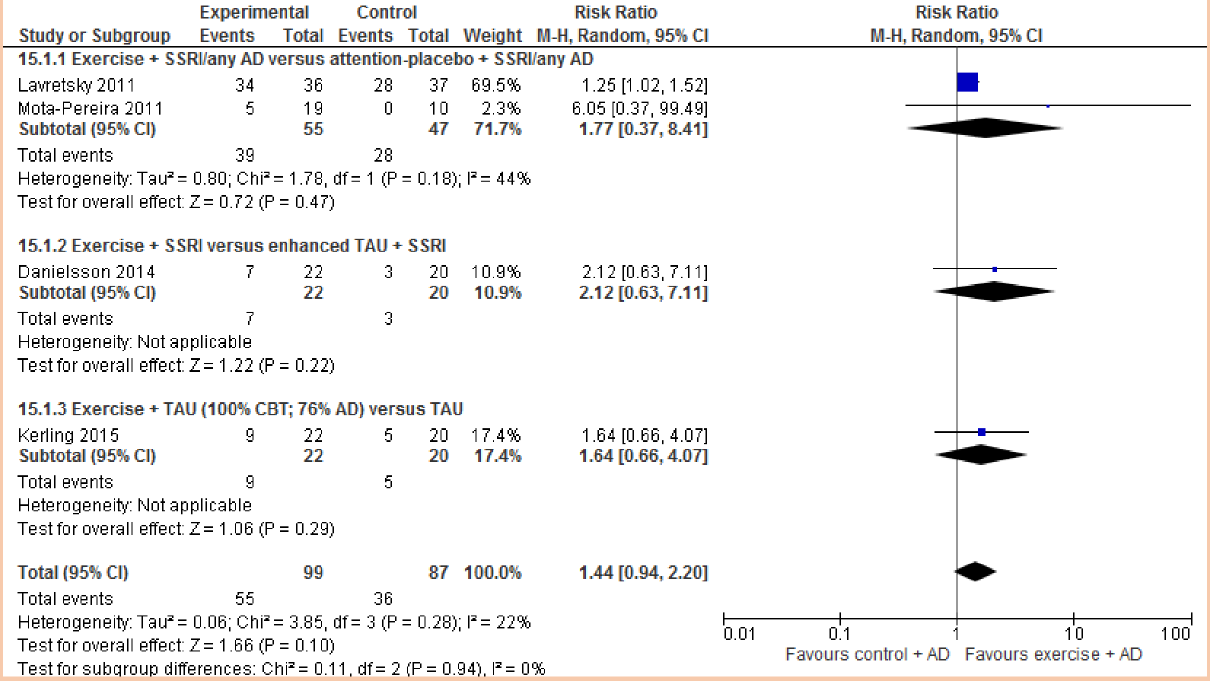


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
14.4.1 CBASP + any AD versus short-term psychodynamic psychotherapy individual + any AD						
Kocsis 2009/Klein 2011	2	200	1	195	100.0%	1.95 [0.18, 21.33]
Subtotal (95% CI)		**200**		**195**	**100.0%**	**1.95 [0.18, 21.33]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
Total (95% CI)		**200**		**195**	**100.0%**	**1.95 [0.18, 21.33]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CBASP + any AD
Favours STPP + any AD

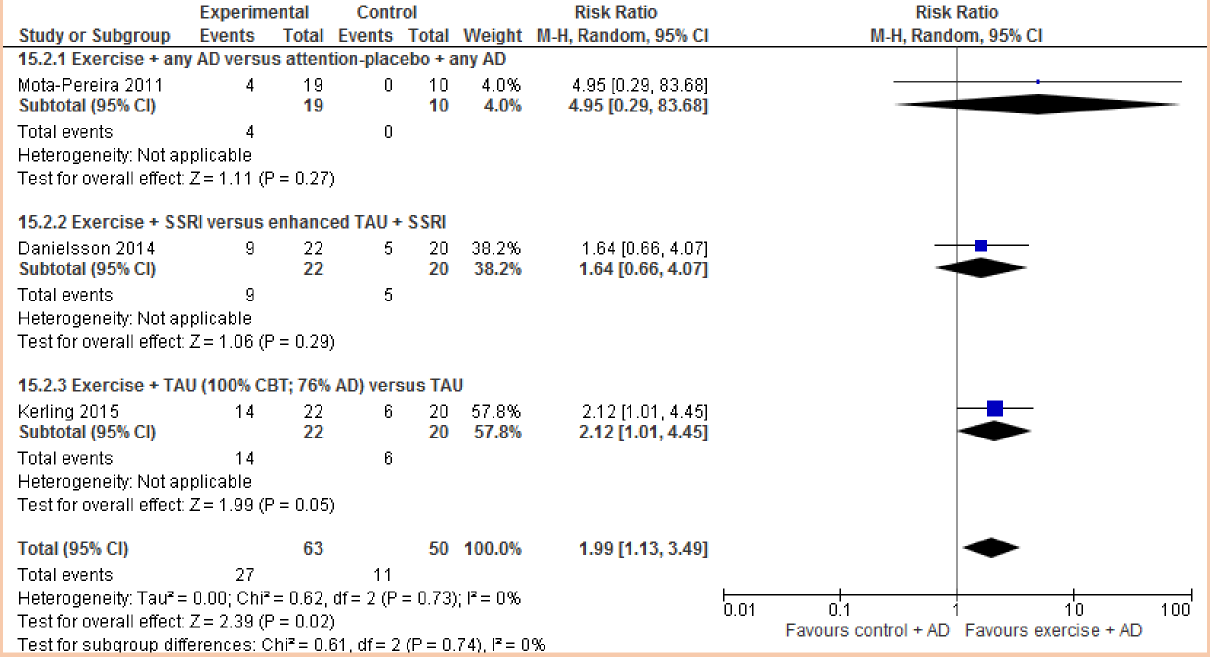
Augmenting the antidepressant/standard treatment with exercise compared to control

Remission (≤7/10 on HAMD/ ≤ 10 on MADRS & ≥ 50% improvement)



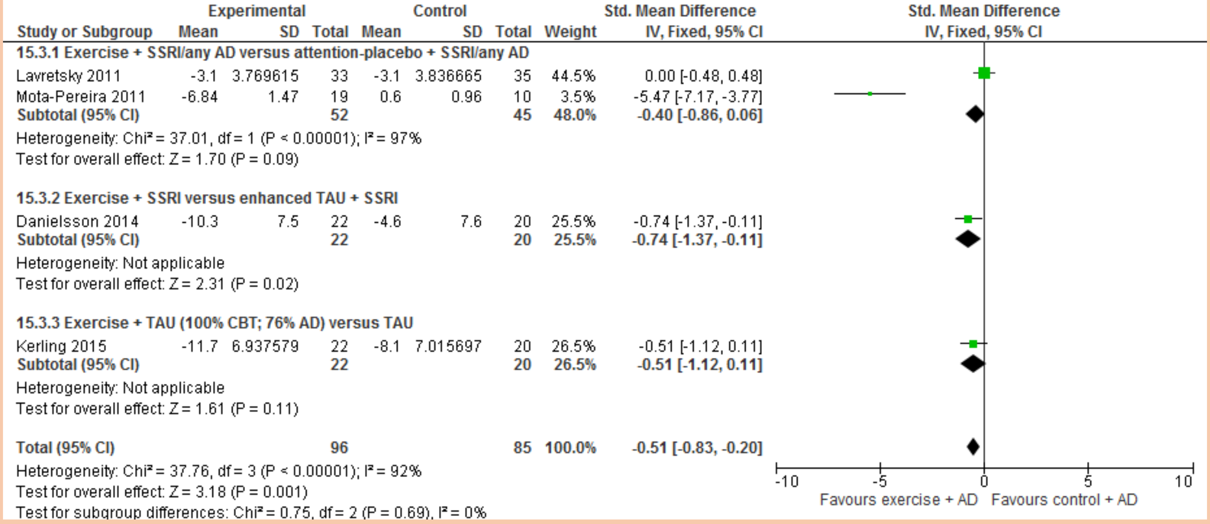
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.1.1 Exercise + SSRI/any AD versus attention-placebo + SSRI/any AD						
Lavretsky 2011	34	36	28	37	69.5%	1.25 [1.02, 1.52]
Mota-Pereira 2011	5	19	0	10	2.3%	6.05 [0.37, 99.49]
Subtotal (95% CI)		**55**		**47**	**71.7%**	**1.77 [0.37, 8.41]**
Total events	39		28			
Heterogeneity: Tau² = 0.80; Chi² = 1.78, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 0.72 (P = 0.47)						
15.1.2 Exercise + SSRI versus enhanced TAU + SSRI						
Danielsson 2014	7	22	3	20	10.9%	2.12 [0.63, 7.11]
Subtotal (95% CI)		**22**		**20**	**10.9%**	**2.12 [0.63, 7.11]**
Total events	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
15.1.3 Exercise + TAU (100% CBT; 76% AD) versus TAU						
Kerling 2015	9	22	5	20	17.4%	1.64 [0.66, 4.07]
Subtotal (95% CI)		**22**		**20**	**17.4%**	**1.64 [0.66, 4.07]**
Total events	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**99**		**87**	**100.0%**	**1.44 [0.94, 2.20]**
Total events	55		36			
Heterogeneity: Tau² = 0.06; Chi² = 3.85, df = 3 (P = 0.28); I² = 22%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi² = 0.11, df = 2 (P = 0.94), I² = 0%						

Response (≥50% improvement on HAMD/MADRS)



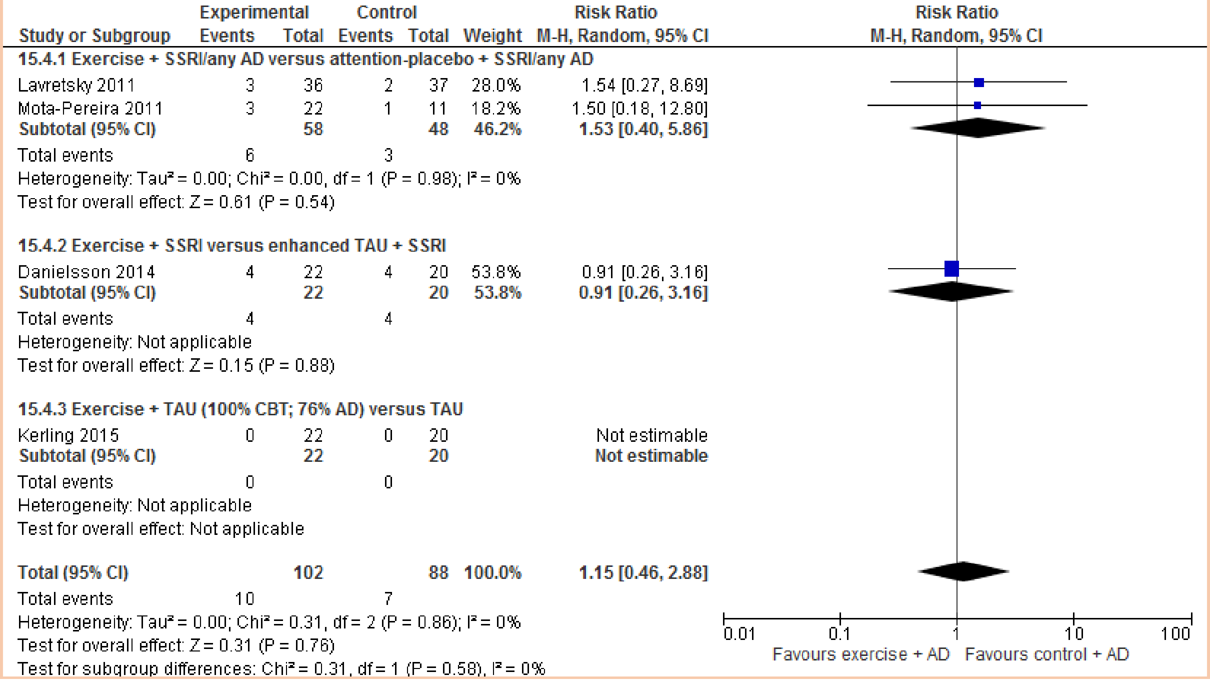
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.2.1 Exercise + any AD versus attention-placebo + any AD						
Mota-Pereira 2011	4	19	0	10	4.0%	4.95 [0.29, 83.68]
Subtotal (95% CI)		**19**		**10**	**4.0%**	**4.95 [0.29, 83.68]**
Total events	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
15.2.2 Exercise + SSRI versus enhanced TAU + SSRI						
Danielsson 2014	9	22	5	20	38.2%	1.64 [0.66, 4.07]
Subtotal (95% CI)		**22**		**20**	**38.2%**	**1.64 [0.66, 4.07]**
Total events	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
15.2.3 Exercise + TAU (100% CBT; 76% AD) versus TAU						
Kerling 2015	14	22	6	20	57.8%	2.12 [1.01, 4.45]
Subtotal (95% CI)		**22**		**20**	**57.8%**	**2.12 [1.01, 4.45]**
Total events	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Total (95% CI)		**63**		**50**	**100.0%**	**1.99 [1.13, 3.49]**
Total events	27		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 2.39 (P = 0.02)						
Test for subgroup differences: Chi² = 0.61, df = 2 (P = 0.74), I² = 0%						

Depression symptomatology (HAMD/MADRS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
15.3.1 Exercise + SSRI/any AD versus attention-placebo + SSRI/any AD								
Lavretsky 2011	-3.1	3.769615	33	-3.1	3.836665	35	44.5%	0.00 [-0.48, 0.48]
Mota-Pereira 2011	-6.84	1.47	19	0.6	0.96	10	3.5%	-5.47 [-7.17, -3.77]
Subtotal (95% CI)			**52**			**45**	**48.0%**	**-0.40 [-0.86, 0.06]**
Heterogeneity: Chi² = 37.01, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.70 (P = 0.09)								
15.3.2 Exercise + SSRI versus enhanced TAU + SSRI								
Danielsson 2014	-10.3	7.5	22	-4.6	7.6	20	25.5%	-0.74 [-1.37, -0.11]
Subtotal (95% CI)			**22**			**20**	**25.5%**	**-0.74 [-1.37, -0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
15.3.3 Exercise + TAU (100% CBT; 76% AD) versus TAU								
Kerling 2015	-11.7	6.937579	22	-8.1	7.015697	20	26.5%	-0.51 [-1.12, 0.11]
Subtotal (95% CI)			**22**			**20**	**26.5%**	**-0.51 [-1.12, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.61 (P = 0.11)								
Total (95% CI)			**96**			**85**	**100.0%**	**-0.51 [-0.83, -0.20]**
Heterogeneity: Chi² = 37.76, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.18 (P = 0.001)								
Test for subgroup differences: Chi² = 0.75, df = 2 (P = 0.69), I² = 0%								

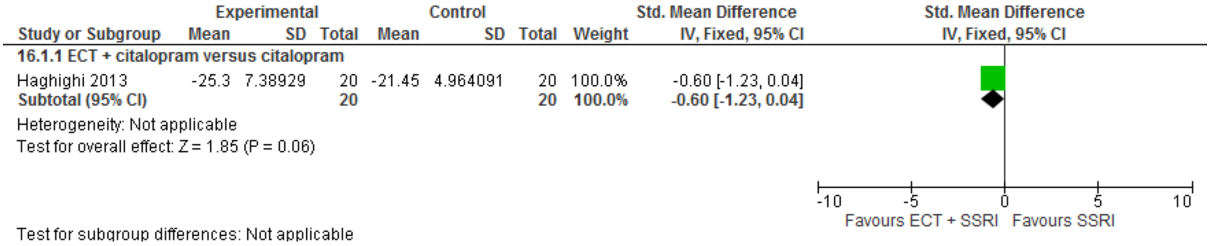
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.4.1 Exercise + SSRI/any AD versus attention-placebo + SSRI/any AD						
Lavretsky 2011	3	36	2	37	28.0%	1.54 [0.27, 8.69]
Mota-Pereira 2011	3	22	1	11	18.2%	1.50 [0.18, 12.80]
Subtotal (95% CI)		**58**		**48**	**46.2%**	**1.53 [0.40, 5.86]**
Total events	6		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
15.4.2 Exercise + SSRI versus enhanced TAU + SSRI						
Danielsson 2014	4	22	4	20	53.8%	0.91 [0.26, 3.16]
Subtotal (95% CI)		**22**		**20**	**53.8%**	**0.91 [0.26, 3.16]**
Total events	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
15.4.3 Exercise + TAU (100% CBT; 76% AD) versus TAU						
Kerling 2015	0	22	0	20		Not estimable
Subtotal (95% CI)		**22**		**20**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**102**		**88**	**100.0%**	**1.15 [0.46, 2.88]**
Total events	10		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%						

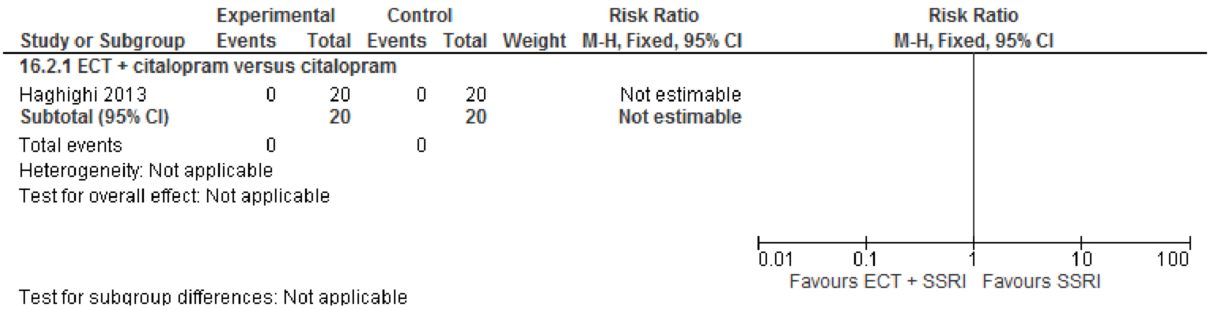
Augmenting the antidepressant with ECT compared to continuing with the antidepressant-only

Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
16.1.1 ECT + citalopram versus citalopram								
Haghighi 2013	-25.3	7.38929	20	-21.45	4.964091	20	100.0%	-0.60 [-1.23, 0.04]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-0.60 [-1.23, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.85 (P = 0.06)								
Test for subgroup differences: Not applicable								

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
16.2.1 ECT + citalopram versus citalopram						
Haghighi 2013	0	20	0	20		Not estimable
Subtotal (95% CI)		**20**		**20**		**Not estimable**
Total events	0		0			

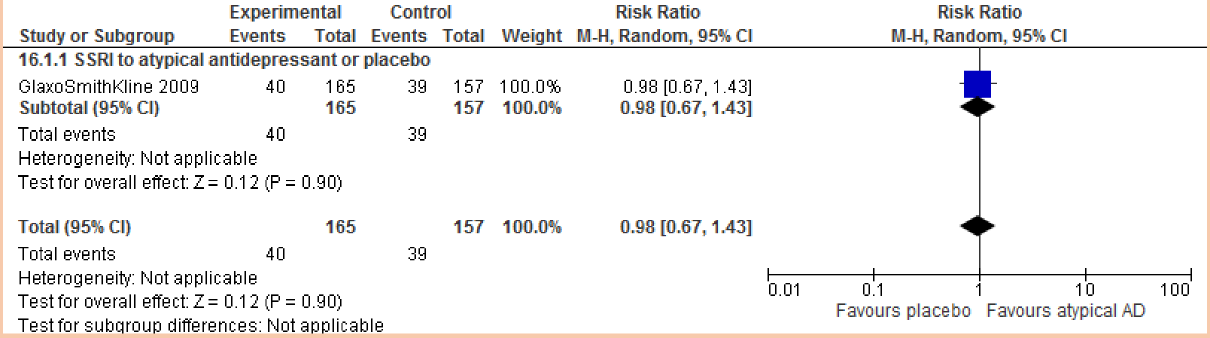
Heterogeneity: Not applicable
Test for overall effect: Not applicable

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours ECT + SSRI
Favours SSRI

Switching to another antidepressant of a different class compared to placebo

Remission (≤7 on HAMD)



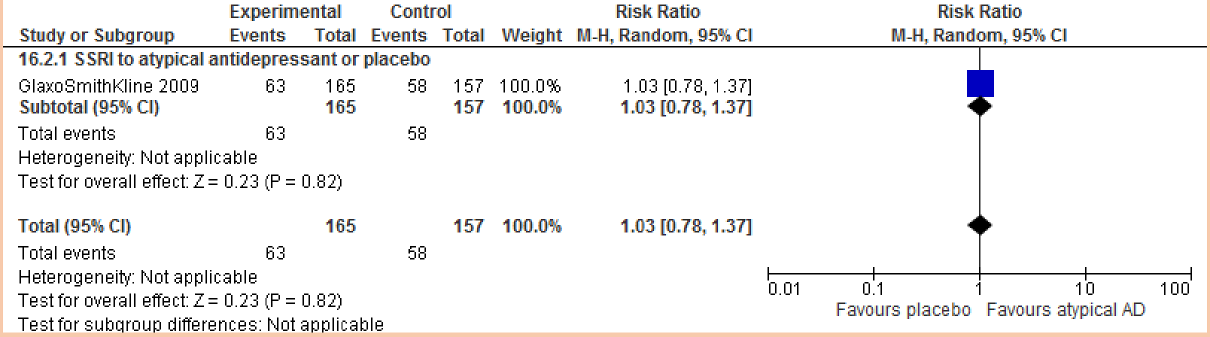
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
16.1.1 SSRI to atypical antidepressant or placebo						
GlaxoSmithKline 2009	40	165	39	157	100.0%	0.98 [0.67, 1.43]
Subtotal (95% CI)		**165**		**157**	**100.0%**	**0.98 [0.67, 1.43]**
Total events	40		39			
Total (95% CI)		**165**		**157**	**100.0%**	**0.98 [0.67, 1.43]**
Total events	40		39			

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

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

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours placebo
Favours atypical AD

Response (≥50% improvement on HAMD)



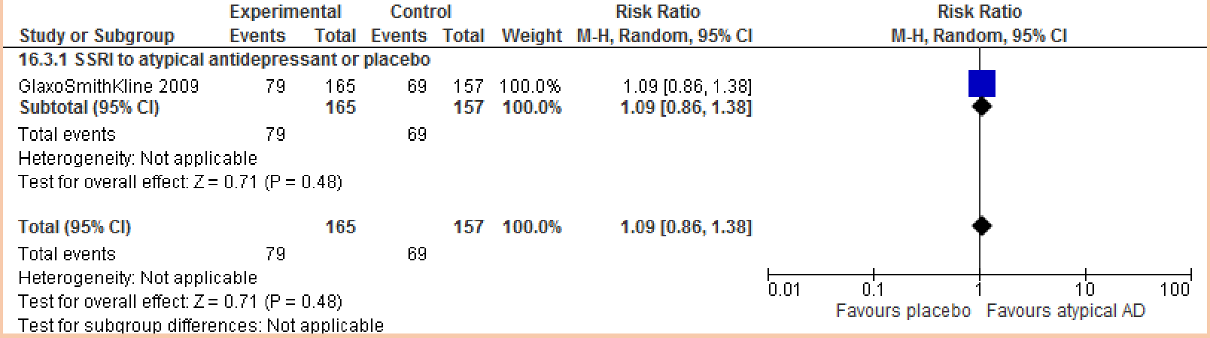
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
16.2.1 SSRI to atypical antidepressant or placebo						
GlaxoSmithKline 2009	63	165	58	157	100.0%	1.03 [0.78, 1.37]
Subtotal (95% CI)		**165**		**157**	**100.0%**	**1.03 [0.78, 1.37]**
Total events	63		58			
Total (95% CI)		**165**		**157**	**100.0%**	**1.03 [0.78, 1.37]**
Total events	63		58			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours placebo
Favours atypical AD

Response (much/very much improved on CGI-I)



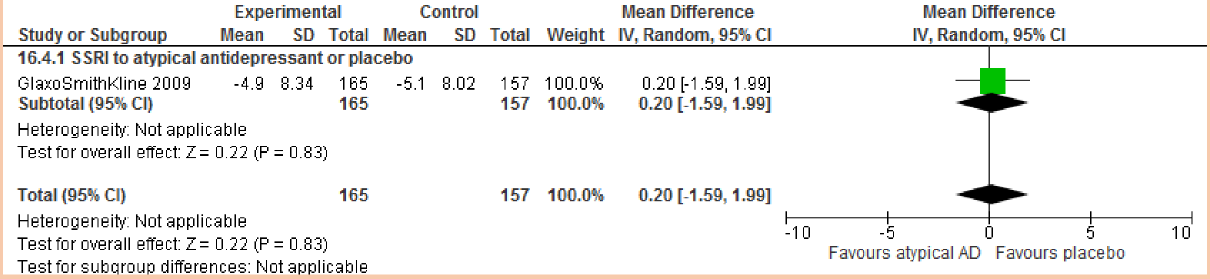
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
16.3.1 SSRI to atypical antidepressant or placebo						
GlaxoSmithKline 2009	79	165	69	157	100.0%	1.09 [0.86, 1.38]
Subtotal (95% CI)		**165**		**157**	**100.0%**	**1.09 [0.86, 1.38]**
Total events	79		69			
Total (95% CI)		**165**		**157**	**100.0%**	**1.09 [0.86, 1.38]**
Total events	79		69			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours placebo
Favours atypical AD

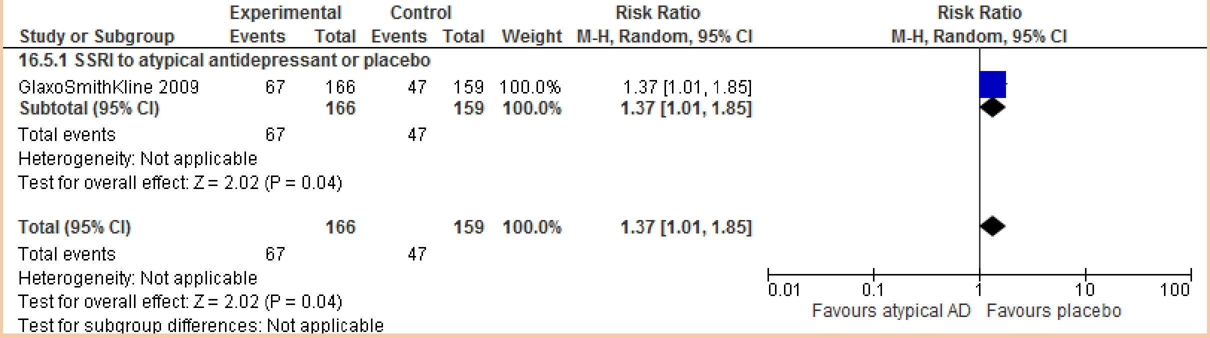
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
16.4.1 SSRI to atypical antidepressant or placebo								
GlaxoSmithKline 2009	-4.9	8.34	165	-5.1	8.02	157	100.0%	0.20 [-1.59, 1.99]
Subtotal (95% CI)			**165**			**157**	**100.0%**	**0.20 [-1.59, 1.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.83)								
Total (95% CI)			**165**			**157**	**100.0%**	**0.20 [-1.59, 1.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.83)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours atypical AD
Favours placebo

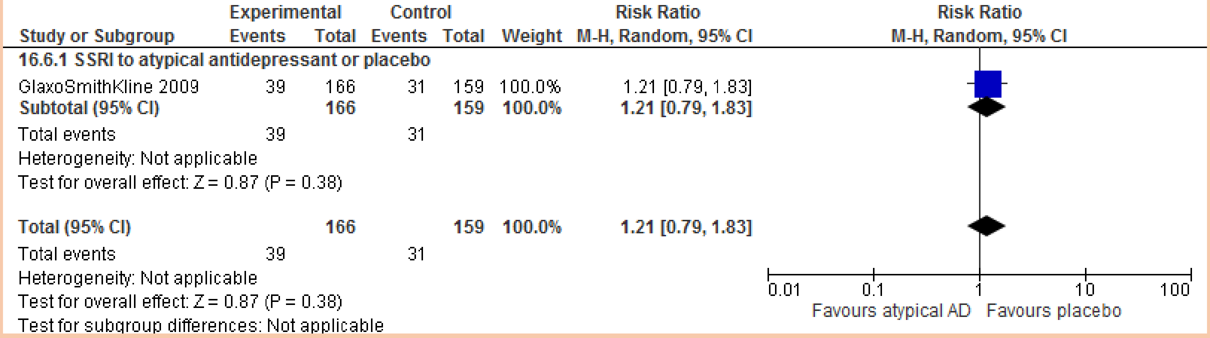
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
16.5.1 SSRI to atypical antidepressant or placebo						
GlaxoSmithKline 2009	67	166	47	159	100.0%	1.37 [1.01, 1.85]
Subtotal (95% CI)		**166**		**159**	**100.0%**	**1.37 [1.01, 1.85]**
Total events	67		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**166**		**159**	**100.0%**	**1.37 [1.01, 1.85]**
Total events	67		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours atypical AD
Favours placebo

Discontinuation due to adverse events

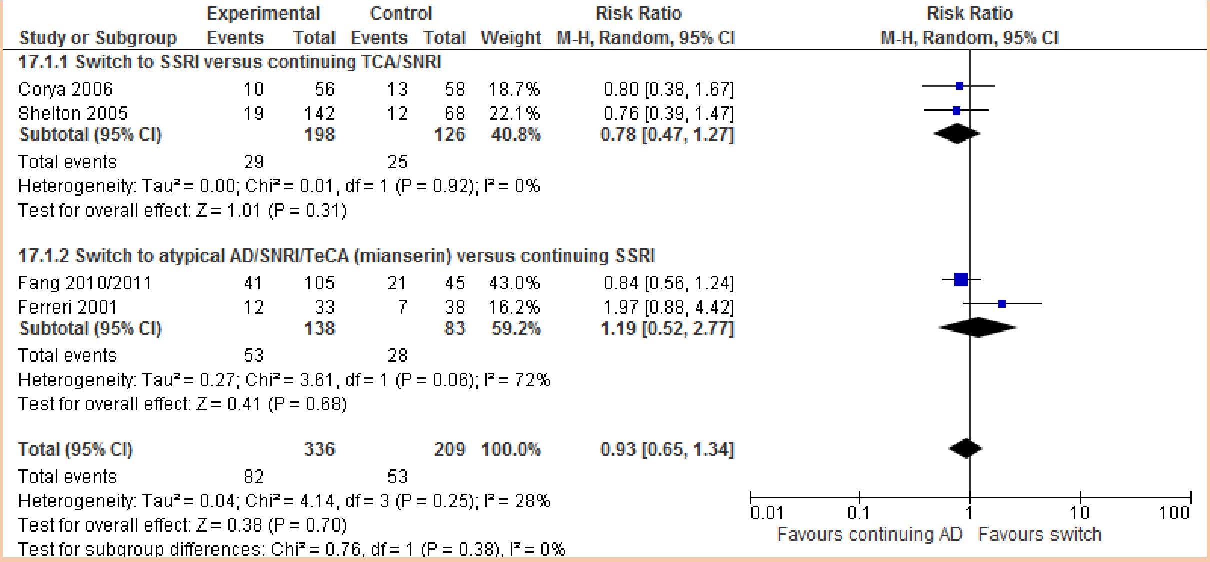


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
16.6.1 SSRI to atypical antidepressant or placebo						
GlaxoSmithKline 2009	39	166	31	159	100.0%	1.21 [0.79, 1.83]
Subtotal (95% CI)		**166**		**159**	**100.0%**	**1.21 [0.79, 1.83]**
Total events	39		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						
Total (95% CI)		**166**		**159**	**100.0%**	**1.21 [0.79, 1.83]**
Total events	39		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours atypical AD
Favours placebo

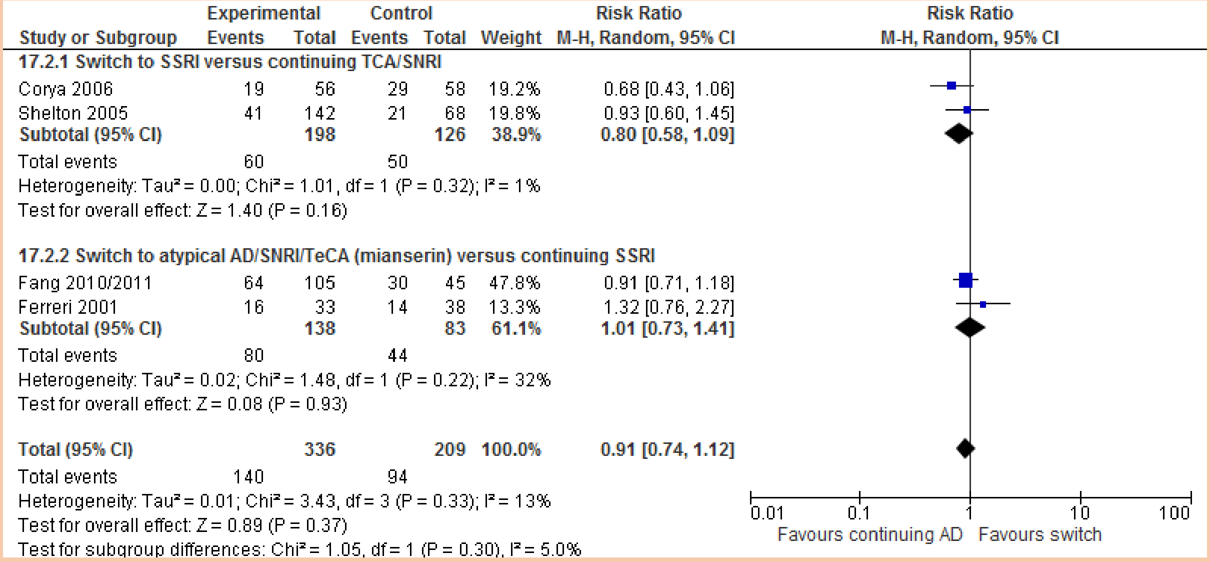
Switching to another antidepressant of a different class compared to continuing with the same antidepressant

Remission (≤8/10 on MADRS/≤7/8 on HAMD)



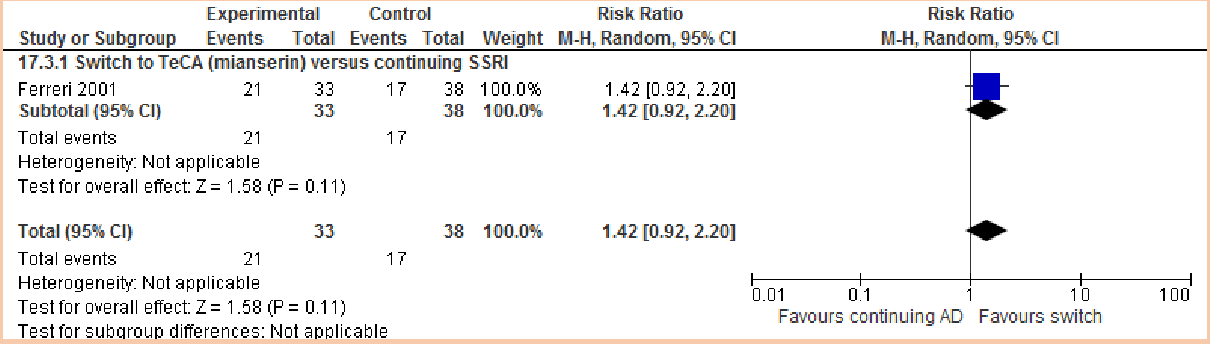
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.1.1 Switch to SSRI versus continuing TCA/SNRI						
Corya 2006	10	56	13	58	18.7%	0.80 [0.38, 1.67]
Shelton 2005	19	142	12	68	22.1%	0.76 [0.39, 1.47]
Subtotal (95% CI)		**198**		**126**	**40.8%**	**0.78 [0.47, 1.27]**
Total events	29		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
17.1.2 Switch to atypical AD/SNRI/TeCA (mianserin) versus continuing SSRI						
Fang 2010/2011	41	105	21	45	43.0%	0.84 [0.56, 1.24]
Ferreri 2001	12	33	7	38	16.2%	1.97 [0.88, 4.42]
Subtotal (95% CI)		**138**		**83**	**59.2%**	**1.19 [0.52, 2.77]**
Total events	53		28			
Heterogeneity: Tau² = 0.27; Chi² = 3.61, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**336**		**209**	**100.0%**	**0.93 [0.65, 1.34]**
Total events	82		53			
Heterogeneity: Tau² = 0.04; Chi² = 4.14, df = 3 (P = 0.25); I² = 28%						
Test for overall effect: Z = 0.38 (P = 0.70)						
Test for subgroup differences: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%						

Response (≥50% improvement on MADRS/HAMD)



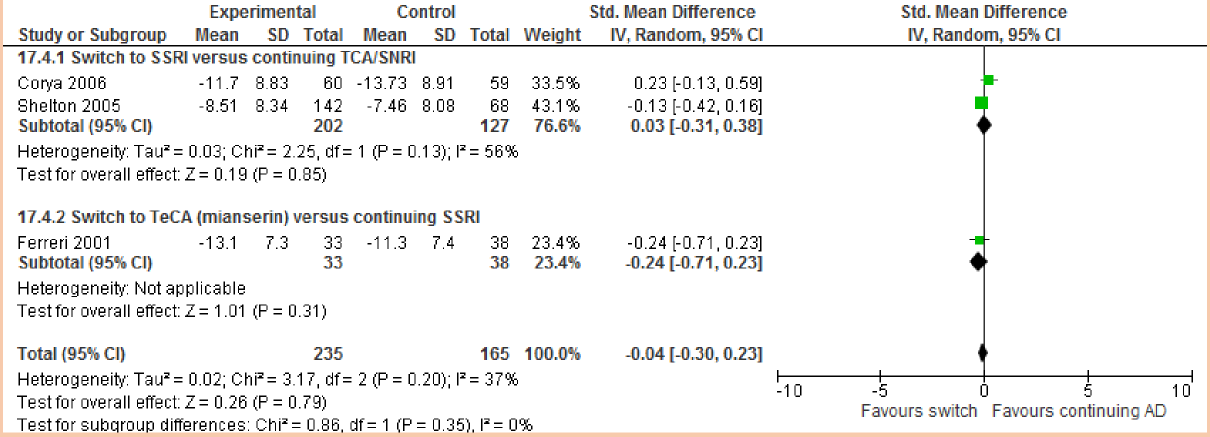
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.2.1 Switch to SSRI versus continuing TCA/SNRI						
Corya 2006	19	56	29	58	19.2%	0.68 [0.43, 1.06]
Shelton 2005	41	142	21	68	19.8%	0.93 [0.60, 1.45]
Subtotal (95% CI)		**198**		**126**	**38.9%**	**0.80 [0.58, 1.09]**
Total events	60		50			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.32); I² = 1%						
Test for overall effect: Z = 1.40 (P = 0.16)						
17.2.2 Switch to atypical AD/SNRI/TeCA (mianserin) versus continuing SSRI						
Fang 2010/2011	64	105	30	45	47.8%	0.91 [0.71, 1.18]
Ferreri 2001	16	33	14	38	13.3%	1.32 [0.76, 2.27]
Subtotal (95% CI)		**138**		**83**	**61.1%**	**1.01 [0.73, 1.41]**
Total events	80		44			
Heterogeneity: Tau² = 0.02; Chi² = 1.48, df = 1 (P = 0.22); I² = 32%						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)		**336**		**209**	**100.0%**	**0.91 [0.74, 1.12]**
Total events	140		94			
Heterogeneity: Tau² = 0.01; Chi² = 3.43, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.30), I² = 5.0%						

Response (much/very much improved on CGI-I)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.3.1 Switch to TeCA (mianserin) versus continuing SSRI						
Ferreri 2001	21	33	17	38	100.0%	1.42 [0.92, 2.20]
Subtotal (95% CI)		**33**		**38**	**100.0%**	**1.42 [0.92, 2.20]**
Total events	21		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**33**		**38**	**100.0%**	**1.42 [0.92, 2.20]**
Total events	21		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Not applicable						

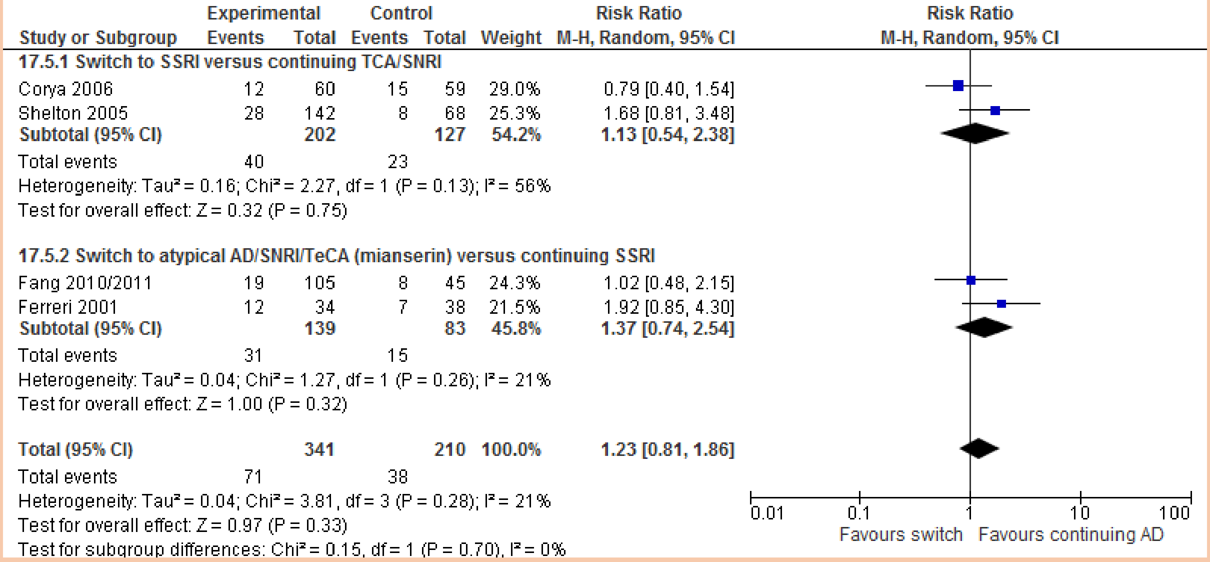
Depression symptomatology (MADRS/HAMD change score)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
17.4.1 Switch to SSRI versus continuing TCA/SNRI								
Corya 2006	-11.7	8.83	60	-13.73	8.91	59	33.5%	0.23 [-0.13, 0.59]
Shelton 2005	-8.51	8.34	142	-7.46	8.08	68	43.1%	-0.13 [-0.42, 0.16]
Subtotal (95% CI)			**202**			**127**	**76.6%**	**0.03 [-0.31, 0.38]**
Heterogeneity: Tau² = 0.03; Chi² = 2.25, df = 1 (P = 0.13); I² = 56%								
Test for overall effect: Z = 0.19 (P = 0.85)								
17.4.2 Switch to TeCA (mianserin) versus continuing SSRI								
Ferreri 2001	-13.1	7.3	33	-11.3	7.4	38	23.4%	-0.24 [-0.71, 0.23]
Subtotal (95% CI)			**33**			**38**	**23.4%**	**-0.24 [-0.71, 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								
Total (95% CI)			**235**			**165**	**100.0%**	**-0.04 [-0.30, 0.23]**

Heterogeneity: Tau² = 0.02; Chi² = 3.17, df = 2 (P = 0.20); I² = 37%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%

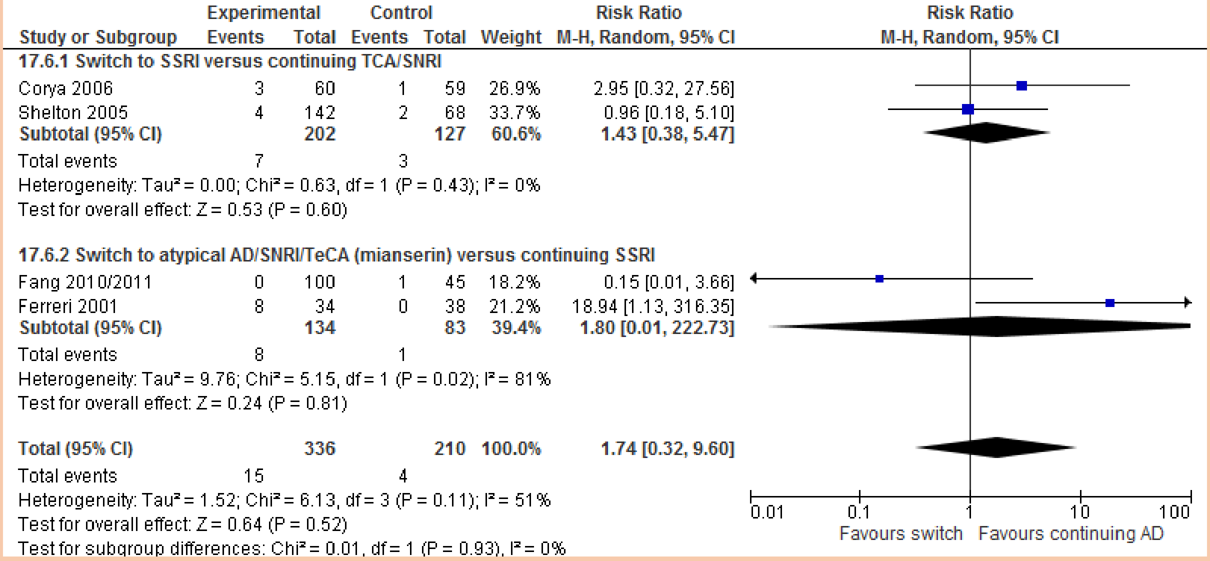
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.5.1 Switch to SSRI versus continuing TCA/SNRI						
Corya 2006	12	60	15	59	29.0%	0.79 [0.40, 1.54]
Shelton 2005	28	142	8	68	25.3%	1.68 [0.81, 3.48]
Subtotal (95% CI)		**202**		**127**	**54.2%**	**1.13 [0.54, 2.38]**
Total events	40		23			
Heterogeneity: Tau² = 0.16; Chi² = 2.27, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 0.32 (P = 0.75)						
17.5.2 Switch to atypical AD/SNRI/TeCA (mianserin) versus continuing SSRI						
Fang 2010/2011	19	105	8	45	24.3%	1.02 [0.48, 2.15]
Ferreri 2001	12	34	7	38	21.5%	1.92 [0.85, 4.30]
Subtotal (95% CI)		**139**		**83**	**45.8%**	**1.37 [0.74, 2.54]**
Total events	31		15			
Heterogeneity: Tau² = 0.04; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**341**		**210**	**100.0%**	**1.23 [0.81, 1.86]**
Total events	71		38			

Heterogeneity: Tau² = 0.04; Chi² = 3.81, df = 3 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%

Discontinuation due to adverse events

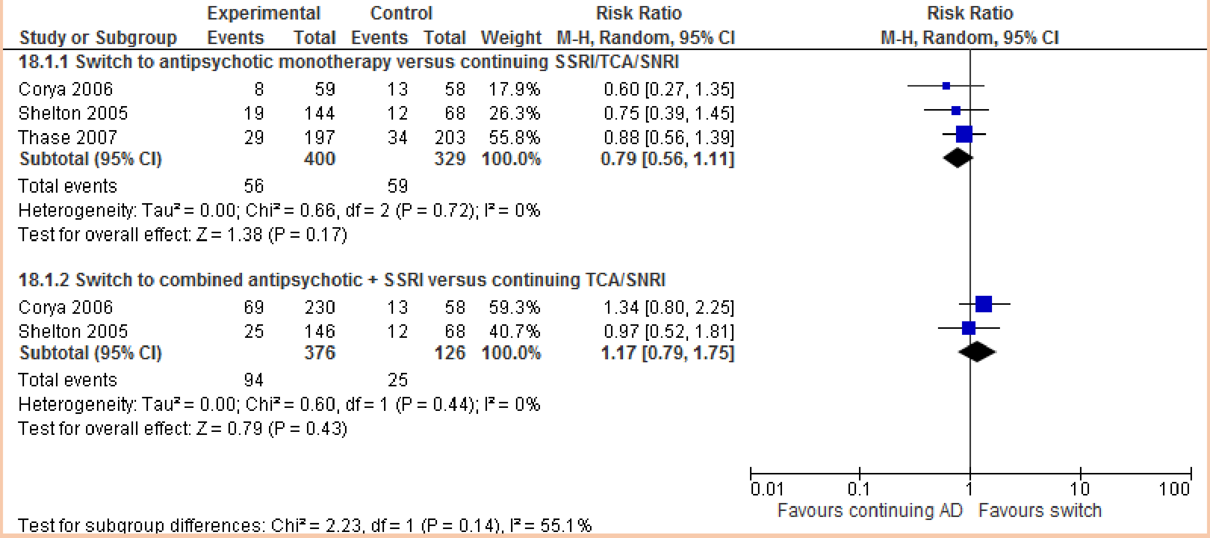


Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.6.1 Switch to SSRI versus continuing TCA/SNRI						
Corya 2006	3	60	1	59	26.9%	2.95 [0.32, 27.56]
Shelton 2005	4	142	2	68	33.7%	0.96 [0.18, 5.10]
Subtotal (95% CI)		**202**		**127**	**60.6%**	**1.43 [0.38, 5.47]**
Total events	7		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
17.6.2 Switch to atypical AD/SNRI/TeCA (mianserin) versus continuing SSRI						
Fang 2010/2011	0	100	1	45	18.2%	0.15 [0.01, 3.66]
Ferreri 2001	8	34	0	38	21.2%	18.94 [1.13, 316.35]
Subtotal (95% CI)		**134**		**83**	**39.4%**	**1.80 [0.01, 222.73]**
Total events	8		1			
Heterogeneity: Tau² = 9.76; Chi² = 5.15, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**336**		**210**	**100.0%**	**1.74 [0.32, 9.60]**
Total events	15		4			

Heterogeneity: Tau² = 1.52; Chi² = 6.13, df = 3 (P = 0.11); I² = 51%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Switching to a non-antidepressant agent compared to continuing with the antidepressant

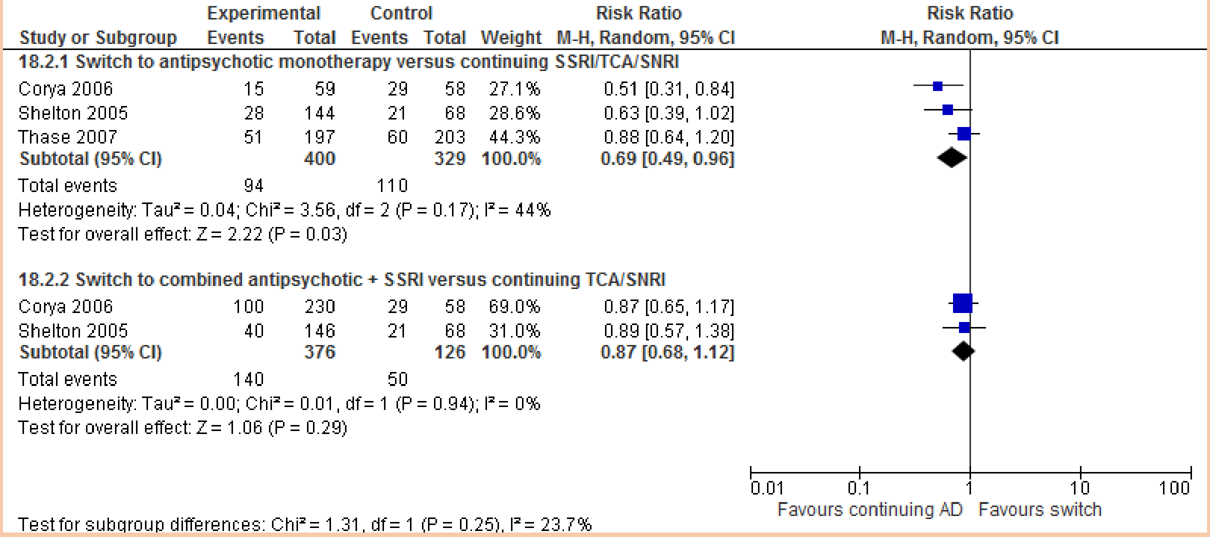
Remission (≤8/10 on MADRS/≤7/8 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.1.1 Switch to antipsychotic monotherapy versus continuing SSRI/TCA/SNRI						
Corya 2006	8	59	13	58	17.9%	0.60 [0.27, 1.35]
Shelton 2005	19	144	12	68	26.3%	0.75 [0.39, 1.45]
Thase 2007	29	197	34	203	55.8%	0.88 [0.56, 1.39]
Subtotal (95% CI)		**400**		**329**	**100.0%**	**0.79 [0.56, 1.11]**
Total events	56		59			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
18.1.2 Switch to combined antipsychotic + SSRI versus continuing TCA/SNRI						
Corya 2006	69	230	13	58	59.3%	1.34 [0.80, 2.25]
Shelton 2005	25	146	12	68	40.7%	0.97 [0.52, 1.81]
Subtotal (95% CI)		**376**		**126**	**100.0%**	**1.17 [0.79, 1.75]**
Total events	94		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						

Test for subgroup differences: Chi² = 2.23, df = 1 (P = 0.14), I² = 55.1%

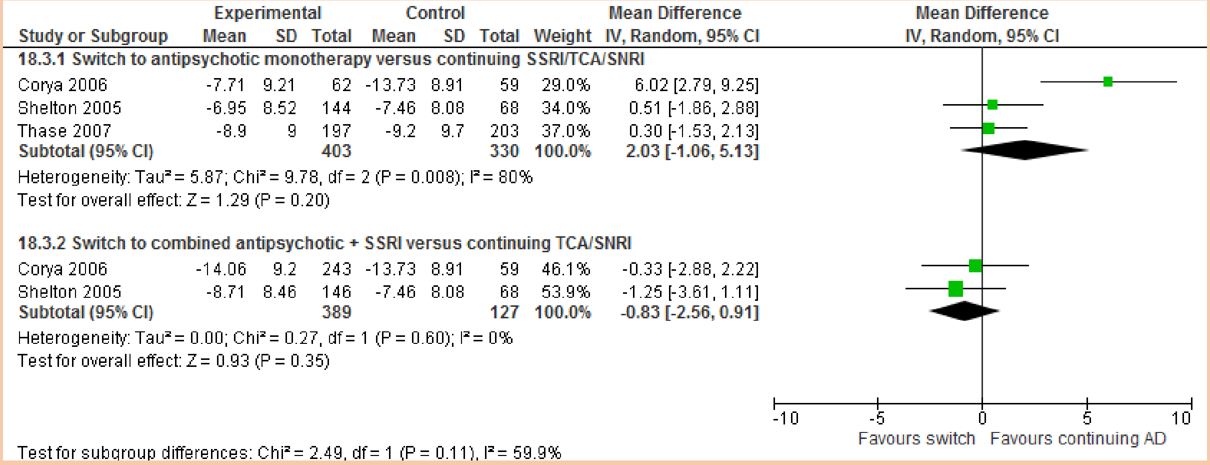
Response (≥50% improvement on MADRS)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.2.1 Switch to antipsychotic monotherapy versus continuing SSRI/TCA/SNRI						
Corya 2006	15	59	29	58	27.1%	0.51 [0.31, 0.84]
Shelton 2005	28	144	21	68	28.6%	0.63 [0.39, 1.02]
Thase 2007	51	197	60	203	44.3%	0.88 [0.64, 1.20]
Subtotal (95% CI)		**400**		**329**	**100.0%**	**0.69 [0.49, 0.96]**
Total events	94		110			
Heterogeneity: Tau² = 0.04; Chi² = 3.56, df = 2 (P = 0.17); I² = 44%						
Test for overall effect: Z = 2.22 (P = 0.03)						
18.2.2 Switch to combined antipsychotic + SSRI versus continuing TCA/SNRI						
Corya 2006	100	230	29	58	69.0%	0.87 [0.65, 1.17]
Shelton 2005	40	146	21	68	31.0%	0.89 [0.57, 1.38]
Subtotal (95% CI)		**376**		**126**	**100.0%**	**0.87 [0.68, 1.12]**
Total events	140		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						

Test for subgroup differences: Chi² = 1.31, df = 1 (P = 0.25), I² = 23.7%

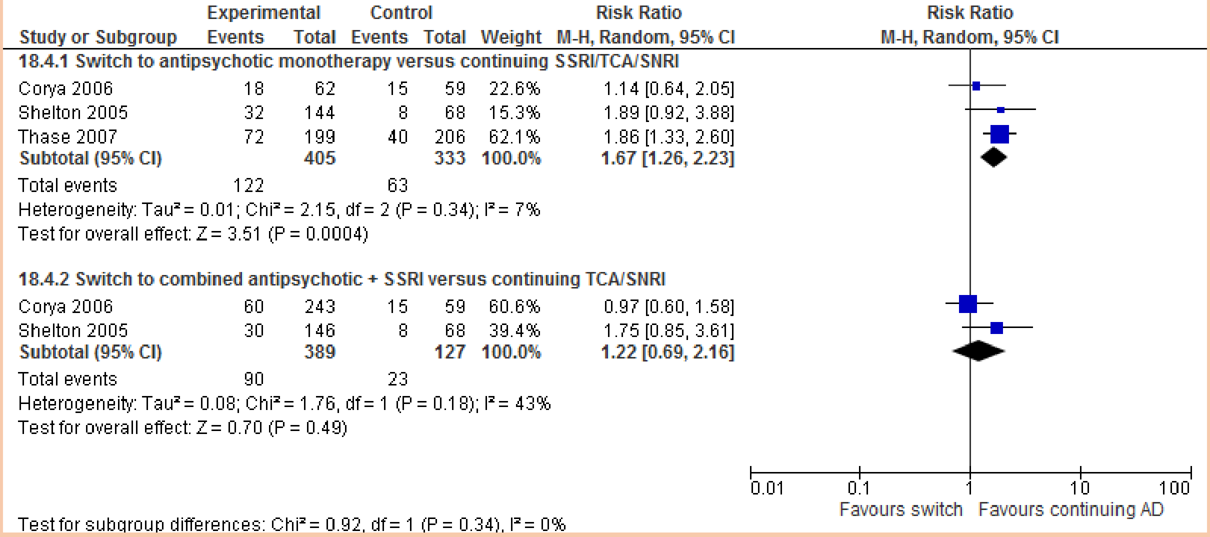
Depression symptomatology (MADRS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
18.3.1 Switch to antipsychotic monotherapy versus continuing SSRI/TCA/SNRI								
Corya 2006	-7.71	9.21	62	-13.73	8.91	59	29.0%	6.02 [2.79, 9.25]
Shelton 2005	-6.95	8.52	144	-7.46	8.08	68	34.0%	0.51 [-1.86, 2.88]
Thase 2007	-8.9	9	197	-9.2	9.7	203	37.0%	0.30 [-1.53, 2.13]
Subtotal (95% CI)			**403**			**330**	**100.0%**	**2.03 [-1.06, 5.13]**
Heterogeneity: Tau^2 = 5.87; Chi^2 = 9.78, df = 2 (P = 0.008); I^2 = 80%								
Test for overall effect: Z = 1.29 (P = 0.20)								
18.3.2 Switch to combined antipsychotic + SSRI versus continuing TCA/SNRI								
Corya 2006	-14.06	9.2	243	-13.73	8.91	59	46.1%	-0.33 [-2.88, 2.22]
Shelton 2005	-8.71	8.46	146	-7.46	8.08	68	53.9%	-1.25 [-3.61, 1.11]
Subtotal (95% CI)			**389**			**127**	**100.0%**	**-0.83 [-2.56, 0.91]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.27, df = 1 (P = 0.60); I^2 = 0%								
Test for overall effect: Z = 0.93 (P = 0.35)								

Test for subgroup differences: Chi^2 = 2.49, df = 1 (P = 0.11), I^2 = 59.9%

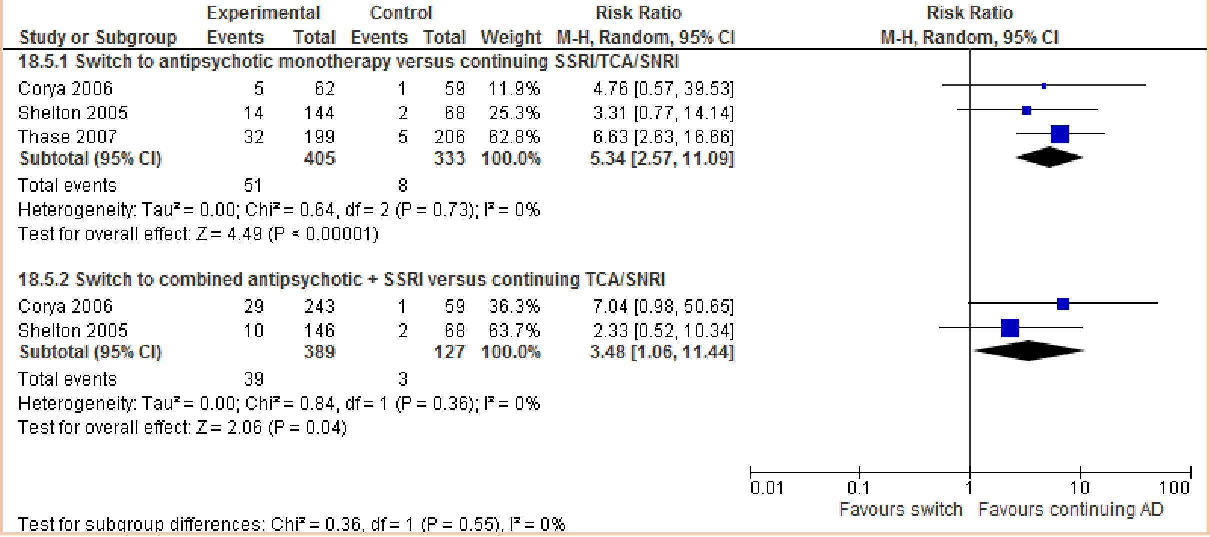
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.4.1 Switch to antipsychotic monotherapy versus continuing SSRI/TCA/SNRI						
Corya 2006	18	62	15	59	22.6%	1.14 [0.64, 2.05]
Shelton 2005	32	144	8	68	15.3%	1.89 [0.92, 3.88]
Thase 2007	72	199	40	206	62.1%	1.86 [1.33, 2.60]
Subtotal (95% CI)		**405**		**333**	**100.0%**	**1.67 [1.26, 2.23]**
Total events	122		63			
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.15, df = 2 (P = 0.34); I^2 = 7%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
18.4.2 Switch to combined antipsychotic + SSRI versus continuing TCA/SNRI						
Corya 2006	60	243	15	59	60.6%	0.97 [0.60, 1.58]
Shelton 2005	30	146	8	68	39.4%	1.75 [0.85, 3.61]
Subtotal (95% CI)		**389**		**127**	**100.0%**	**1.22 [0.69, 2.16]**
Total events	90		23			
Heterogeneity: Tau^2 = 0.08; Chi^2 = 1.76, df = 1 (P = 0.18); I^2 = 43%						
Test for overall effect: Z = 0.70 (P = 0.49)						

Test for subgroup differences: Chi^2 = 0.92, df = 1 (P = 0.34), I^2 = 0%

Discontinuation due to adverse events

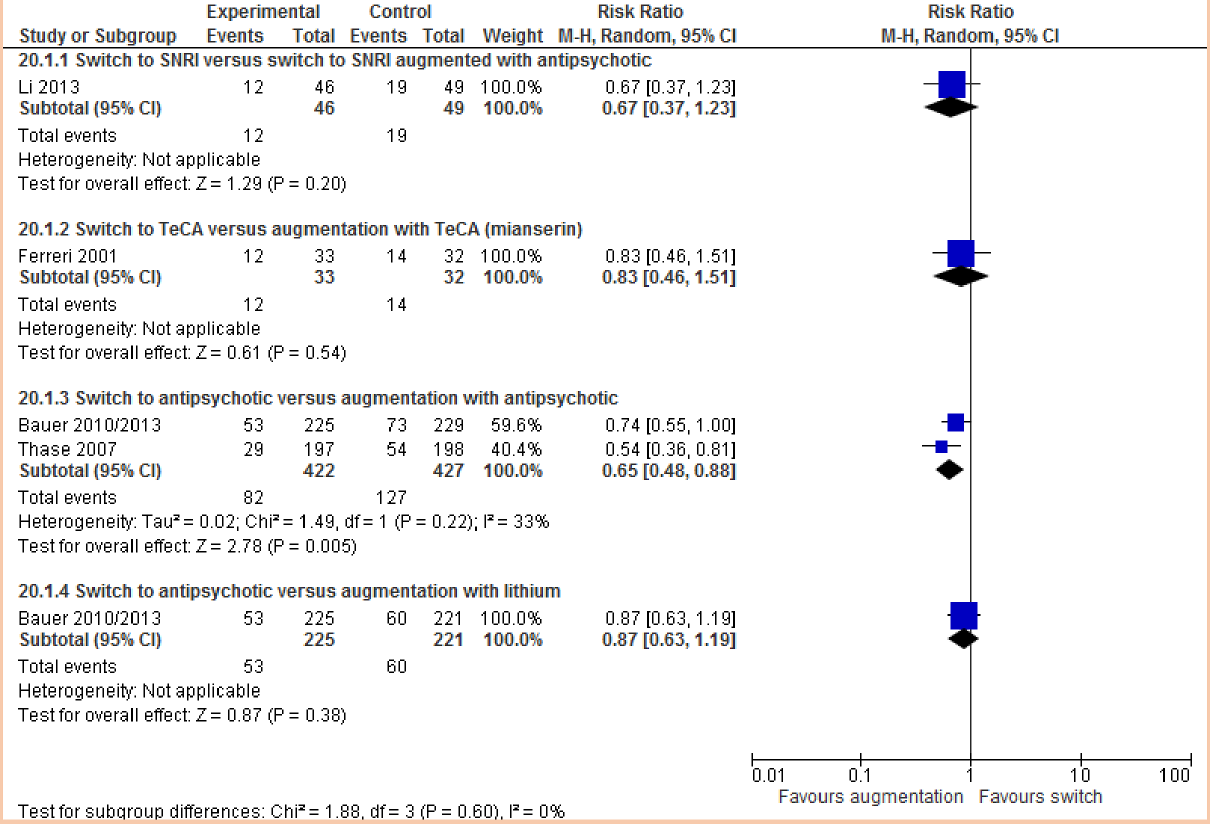


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.5.1 Switch to antipsychotic monotherapy versus continuing SSRI/TCA/SNRI						
Corya 2006	5	62	1	59	11.9%	4.76 [0.57, 39.53]
Shelton 2005	14	144	2	68	25.3%	3.31 [0.77, 14.14]
Thase 2007	32	199	5	206	62.8%	6.63 [2.63, 16.66]
Subtotal (95% CI)		**405**		**333**	**100.0%**	**5.34 [2.57, 11.09]**
Total events	51		8			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.64, df = 2 (P = 0.73); I^2 = 0%						
Test for overall effect: Z = 4.49 (P < 0.00001)						
18.5.2 Switch to combined antipsychotic + SSRI versus continuing TCA/SNRI						
Corya 2006	29	243	1	59	36.3%	7.04 [0.98, 50.65]
Shelton 2005	10	146	2	68	63.7%	2.33 [0.52, 10.34]
Subtotal (95% CI)		**389**		**127**	**100.0%**	**3.48 [1.06, 11.44]**
Total events	39		3			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.84, df = 1 (P = 0.36); I^2 = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						

Test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 = 0%

Switching to another antidepressant or non-antidepressant agent compared to augmenting with another antidepressant or non-antidepressant agent

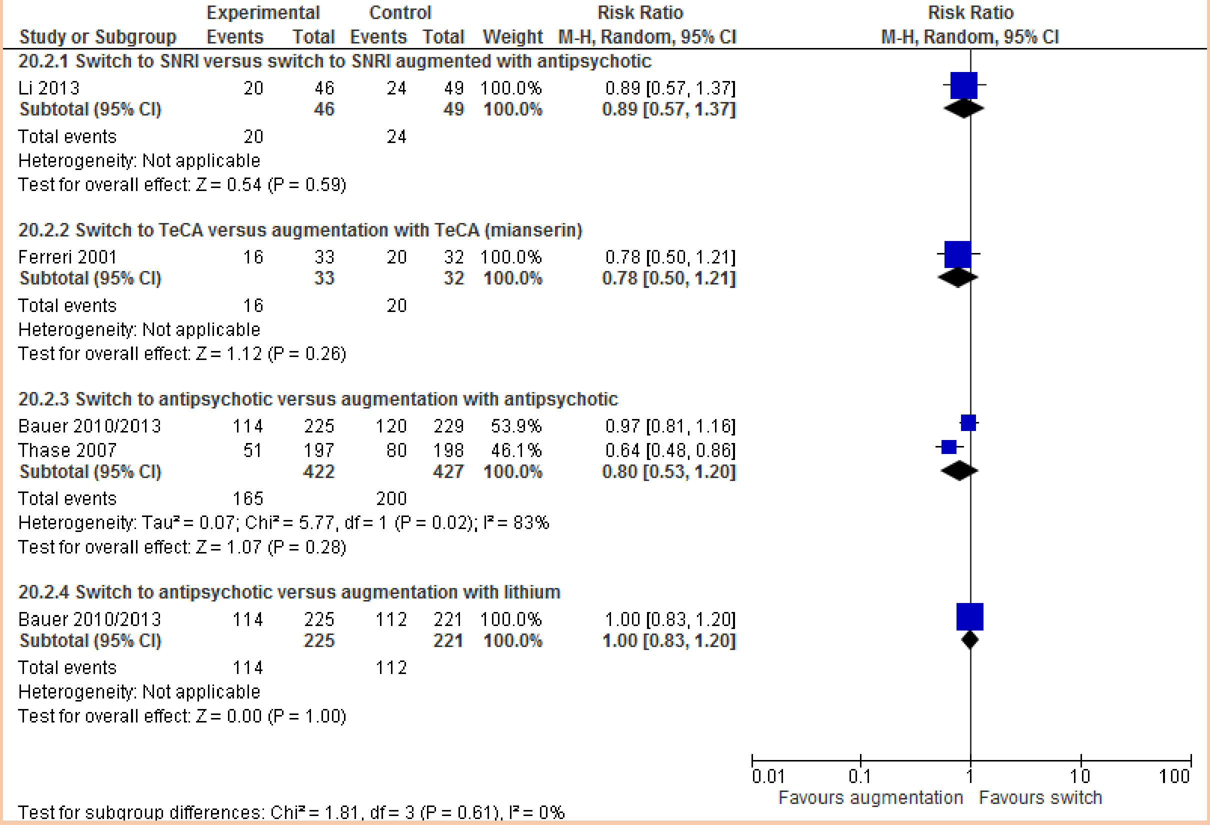
Remission (≤10 on MADRS/≤8 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
20.1.1 Switch to SNRI versus switch to SNRI augmented with antipsychotic						
Li 2013	12	46	19	49	100.0%	0.67 [0.37, 1.23]
Subtotal (95% CI)		**46**		**49**	**100.0%**	**0.67 [0.37, 1.23]**
Total events	12		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
20.1.2 Switch to TeCA versus augmentation with TeCA (mianserin)						
Ferreri 2001	12	33	14	32	100.0%	0.83 [0.46, 1.51]
Subtotal (95% CI)		**33**		**32**	**100.0%**	**0.83 [0.46, 1.51]**
Total events	12		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
20.1.3 Switch to antipsychotic versus augmentation with antipsychotic						
Bauer 2010/2013	53	225	73	229	59.6%	0.74 [0.55, 1.00]
Thase 2007	29	197	54	198	40.4%	0.54 [0.36, 0.81]
Subtotal (95% CI)		**422**		**427**	**100.0%**	**0.65 [0.48, 0.88]**
Total events	82		127			
Heterogeneity: Tau² = 0.02; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 2.78 (P = 0.005)						
20.1.4 Switch to antipsychotic versus augmentation with lithium						
Bauer 2010/2013	53	225	60	221	100.0%	0.87 [0.63, 1.19]
Subtotal (95% CI)		**225**		**221**	**100.0%**	**0.87 [0.63, 1.19]**
Total events	53		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						

Test for subgroup differences: Chi² = 1.88, df = 3 (P = 0.60), I² = 0%

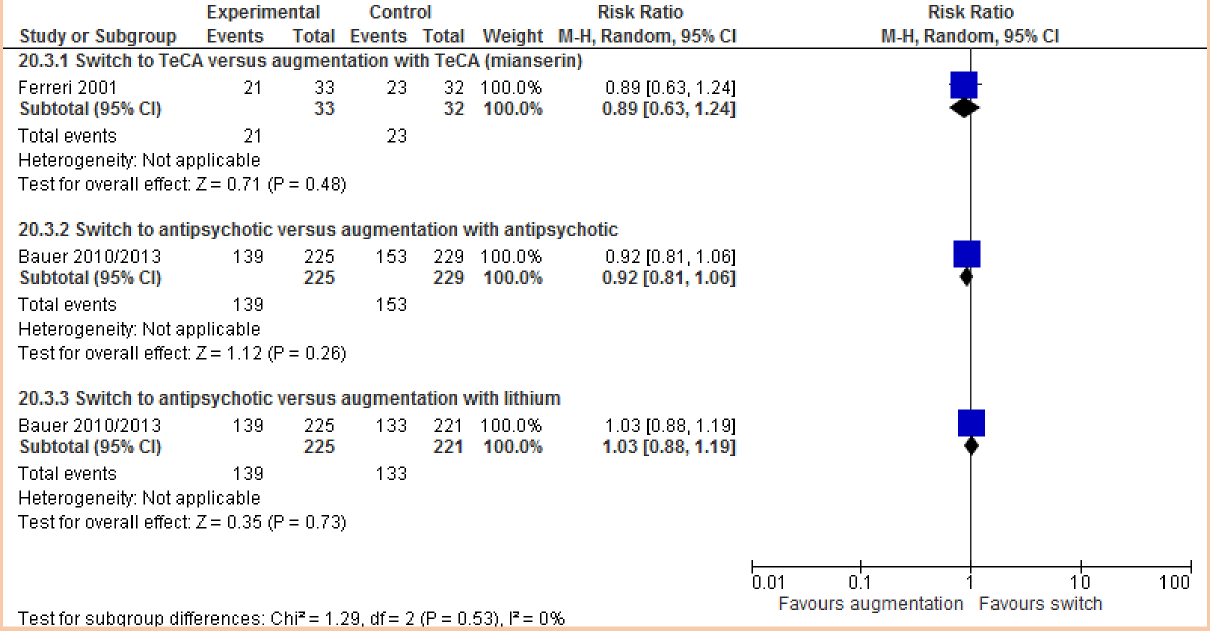
Response (≥50% improvement on MADRS/HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
20.2.1 Switch to SNRI versus switch to SNRI augmented with antipsychotic						
Li 2013	20	46	24	49	100.0%	0.89 [0.57, 1.37]
Subtotal (95% CI)		**46**		**49**	**100.0%**	**0.89 [0.57, 1.37]**
Total events	20		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
20.2.2 Switch to TeCA versus augmentation with TeCA (mianserin)						
Ferreri 2001	16	33	20	32	100.0%	0.78 [0.50, 1.21]
Subtotal (95% CI)		**33**		**32**	**100.0%**	**0.78 [0.50, 1.21]**
Total events	16		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
20.2.3 Switch to antipsychotic versus augmentation with antipsychotic						
Bauer 2010/2013	114	225	120	229	53.9%	0.97 [0.81, 1.16]
Thase 2007	51	197	80	198	46.1%	0.64 [0.48, 0.86]
Subtotal (95% CI)		**422**		**427**	**100.0%**	**0.80 [0.53, 1.20]**
Total events	165		200			
Heterogeneity: Tau² = 0.07; Chi² = 5.77, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 1.07 (P = 0.28)						
20.2.4 Switch to antipsychotic versus augmentation with lithium						
Bauer 2010/2013	114	225	112	221	100.0%	1.00 [0.83, 1.20]
Subtotal (95% CI)		**225**		**221**	**100.0%**	**1.00 [0.83, 1.20]**
Total events	114		112			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						

Test for subgroup differences: Chi² = 1.81, df = 3 (P = 0.61), I² = 0%

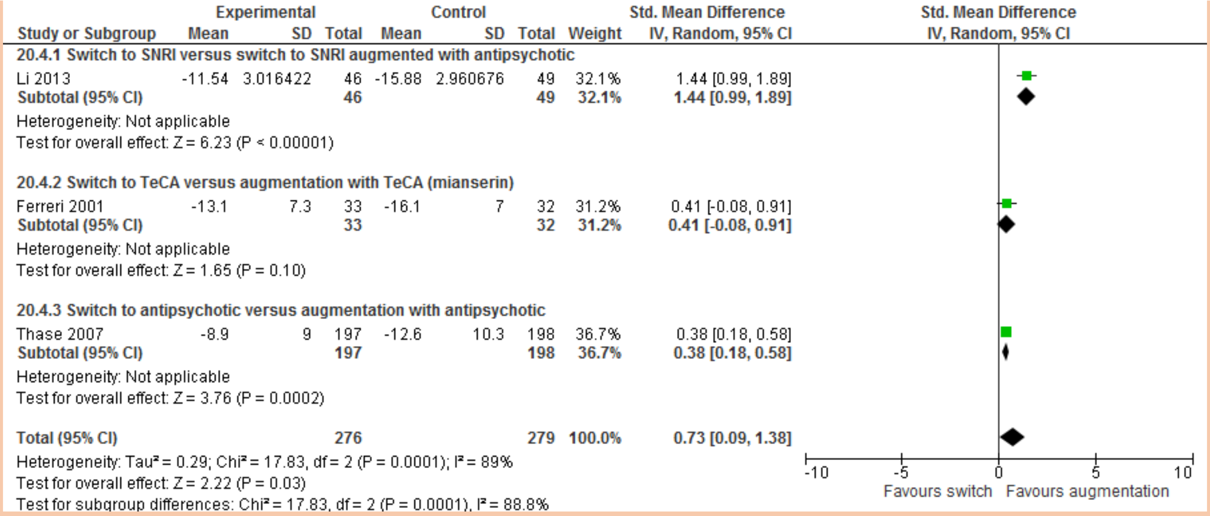
Response (much/very much improved on CGI-I)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
20.3.1 Switch to TeCA versus augmentation with TeCA (mianserin)						
Ferreri 2001	21	33	23	32	100.0%	0.89 [0.63, 1.24]
Subtotal (95% CI)		**33**		**32**	**100.0%**	**0.89 [0.63, 1.24]**
Total events	21		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
20.3.2 Switch to antipsychotic versus augmentation with antipsychotic						
Bauer 2010/2013	139	225	153	229	100.0%	0.92 [0.81, 1.06]
Subtotal (95% CI)		**225**		**229**	**100.0%**	**0.92 [0.81, 1.06]**
Total events	139		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
20.3.3 Switch to antipsychotic versus augmentation with lithium						
Bauer 2010/2013	139	225	133	221	100.0%	1.03 [0.88, 1.19]
Subtotal (95% CI)		**225**		**221**	**100.0%**	**1.03 [0.88, 1.19]**
Total events	139		133			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						

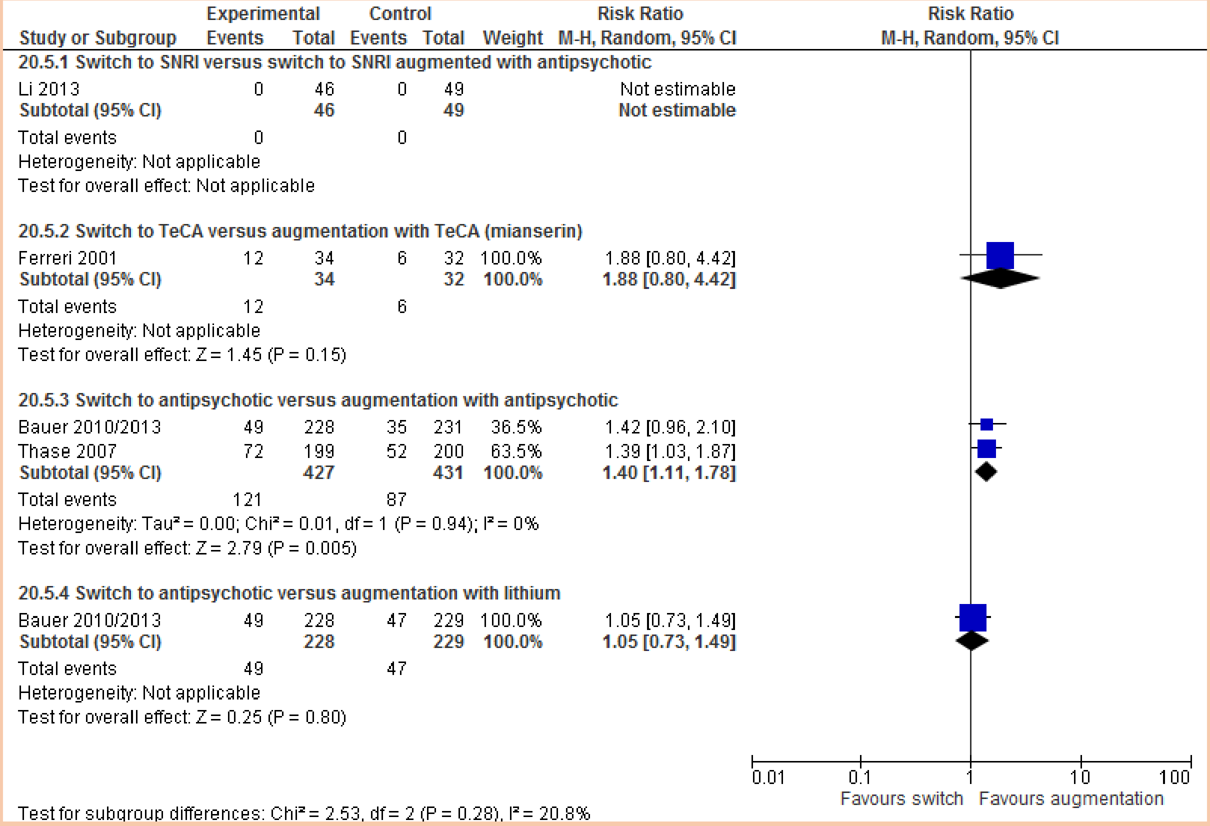
Test for subgroup differences: Chi² = 1.29, df = 2 (P = 0.53), I² = 0%

Depression symptomatology (MADRS/HAMD change score)



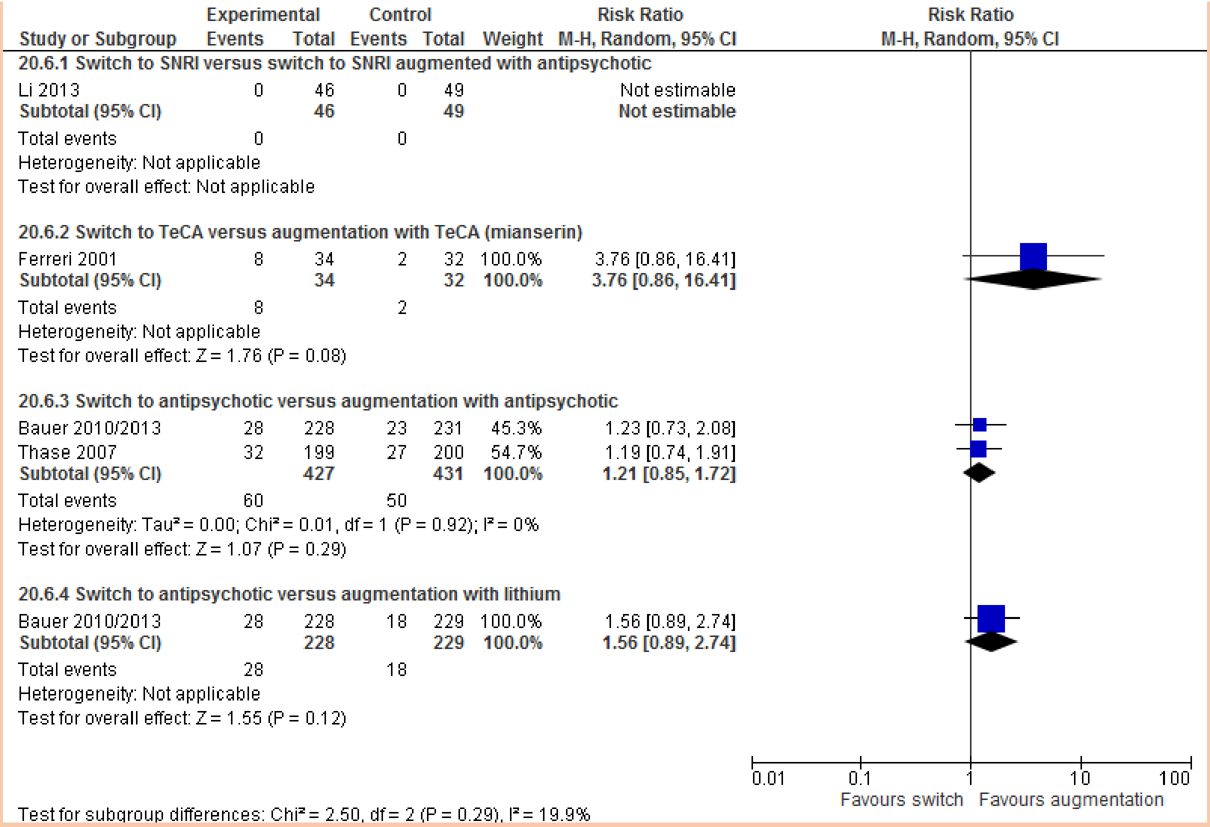
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
20.4.1 Switch to SNRI versus switch to SNRI augmented with antipsychotic								
Li 2013	-11.54	3.016422	46	-15.88	2.960676	49	32.1%	1.44 [0.99, 1.89]
Subtotal (95% CI)			**46**			**49**	**32.1%**	**1.44 [0.99, 1.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.23 (P < 0.00001)								
20.4.2 Switch to TeCA versus augmentation with TeCA (mianserin)								
Ferreri 2001	-13.1	7.3	33	-16.1	7	32	31.2%	0.41 [-0.08, 0.91]
Subtotal (95% CI)			**33**			**32**	**31.2%**	**0.41 [-0.08, 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
20.4.3 Switch to antipsychotic versus augmentation with antipsychotic								
Thase 2007	-8.9	9	197	-12.6	10.3	198	36.7%	0.38 [0.18, 0.58]
Subtotal (95% CI)			**197**			**198**	**36.7%**	**0.38 [0.18, 0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.76 (P = 0.0002)								
Total (95% CI)			**276**			**279**	**100.0%**	**0.73 [0.09, 1.38]**
Heterogeneity: Tau^2 = 0.29; Chi^2 = 17.83, df = 2 (P = 0.0001); I^2 = 89%								
Test for overall effect: Z = 2.22 (P = 0.03)								
Test for subgroup differences: Chi^2 = 17.83, df = 2 (P = 0.0001), I^2 = 88.8%								

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
20.5.1 Switch to SNRI versus switch to SNRI augmented with antipsychotic						
Li 2013	0	46	0	49		Not estimable
Subtotal (95% CI)		**46**		**49**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
20.5.2 Switch to TeCA versus augmentation with TeCA (mianserin)						
Ferreri 2001	12	34	6	32	100.0%	1.88 [0.80, 4.42]
Subtotal (95% CI)		**34**		**32**	**100.0%**	**1.88 [0.80, 4.42]**
Total events	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
20.5.3 Switch to antipsychotic versus augmentation with antipsychotic						
Bauer 2010/2013	49	228	35	231	36.5%	1.42 [0.96, 2.10]
Thase 2007	72	199	52	200	63.5%	1.39 [1.03, 1.87]
Subtotal (95% CI)		**427**		**431**	**100.0%**	**1.40 [1.11, 1.78]**
Total events	121		87			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.01, df = 1 (P = 0.94); I^2 = 0%						
Test for overall effect: Z = 2.79 (P = 0.005)						
20.5.4 Switch to antipsychotic versus augmentation with lithium						
Bauer 2010/2013	49	228	47	229	100.0%	1.05 [0.73, 1.49]
Subtotal (95% CI)		**228**		**229**	**100.0%**	**1.05 [0.73, 1.49]**
Total events	49		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: Chi^2 = 2.53, df = 2 (P = 0.28), I^2 = 20.8%						

Discontinuation due to adverse events

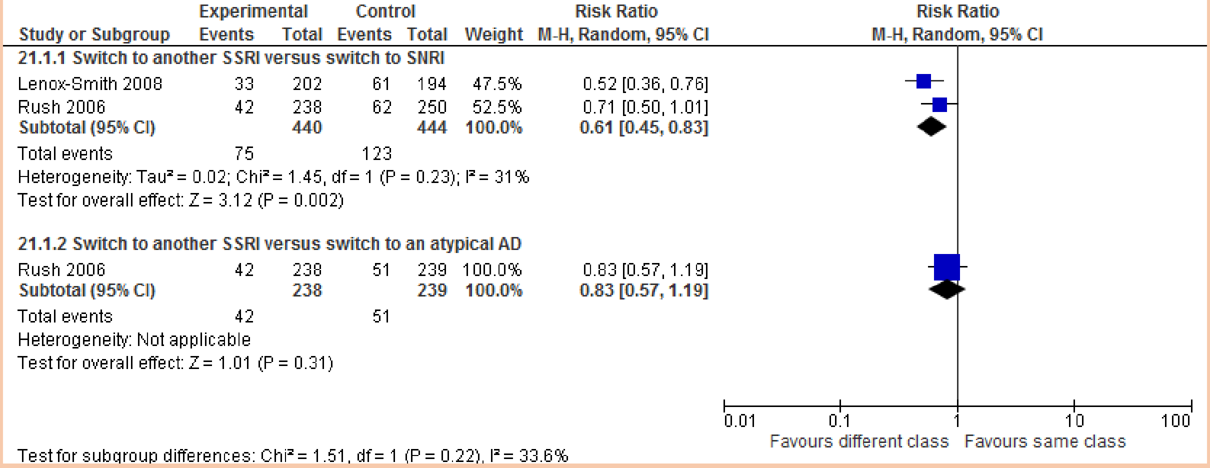


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
20.6.1 Switch to SNRI versus switch to SNRI augmented with antipsychotic						
Li 2013	0	46	0	49		Not estimable
Subtotal (95% CI)		**46**		**49**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
20.6.2 Switch to TeCA versus augmentation with TeCA (mianserin)						
Ferreri 2001	8	34	2	32	100.0%	3.76 [0.86, 16.41]
Subtotal (95% CI)		**34**		**32**	**100.0%**	**3.76 [0.86, 16.41]**
Total events	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
20.6.3 Switch to antipsychotic versus augmentation with antipsychotic						
Bauer 2010/2013	28	228	23	231	45.3%	1.23 [0.73, 2.08]
Thase 2007	32	199	27	200	54.7%	1.19 [0.74, 1.91]
Subtotal (95% CI)		**427**		**431**	**100.0%**	**1.21 [0.85, 1.72]**
Total events	60		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						
20.6.4 Switch to antipsychotic versus augmentation with lithium						
Bauer 2010/2013	28	228	18	229	100.0%	1.56 [0.89, 2.74]
Subtotal (95% CI)		**228**		**229**	**100.0%**	**1.56 [0.89, 2.74]**
Total events	28		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						

Test for subgroup differences: Chi² = 2.50, df = 2 (P = 0.29), I² = 19.9%

Switching to another antidepressant of the same class compared to switching to another antidepressant of a different class

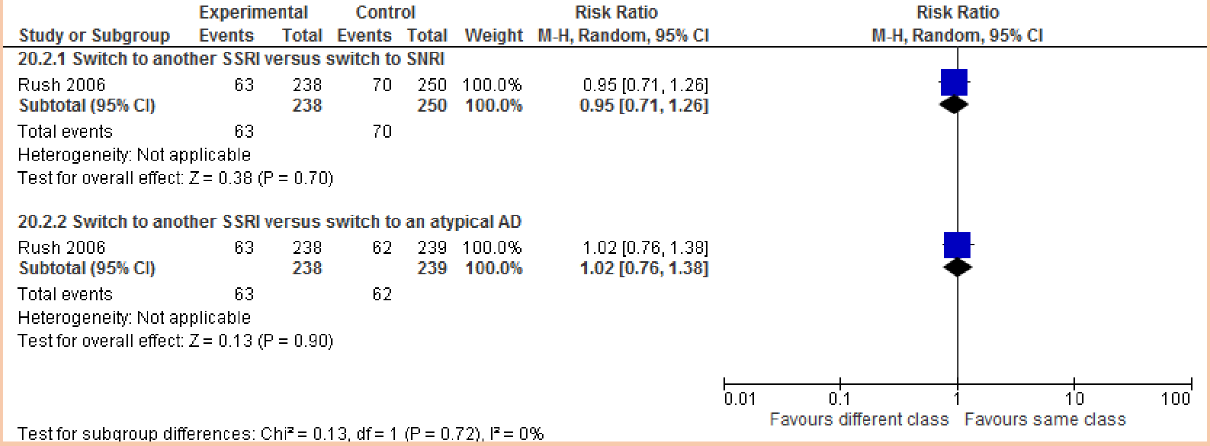
Remission (≤8 on MADRS/≤4/7/9 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 Switch to another SSRI versus switch to SNRI						
Lenox-Smith 2008	33	202	61	194	47.5%	0.52 [0.36, 0.76]
Rush 2006	42	238	62	250	52.5%	0.71 [0.50, 1.01]
Subtotal (95% CI)		**440**		**444**	**100.0%**	**0.61 [0.45, 0.83]**
Total events	75		123			
Heterogeneity: Tau² = 0.02; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 3.12 (P = 0.002)						
21.1.2 Switch to another SSRI versus switch to an atypical AD						
Rush 2006	42	238	51	239	100.0%	0.83 [0.57, 1.19]
Subtotal (95% CI)		**238**		**239**	**100.0%**	**0.83 [0.57, 1.19]**
Total events	42		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						

Test for subgroup differences: Chi² = 1.51, df = 1 (P = 0.22), I² = 33.6%

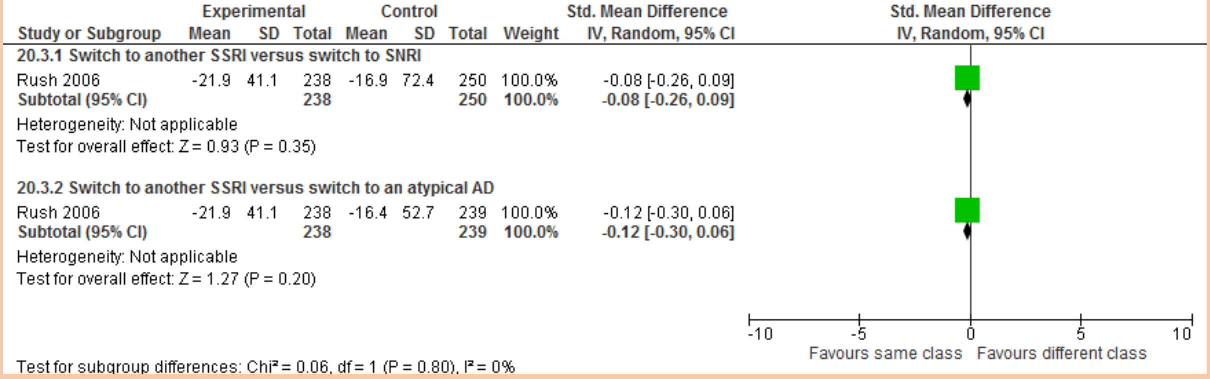
Response (≥50% improvement on MADRS/HAMD/QIDS)



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
20.2.1 Switch to another SSRI versus switch to SNRI						
Rush 2006	63	238	70	250	100.0%	0.95 [0.71, 1.26]
Subtotal (95% CI)		**238**		**250**	**100.0%**	**0.95 [0.71, 1.26]**
Total events	63		70			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
20.2.2 Switch to another SSRI versus switch to an atypical AD						
Rush 2006	63	238	62	239	100.0%	1.02 [0.76, 1.38]
Subtotal (95% CI)		**238**		**239**	**100.0%**	**1.02 [0.76, 1.38]**
Total events	63		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						

Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

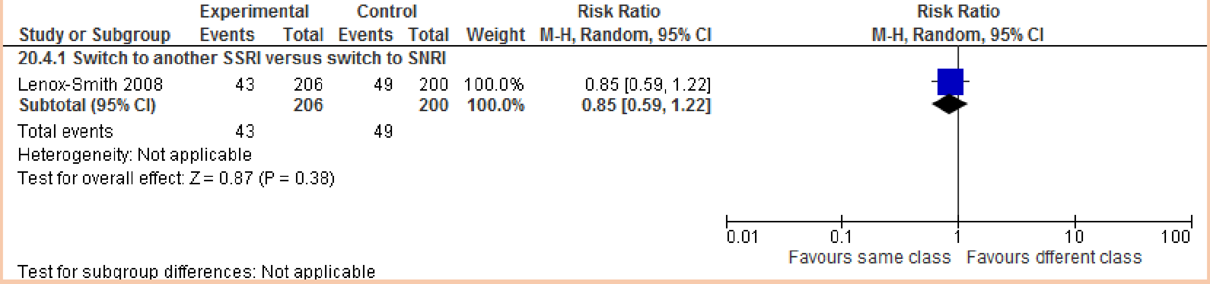
Depression symptomatology (MADRS/HAMD/QIDS change score)



	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
20.3.1 Switch to another SSRI versus switch to SNRI								
Rush 2006	-21.9	41.1	238	-16.9	72.4	250	100.0%	-0.08 [-0.26, 0.09]
Subtotal (95% CI)			**238**			**250**	**100.0%**	**-0.08 [-0.26, 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
20.3.2 Switch to another SSRI versus switch to an atypical AD								
Rush 2006	-21.9	41.1	238	-16.4	52.7	239	100.0%	-0.12 [-0.30, 0.06]
Subtotal (95% CI)			**238**			**239**	**100.0%**	**-0.12 [-0.30, 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								

Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%

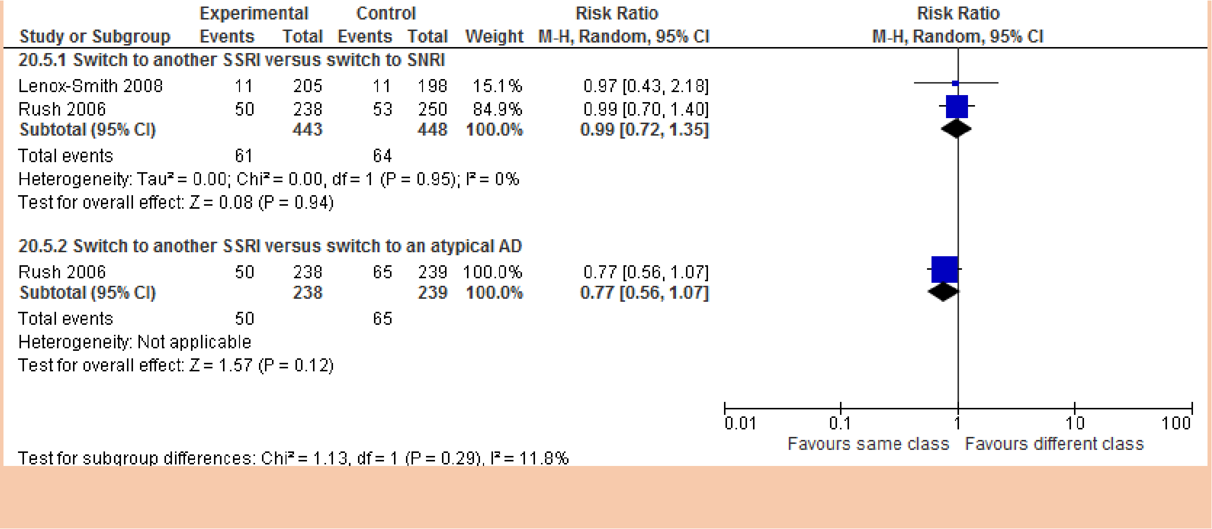
Discontinuation for any reason (including adverse events)



	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
20.4.1 Switch to another SSRI versus switch to SNRI						
Lenox-Smith 2008	43	206	49	200	100.0%	0.85 [0.59, 1.22]
Subtotal (95% CI)		**206**		**200**	**100.0%**	**0.85 [0.59, 1.22]**
Total events	43		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.38)						

Test for subgroup differences: Not applicable

Discontinuation due to adverse events



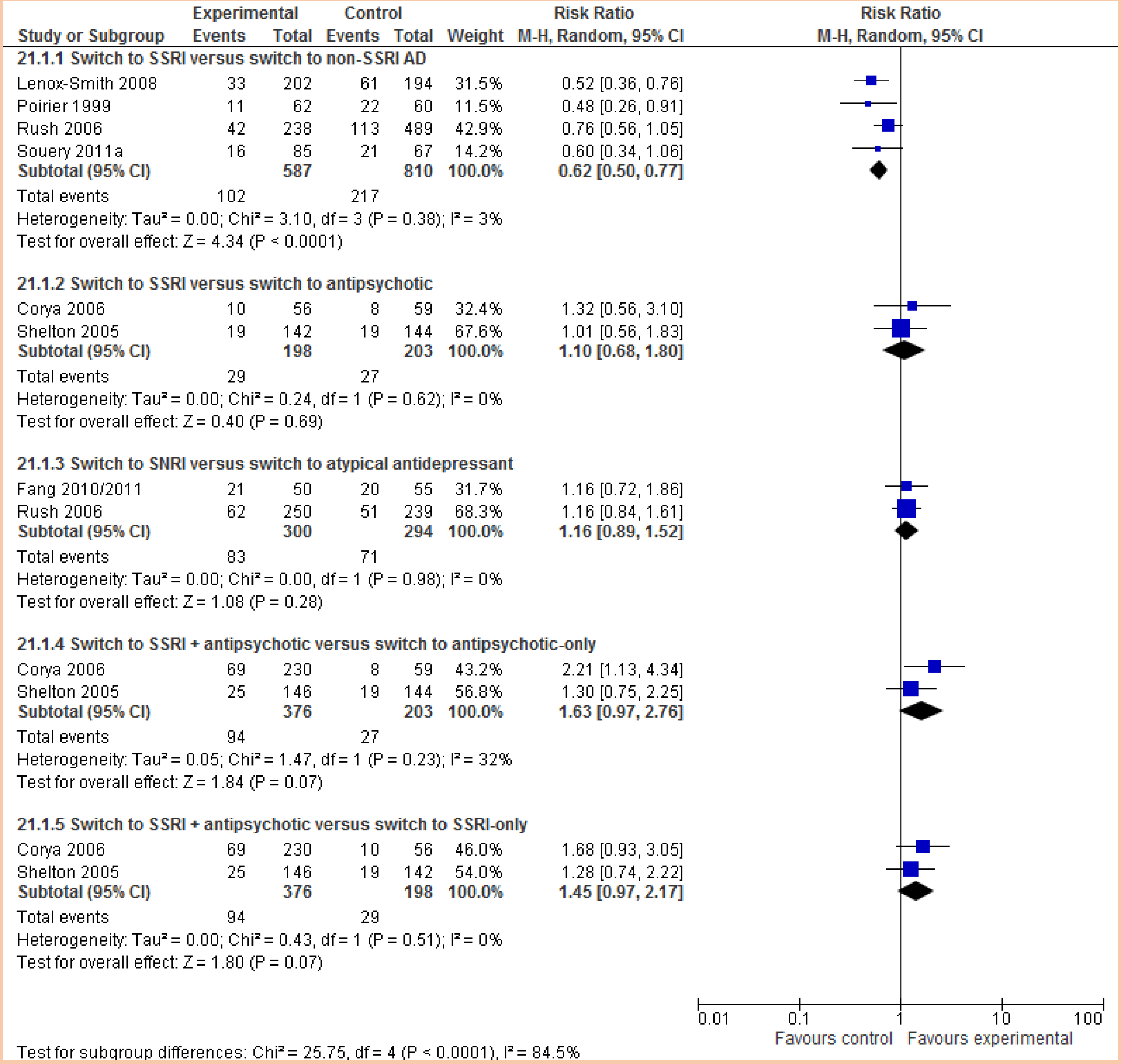
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
20.5.1 Switch to another SSRI versus switch to SNRI						
Lenox-Smith 2008	11	205	11	198	15.1%	0.97 [0.43, 2.18]
Rush 2006	50	238	53	250	84.9%	0.99 [0.70, 1.40]
Subtotal (95% CI)		**443**		**448**	**100.0%**	**0.99 [0.72, 1.35]**
Total events	61		64			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
20.5.2 Switch to another SSRI versus switch to an atypical AD						
Rush 2006	50	238	65	239	100.0%	0.77 [0.56, 1.07]
Subtotal (95% CI)		**238**		**239**	**100.0%**	**0.77 [0.56, 1.07]**
Total events	50		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						

Test for subgroup differences: Chi² = 1.13, df = 1 (P = 0.29), I² = 11.8%

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours same class
Favours different class

Switching to another antidepressant or non-antidepressant agent (head-to-head comparisons)

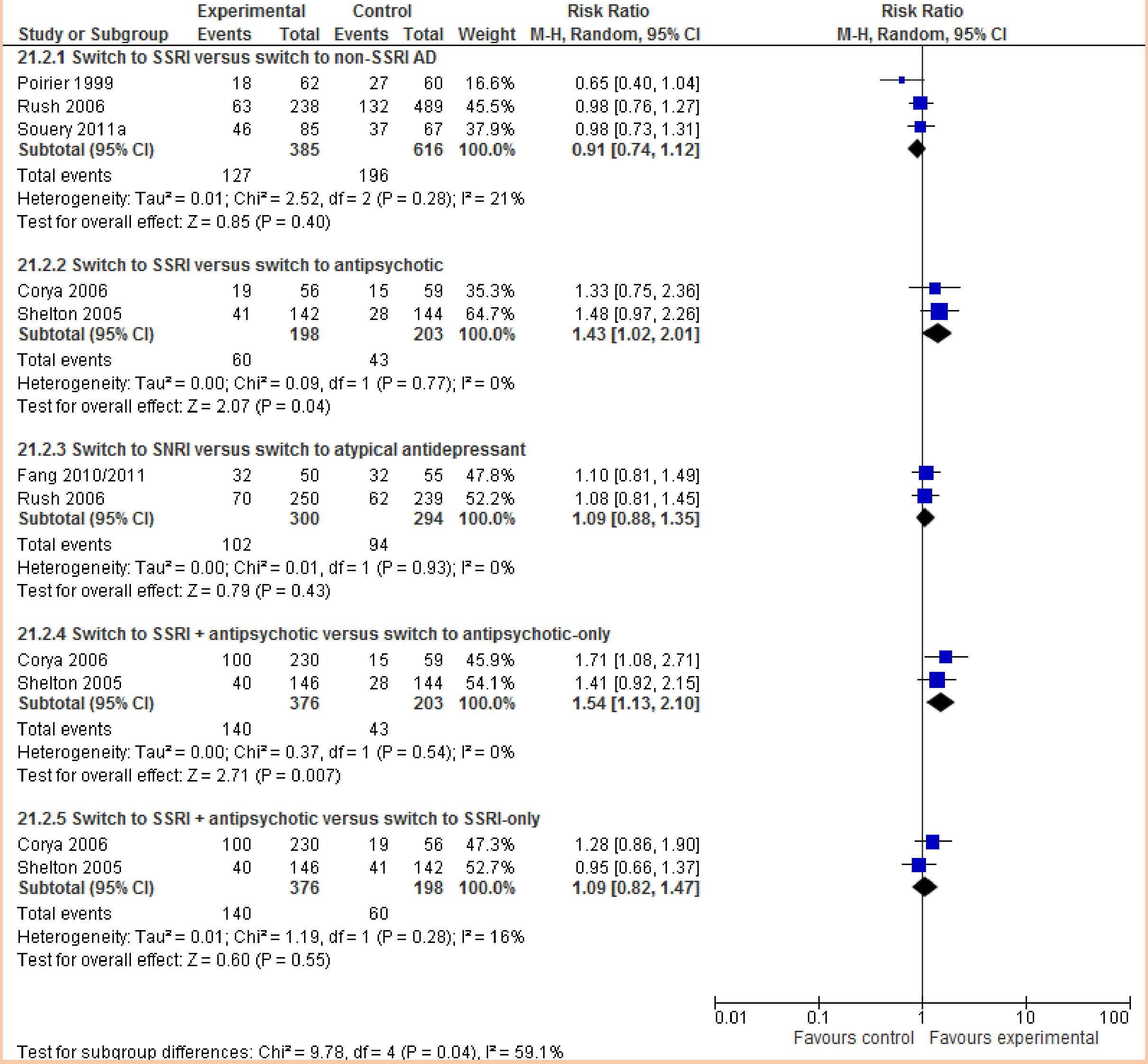
Remission (≤8 on MADRS/≤4/7/9 on HAMD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 Switch to SSRI versus switch to non-SSRI AD						
Lenox-Smith 2008	33	202	61	194	31.5%	0.52 [0.36, 0.76]
Poirier 1999	11	62	22	60	11.5%	0.48 [0.26, 0.91]
Rush 2006	42	238	113	489	42.9%	0.76 [0.56, 1.05]
Souery 2011a	16	85	21	67	14.2%	0.60 [0.34, 1.06]
Subtotal (95% CI)		**587**		**810**	**100.0%**	**0.62 [0.50, 0.77]**
Total events	102		217			
Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 3 (P = 0.38); I² = 3%						
Test for overall effect: Z = 4.34 (P < 0.0001)						
21.1.2 Switch to SSRI versus switch to antipsychotic						
Corya 2006	10	56	8	59	32.4%	1.32 [0.56, 3.10]
Shelton 2005	19	142	19	144	67.6%	1.01 [0.56, 1.83]
Subtotal (95% CI)		**198**		**203**	**100.0%**	**1.10 [0.68, 1.80]**
Total events	29		27			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
21.1.3 Switch to SNRI versus switch to atypical antidepressant						
Fang 2010/2011	21	50	20	55	31.7%	1.16 [0.72, 1.86]
Rush 2006	62	250	51	239	68.3%	1.16 [0.84, 1.61]
Subtotal (95% CI)		**300**		**294**	**100.0%**	**1.16 [0.89, 1.52]**
Total events	83		71			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
21.1.4 Switch to SSRI + antipsychotic versus switch to antipsychotic-only						
Corya 2006	69	230	8	59	43.2%	2.21 [1.13, 4.34]
Shelton 2005	25	146	19	144	56.8%	1.30 [0.75, 2.25]
Subtotal (95% CI)		**376**		**203**	**100.0%**	**1.63 [0.97, 2.76]**
Total events	94		27			
Heterogeneity: Tau² = 0.05; Chi² = 1.47, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 1.84 (P = 0.07)						
21.1.5 Switch to SSRI + antipsychotic versus switch to SSRI-only						
Corya 2006	69	230	10	56	46.0%	1.68 [0.93, 3.05]
Shelton 2005	25	146	19	142	54.0%	1.28 [0.74, 2.22]
Subtotal (95% CI)		**376**		**198**	**100.0%**	**1.45 [0.97, 2.17]**
Total events	94		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						

Test for subgroup differences: Chi² = 25.75, df = 4 (P < 0.0001), I² = 84.5%

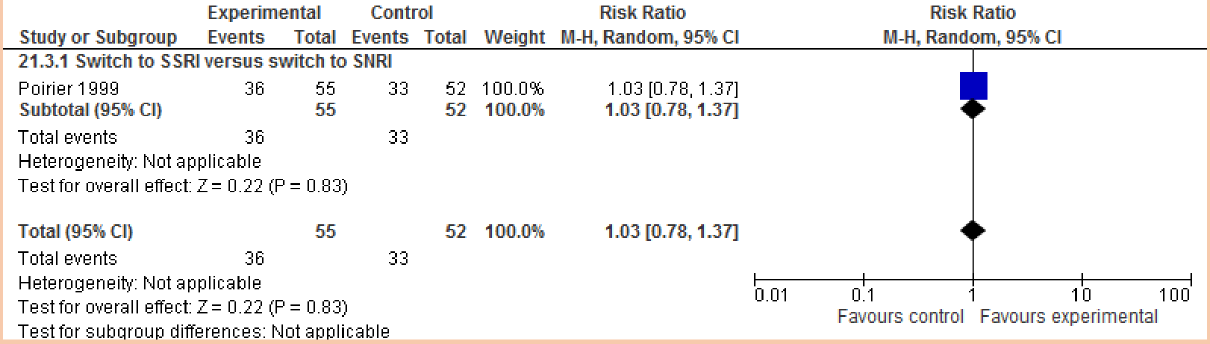
Response (≥50% improvement on MADRS/HAMD/QIDS)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.2.1 Switch to SSRI versus switch to non-SSRI AD						
Poirier 1999	18	62	27	60	16.6%	0.65 [0.40, 1.04]
Rush 2006	63	238	132	489	45.5%	0.98 [0.76, 1.27]
Souery 2011a	46	85	37	67	37.9%	0.98 [0.73, 1.31]
Subtotal (95% CI)		**385**		**616**	**100.0%**	**0.91 [0.74, 1.12]**
Total events	127		196			
Heterogeneity: Tau² = 0.01; Chi² = 2.52, df = 2 (P = 0.28); I² = 21%						
Test for overall effect: Z = 0.85 (P = 0.40)						
21.2.2 Switch to SSRI versus switch to antipsychotic						
Corya 2006	19	56	15	59	35.3%	1.33 [0.75, 2.36]
Shelton 2005	41	142	28	144	64.7%	1.48 [0.97, 2.26]
Subtotal (95% CI)		**198**		**203**	**100.0%**	**1.43 [1.02, 2.01]**
Total events	60		43			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
21.2.3 Switch to SNRI versus switch to atypical antidepressant						
Fang 2010/2011	32	50	32	55	47.8%	1.10 [0.81, 1.49]
Rush 2006	70	250	62	239	52.2%	1.08 [0.81, 1.45]
Subtotal (95% CI)		**300**		**294**	**100.0%**	**1.09 [0.88, 1.35]**
Total events	102		94			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
21.2.4 Switch to SSRI + antipsychotic versus switch to antipsychotic-only						
Corya 2006	100	230	15	59	45.9%	1.71 [1.08, 2.71]
Shelton 2005	40	146	28	144	54.1%	1.41 [0.92, 2.15]
Subtotal (95% CI)		**376**		**203**	**100.0%**	**1.54 [1.13, 2.10]**
Total events	140		43			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.71 (P = 0.007)						
21.2.5 Switch to SSRI + antipsychotic versus switch to SSRI-only						
Corya 2006	100	230	19	56	47.3%	1.28 [0.86, 1.90]
Shelton 2005	40	146	41	142	52.7%	0.95 [0.66, 1.37]
Subtotal (95% CI)		**376**		**198**	**100.0%**	**1.09 [0.82, 1.47]**
Total events	140		60			
Heterogeneity: Tau² = 0.01; Chi² = 1.19, df = 1 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.60 (P = 0.55)						

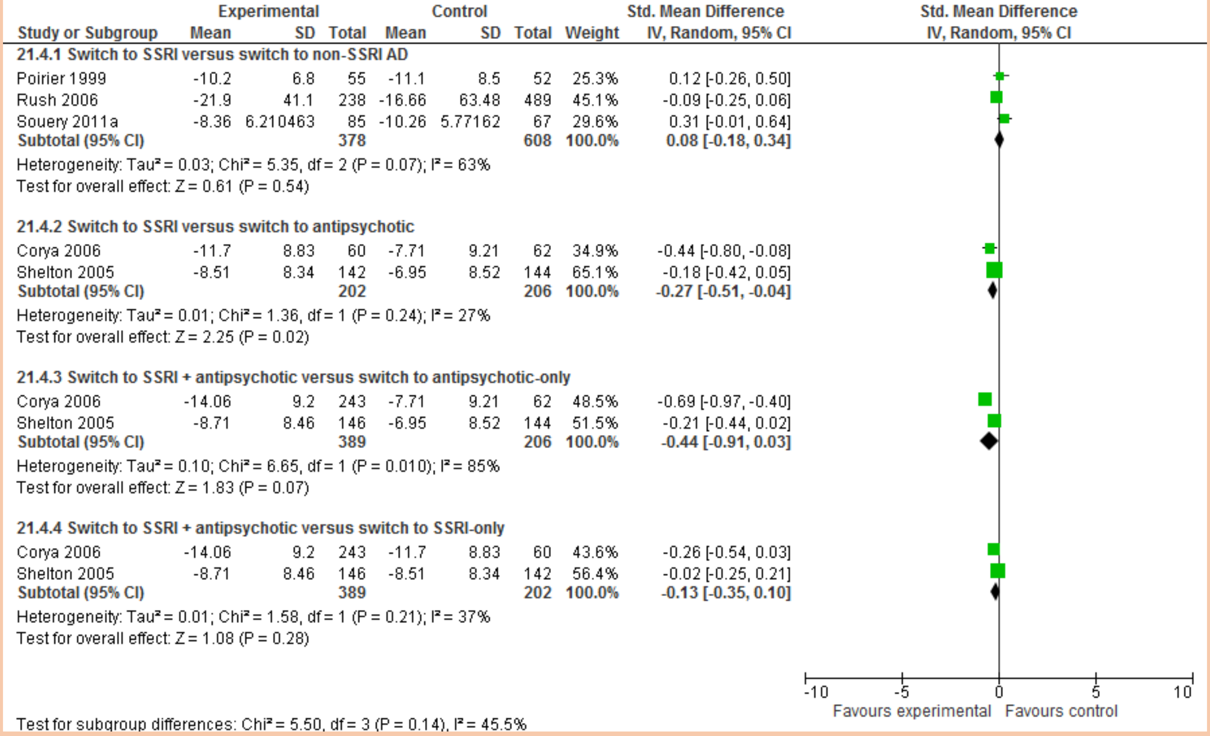
Test for subgroup differences: Chi² = 9.78, df = 4 (P = 0.04), I² = 59.1%

Response (much/very much improved on CGI-I)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.3.1 Switch to SSRI versus switch to SNRI						
Poirier 1999	36	55	33	52	100.0%	1.03 [0.78, 1.37]
Subtotal (95% CI)		**55**		**52**	**100.0%**	**1.03 [0.78, 1.37]**
Total events	36		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
Total (95% CI)		**55**		**52**	**100.0%**	**1.03 [0.78, 1.37]**
Total events	36		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Not applicable						

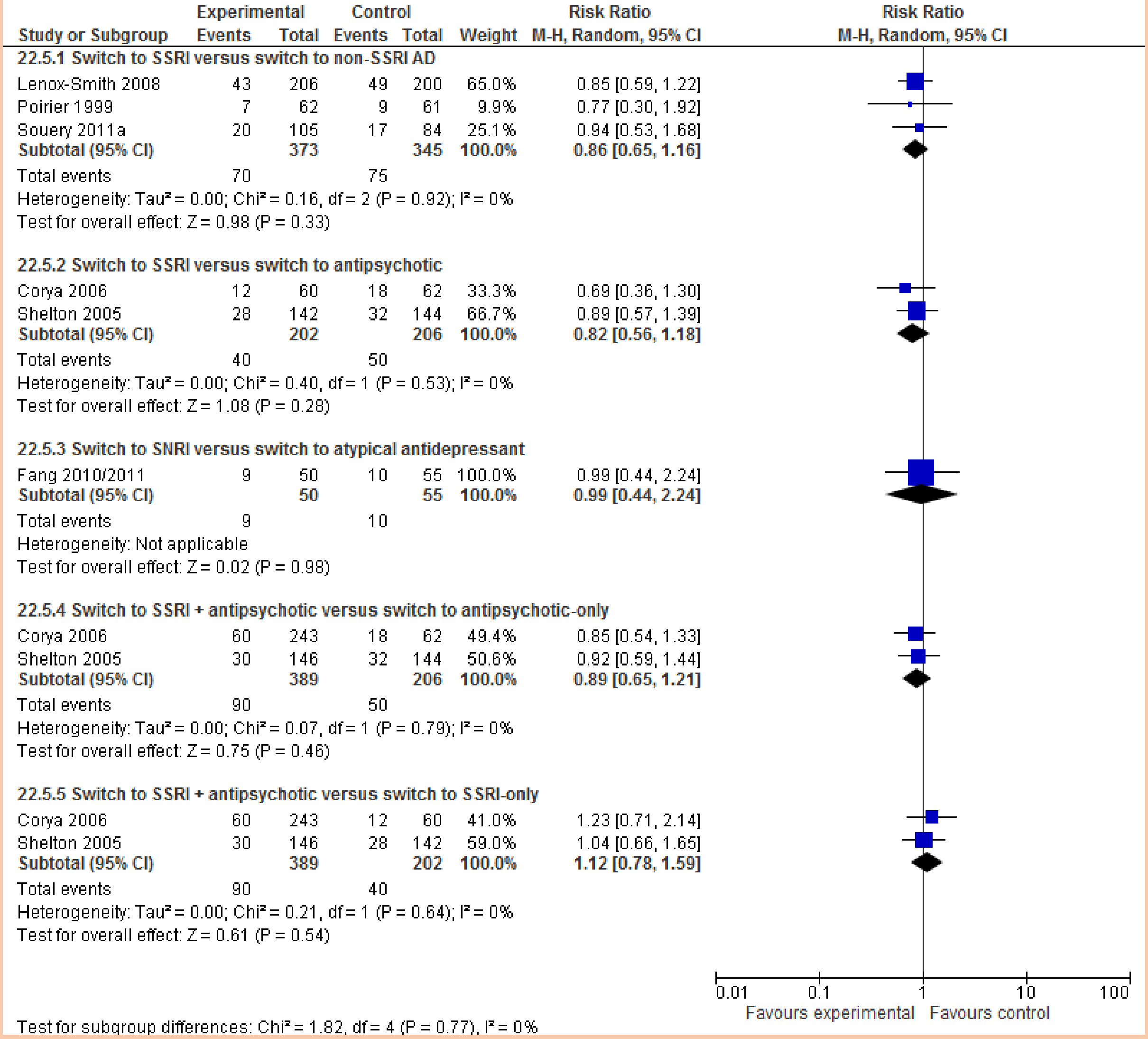
Depression symptomatology (MADRS/HAMD/QIDS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
21.4.1 Switch to SSRI versus switch to non-SSRI AD								
Poirier 1999	-10.2	6.8	55	-11.1	8.5	52	25.3%	0.12 [-0.26, 0.50]
Rush 2006	-21.9	41.1	238	-16.66	63.48	489	45.1%	-0.09 [-0.25, 0.06]
Souery 2011a	-8.36	6.210463	85	-10.26	5.77162	67	29.6%	0.31 [-0.01, 0.64]
Subtotal (95% CI)			**378**			**608**	**100.0%**	**0.08 [-0.18, 0.34]**
Heterogeneity: Tau² = 0.03; Chi² = 5.35, df = 2 (P = 0.07); I² = 63%								
Test for overall effect: Z = 0.61 (P = 0.54)								
21.4.2 Switch to SSRI versus switch to antipsychotic								
Corya 2006	-11.7	8.83	60	-7.71	9.21	62	34.9%	-0.44 [-0.80, -0.08]
Shelton 2005	-8.51	8.34	142	-6.95	8.52	144	65.1%	-0.18 [-0.42, 0.05]
Subtotal (95% CI)			**202**			**206**	**100.0%**	**-0.27 [-0.51, -0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 1.36, df = 1 (P = 0.24); I² = 27%								
Test for overall effect: Z = 2.25 (P = 0.02)								
21.4.3 Switch to SSRI + antipsychotic versus switch to antipsychotic-only								
Corya 2006	-14.06	9.2	243	-7.71	9.21	62	48.5%	-0.69 [-0.97, -0.40]
Shelton 2005	-8.71	8.46	146	-6.95	8.52	144	51.5%	-0.21 [-0.44, 0.02]
Subtotal (95% CI)			**389**			**206**	**100.0%**	**-0.44 [-0.91, 0.03]**
Heterogeneity: Tau² = 0.10; Chi² = 6.65, df = 1 (P = 0.010); I² = 85%								
Test for overall effect: Z = 1.83 (P = 0.07)								
21.4.4 Switch to SSRI + antipsychotic versus switch to SSRI-only								
Corya 2006	-14.06	9.2	243	-11.7	8.83	60	43.6%	-0.26 [-0.54, 0.03]
Shelton 2005	-8.71	8.46	146	-8.51	8.34	142	56.4%	-0.02 [-0.25, 0.21]
Subtotal (95% CI)			**389**			**202**	**100.0%**	**-0.13 [-0.35, 0.10]**
Heterogeneity: Tau² = 0.01; Chi² = 1.58, df = 1 (P = 0.21); I² = 37%								
Test for overall effect: Z = 1.08 (P = 0.28)								

Test for subgroup differences: Chi² = 5.50, df = 3 (P = 0.14), I² = 45.5%

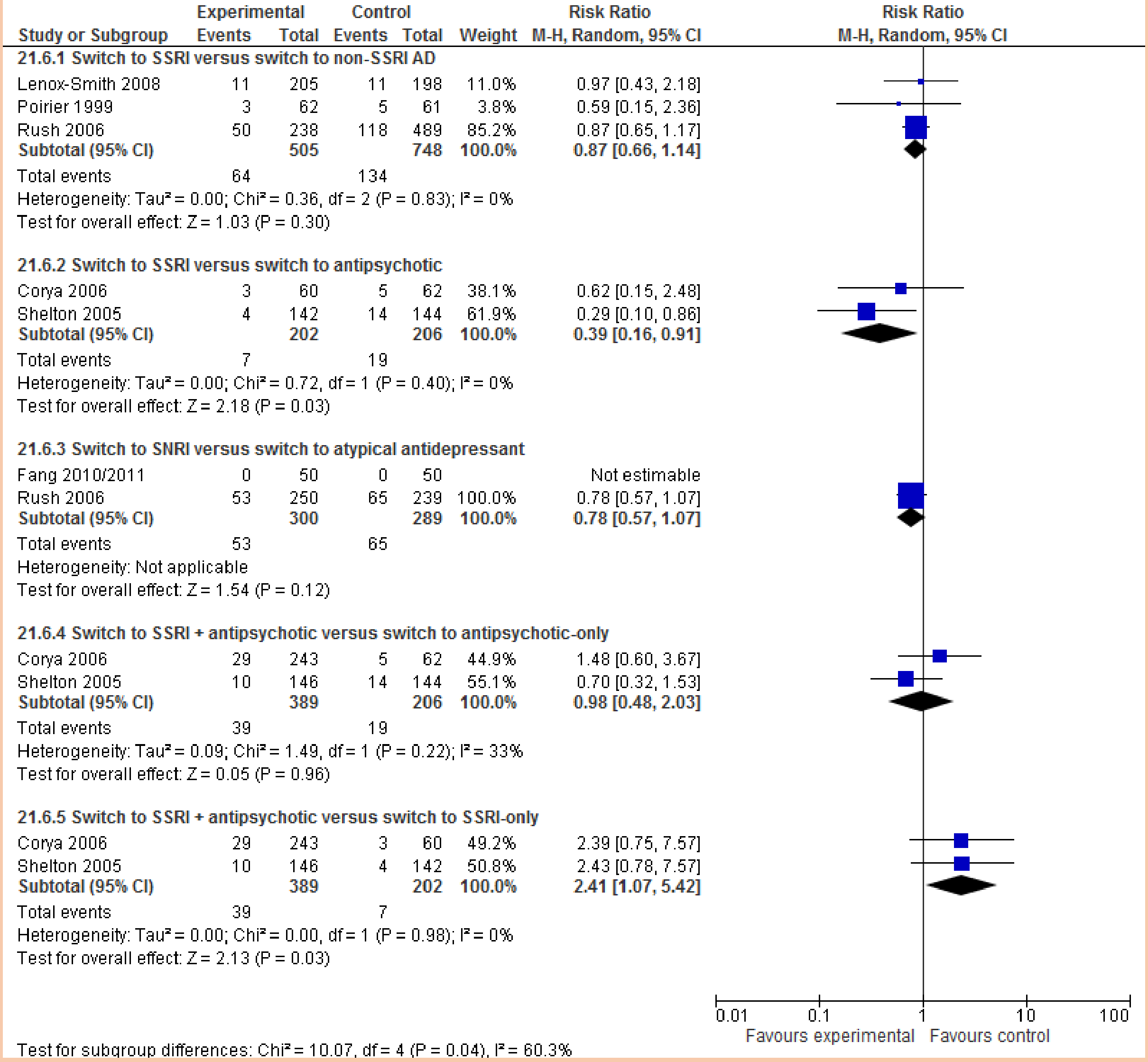
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.5.1 Switch to SSRI versus switch to non-SSRI AD						
Lenox-Smith 2008	43	206	49	200	65.0%	0.85 [0.59, 1.22]
Poirier 1999	7	62	9	61	9.9%	0.77 [0.30, 1.92]
Souery 2011a	20	105	17	84	25.1%	0.94 [0.53, 1.68]
Subtotal (95% CI)		**373**		**345**	**100.0%**	**0.86 [0.65, 1.16]**
Total events	70		75			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						
22.5.2 Switch to SSRI versus switch to antipsychotic						
Corya 2006	12	60	18	62	33.3%	0.69 [0.36, 1.30]
Shelton 2005	28	142	32	144	66.7%	0.89 [0.57, 1.39]
Subtotal (95% CI)		**202**		**206**	**100.0%**	**0.82 [0.56, 1.18]**
Total events	40		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
22.5.3 Switch to SNRI versus switch to atypical antidepressant						
Fang 2010/2011	9	50	10	55	100.0%	0.99 [0.44, 2.24]
Subtotal (95% CI)		**50**		**55**	**100.0%**	**0.99 [0.44, 2.24]**
Total events	9		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
22.5.4 Switch to SSRI + antipsychotic versus switch to antipsychotic-only						
Corya 2006	60	243	18	62	49.4%	0.85 [0.54, 1.33]
Shelton 2005	30	146	32	144	50.6%	0.92 [0.59, 1.44]
Subtotal (95% CI)		**389**		**206**	**100.0%**	**0.89 [0.65, 1.21]**
Total events	90		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.46)						
22.5.5 Switch to SSRI + antipsychotic versus switch to SSRI-only						
Corya 2006	60	243	12	60	41.0%	1.23 [0.71, 2.14]
Shelton 2005	30	146	28	142	59.0%	1.04 [0.66, 1.65]
Subtotal (95% CI)		**389**		**202**	**100.0%**	**1.12 [0.78, 1.59]**
Total events	90		40			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						

Test for subgroup differences: Chi² = 1.82, df = 4 (P = 0.77), I² = 0%

Discontinuation due to adverse events

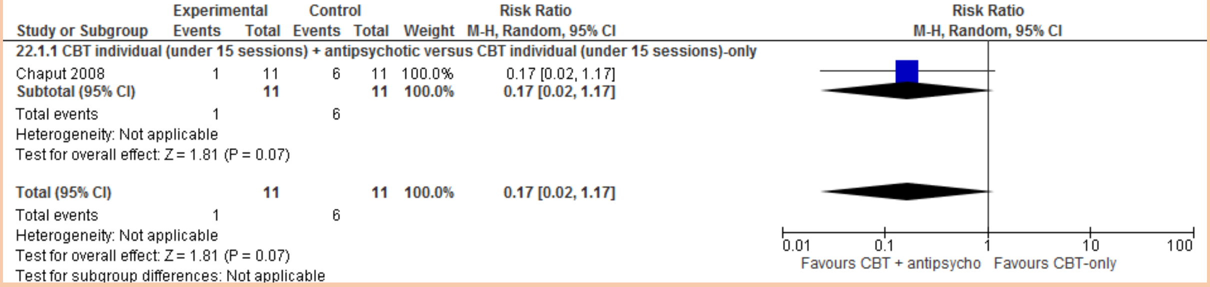


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.6.1 Switch to SSRI versus switch to non-SSRI AD						
Lenox-Smith 2008	11	205	11	198	11.0%	0.97 [0.43, 2.18]
Poirier 1999	3	62	5	61	3.8%	0.59 [0.15, 2.36]
Rush 2006	50	238	118	489	85.2%	0.87 [0.65, 1.17]
Subtotal (95% CI)		**505**		**748**	**100.0%**	**0.87 [0.66, 1.14]**
Total events	64		134			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
21.6.2 Switch to SSRI versus switch to antipsychotic						
Corya 2006	3	60	5	62	38.1%	0.62 [0.15, 2.48]
Shelton 2005	4	142	14	144	61.9%	0.29 [0.10, 0.86]
Subtotal (95% CI)		**202**		**206**	**100.0%**	**0.39 [0.16, 0.91]**
Total events	7		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 2.18 (P = 0.03)						
21.6.3 Switch to SNRI versus switch to atypical antidepressant						
Fang 2010/2011	0	50	0	50		Not estimable
Rush 2006	53	250	65	239	100.0%	0.78 [0.57, 1.07]
Subtotal (95% CI)		**300**		**289**	**100.0%**	**0.78 [0.57, 1.07]**
Total events	53		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
21.6.4 Switch to SSRI + antipsychotic versus switch to antipsychotic-only						
Corya 2006	29	243	5	62	44.9%	1.48 [0.60, 3.67]
Shelton 2005	10	146	14	144	55.1%	0.70 [0.32, 1.53]
Subtotal (95% CI)		**389**		**206**	**100.0%**	**0.98 [0.48, 2.03]**
Total events	39		19			
Heterogeneity: Tau² = 0.09; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 0.05 (P = 0.96)						
21.6.5 Switch to SSRI + antipsychotic versus switch to SSRI-only						
Corya 2006	29	243	3	60	49.2%	2.39 [0.75, 7.57]
Shelton 2005	10	146	4	142	50.8%	2.43 [0.78, 7.57]
Subtotal (95% CI)		**389**		**202**	**100.0%**	**2.41 [1.07, 5.42]**
Total events	39		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						

Test for subgroup differences: Chi² = 10.07, df = 4 (P = 0.04), I² = 60.3%

Switching to a combined psychological and pharmacological intervention versus switching to a psychological intervention-only

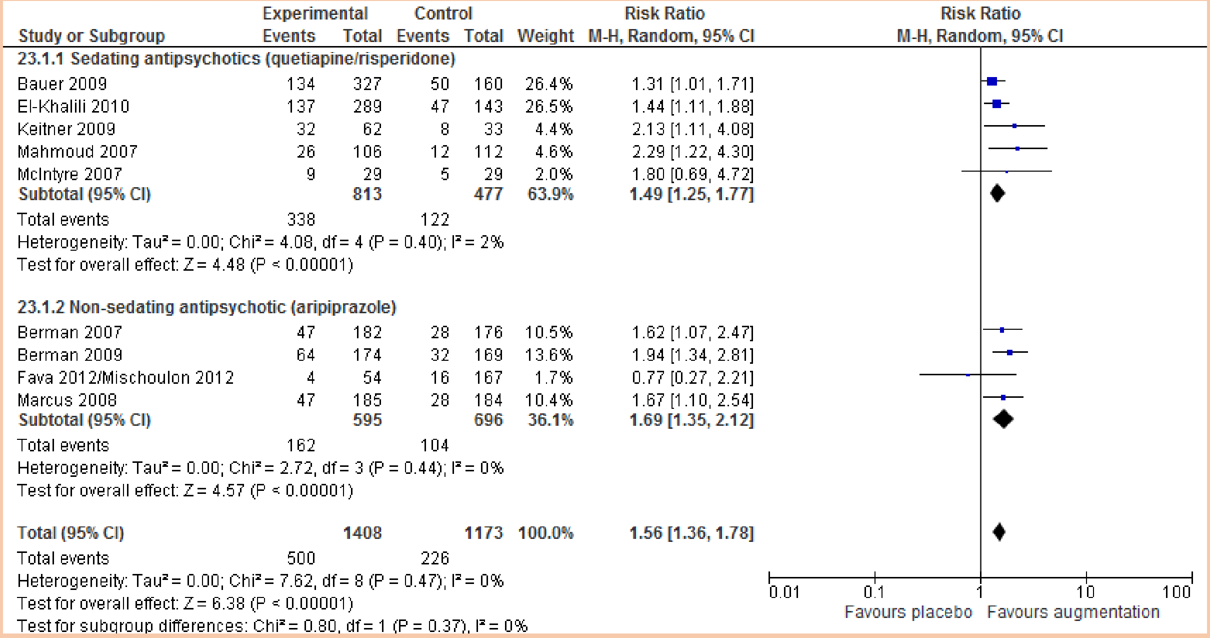
Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.1.1 CBT individual (under 15 sessions) + antipsychotic versus CBT individual (under 15 sessions)-only						
Chaput 2008	1	11	6	11	100.0%	0.17 [0.02, 1.17]
Subtotal (95% CI)		**11**		**11**	**100.0%**	**0.17 [0.02, 1.17]**
Total events	1		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
Total (95% CI)		**11**		**11**	**100.0%**	**0.17 [0.02, 1.17]**
Total events	1		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
Test for subgroup differences: Not applicable						

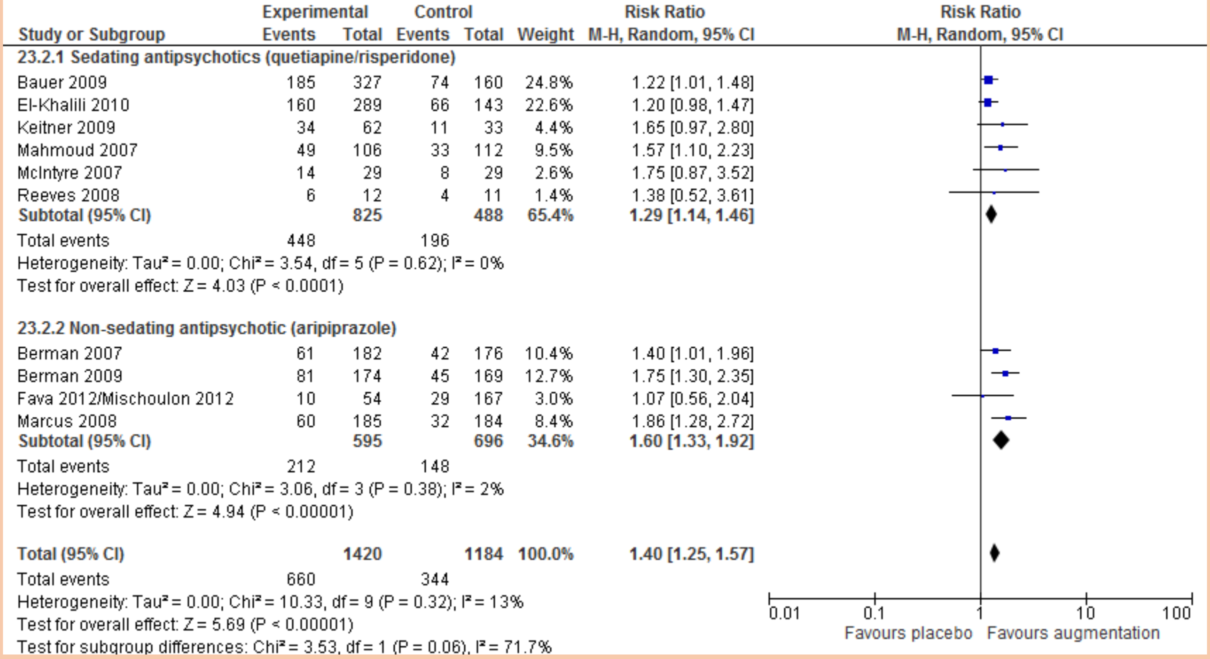
Antipsychotic augmentation versus placebo: Sub-analysis by sedating versus non-sedating antipsychotics

Remission (<10/11 on MADRS/<7/8/10 on HAMD)



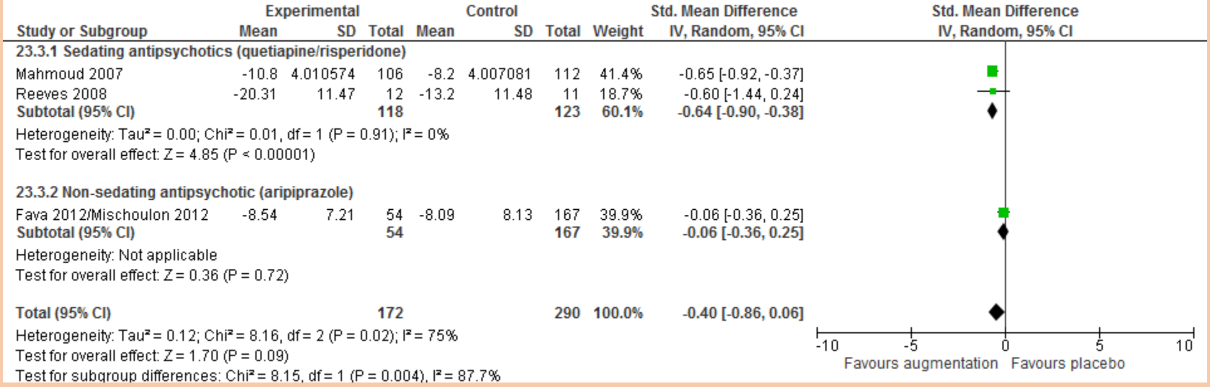
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
23.1.1 Sedating antipsychotics (quetiapine/risperidone)						
Bauer 2009	134	327	50	160	26.4%	1.31 [1.01, 1.71]
El-Khalili 2010	137	289	47	143	26.5%	1.44 [1.11, 1.88]
Keitner 2009	32	62	8	33	4.4%	2.13 [1.11, 4.08]
Mahmoud 2007	26	106	12	112	4.6%	2.29 [1.22, 4.30]
McIntyre 2007	9	29	5	29	2.0%	1.80 [0.69, 4.72]
Subtotal (95% CI)		**813**		**477**	**63.9%**	**1.49 [1.25, 1.77]**
Total events	338		122			
Heterogeneity: Tau² = 0.00; Chi² = 4.08, df = 4 (P = 0.40); I² = 2%						
Test for overall effect: Z = 4.48 (P < 0.00001)						
23.1.2 Non-sedating antipsychotic (aripiprazole)						
Berman 2007	47	182	28	176	10.5%	1.62 [1.07, 2.47]
Berman 2009	64	174	32	169	13.6%	1.94 [1.34, 2.81]
Fava 2012/Mischoulon 2012	4	54	16	167	1.7%	0.77 [0.27, 2.21]
Marcus 2008	47	185	28	184	10.4%	1.67 [1.10, 2.54]
Subtotal (95% CI)		**595**		**696**	**36.1%**	**1.69 [1.35, 2.12]**
Total events	162		104			
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 4.57 (P < 0.00001)						
Total (95% CI)		**1408**		**1173**	**100.0%**	**1.56 [1.36, 1.78]**
Total events	500		226			
Heterogeneity: Tau² = 0.00; Chi² = 7.62, df = 8 (P = 0.47); I² = 0%						
Test for overall effect: Z = 6.38 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%						

Response (≥50% improvement on MADRS/HAMD)



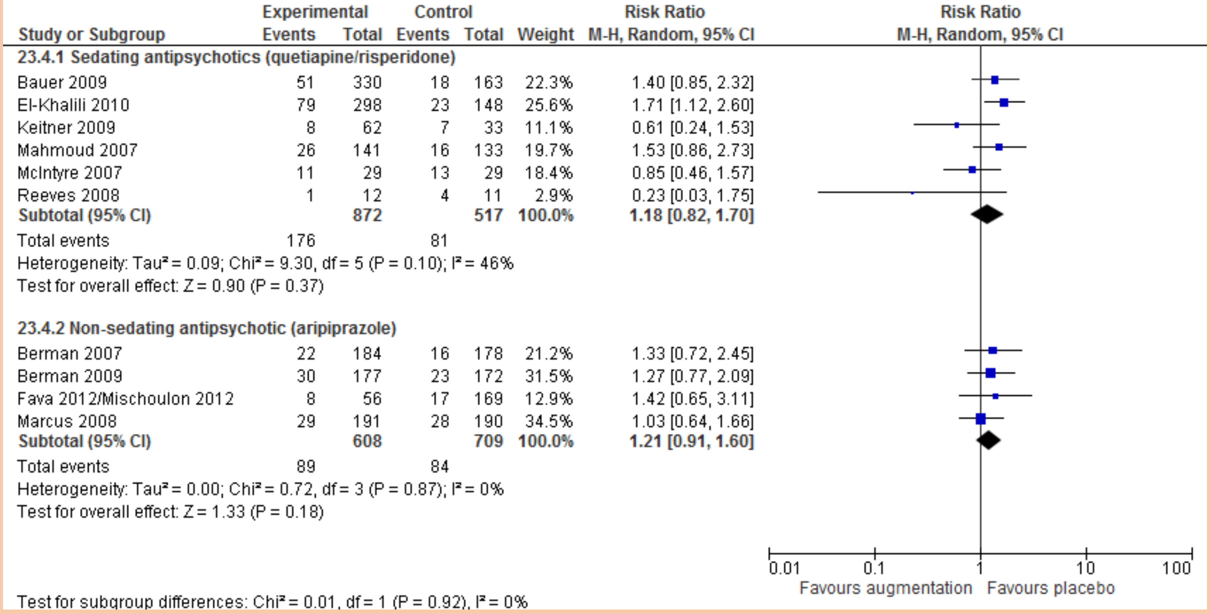
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
23.2.1 Sedating antipsychotics (quetiapine/risperidone)						
Bauer 2009	185	327	74	160	24.8%	1.22 [1.01, 1.48]
El-Khalili 2010	160	289	66	143	22.6%	1.20 [0.98, 1.47]
Keitner 2009	34	62	11	33	4.4%	1.65 [0.97, 2.80]
Mahmoud 2007	49	106	33	112	9.5%	1.57 [1.10, 2.23]
McIntyre 2007	14	29	8	29	2.6%	1.75 [0.87, 3.52]
Reeves 2008	6	12	4	11	1.4%	1.38 [0.52, 3.61]
Subtotal (95% CI)		**825**		**488**	**65.4%**	**1.29 [1.14, 1.46]**
Total events	448		196			
Heterogeneity: Tau² = 0.00; Chi² = 3.54, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
23.2.2 Non-sedating antipsychotic (aripiprazole)						
Berman 2007	61	182	42	176	10.4%	1.40 [1.01, 1.96]
Berman 2009	81	174	45	169	12.7%	1.75 [1.30, 2.35]
Fava 2012/Mischoulon 2012	10	54	29	167	3.0%	1.07 [0.56, 2.04]
Marcus 2008	60	185	32	184	8.4%	1.86 [1.28, 2.72]
Subtotal (95% CI)		**595**		**696**	**34.6%**	**1.60 [1.33, 1.92]**
Total events	212		148			
Heterogeneity: Tau² = 0.00; Chi² = 3.06, df = 3 (P = 0.38); I² = 2%						
Test for overall effect: Z = 4.94 (P < 0.00001)						
Total (95% CI)		**1420**		**1184**	**100.0%**	**1.40 [1.25, 1.57]**
Total events	660		344			
Heterogeneity: Tau² = 0.00; Chi² = 10.33, df = 9 (P = 0.32); I² = 13%						
Test for overall effect: Z = 5.69 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.53, df = 1 (P = 0.06), I² = 71.7%						

Depression symptomatology (MADRS/HAMD change score)



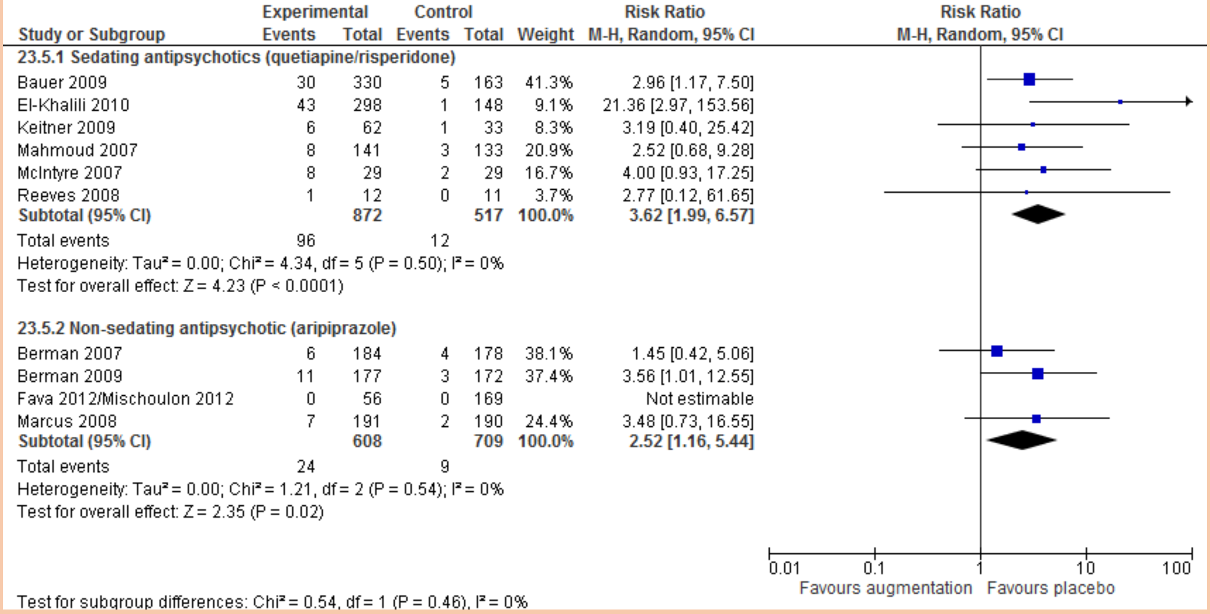
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
23.3.1 Sedating antipsychotics (quetiapine/risperidone)								
Mahmoud 2007	-10.8	4.010574	106	-8.2	4.007081	112	41.4%	-0.65 [-0.92, -0.37]
Reeves 2008	-20.31	11.47	12	-13.2	11.48	11	18.7%	-0.60 [-1.44, 0.24]
Subtotal (95% CI)			**118**			**123**	**60.1%**	**-0.64 [-0.90, -0.38]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 4.85 (P < 0.00001)								
23.3.2 Non-sedating antipsychotic (aripiprazole)								
Fava 2012/Mischoulon 2012	-8.54	7.21	54	-8.09	8.13	167	39.9%	-0.06 [-0.36, 0.25]
Subtotal (95% CI)			**54**			**167**	**39.9%**	**-0.06 [-0.36, 0.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								
Total (95% CI)			**172**			**290**	**100.0%**	**-0.40 [-0.86, 0.06]**
Heterogeneity: Tau² = 0.12; Chi² = 8.16, df = 2 (P = 0.02); I² = 75%								
Test for overall effect: Z = 1.70 (P = 0.09)								
Test for subgroup differences: Chi² = 8.15, df = 1 (P = 0.004), I² = 87.7%								

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
23.4.1 Sedating antipsychotics (quetiapine/risperidone)						
Bauer 2009	51	330	18	163	22.3%	1.40 [0.85, 2.32]
El-Khalili 2010	79	298	23	148	25.6%	1.71 [1.12, 2.60]
Keitner 2009	8	62	7	33	11.1%	0.61 [0.24, 1.53]
Mahmoud 2007	26	141	16	133	19.7%	1.53 [0.86, 2.73]
McIntyre 2007	11	29	13	29	18.4%	0.85 [0.46, 1.57]
Reeves 2008	1	12	4	11	2.9%	0.23 [0.03, 1.75]
Subtotal (95% CI)		**872**		**517**	**100.0%**	**1.18 [0.82, 1.70]**
Total events	176		81			
Heterogeneity: Tau² = 0.09; Chi² = 9.30, df = 5 (P = 0.10); I² = 46%						
Test for overall effect: Z = 0.90 (P = 0.37)						
23.4.2 Non-sedating antipsychotic (aripiprazole)						
Berman 2007	22	184	16	178	21.2%	1.33 [0.72, 2.45]
Berman 2009	30	177	23	172	31.5%	1.27 [0.77, 2.09]
Fava 2012/Mischoulon 2012	8	56	17	169	12.9%	1.42 [0.65, 3.11]
Marcus 2008	29	191	28	190	34.5%	1.03 [0.64, 1.66]
Subtotal (95% CI)		**608**		**709**	**100.0%**	**1.21 [0.91, 1.60]**
Total events	89		84			
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

Discontinuation due to adverse events



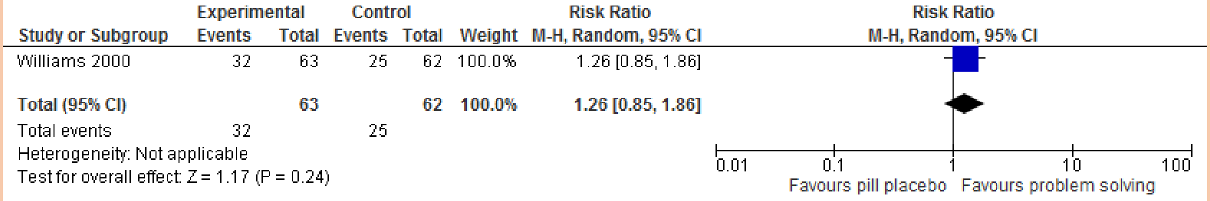
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
23.5.1 Sedating antipsychotics (quetiapine/risperidone)						
Bauer 2009	30	330	5	163	41.3%	2.96 [1.17, 7.50]
El-Khalili 2010	43	298	1	148	9.1%	21.36 [2.97, 153.56]
Keitner 2009	6	62	1	33	8.3%	3.19 [0.40, 25.42]
Mahmoud 2007	8	141	3	133	20.9%	2.52 [0.68, 9.28]
McIntyre 2007	8	29	2	29	16.7%	4.00 [0.93, 17.25]
Reeves 2008	1	12	0	11	3.7%	2.77 [0.12, 61.65]
Subtotal (95% CI)		**872**		**517**	**100.0%**	**3.62 [1.99, 6.57]**
Total events	96		12			
Heterogeneity: Tau² = 0.00; Chi² = 4.34, df = 5 (P = 0.50); I² = 0%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
23.5.2 Non-sedating antipsychotic (aripiprazole)						
Berman 2007	6	184	4	178	38.1%	1.45 [0.42, 5.06]
Berman 2009	11	177	3	172	37.4%	3.56 [1.01, 12.55]
Fava 2012/Mischoulon 2012	0	56	0	169		Not estimable
Marcus 2008	7	191	2	190	24.4%	3.48 [0.73, 16.55]
Subtotal (95% CI)		**608**		**709**	**100.0%**	**2.52 [1.16, 5.44]**
Total events	24		9			
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						

Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%

Chronic depressive symptoms (chapter 9)

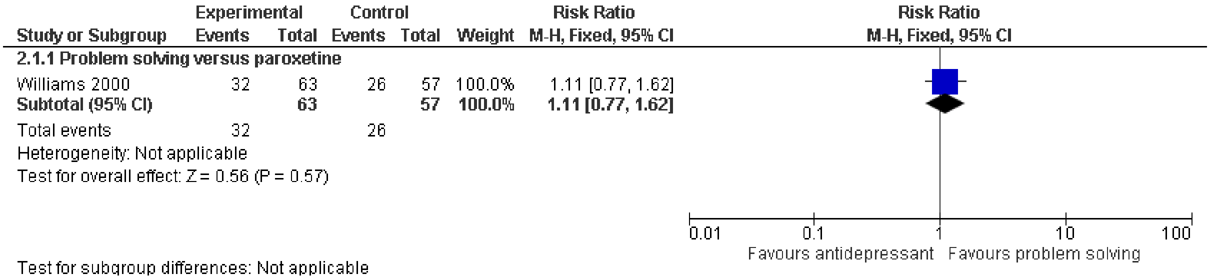
Problem solving versus pill placebo for chronic depressive symptoms

Remission (score <7 on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Williams 2000	32	63	25	62	100.0%	1.26 [0.85, 1.86]
Total (95% CI)		**63**		**62**	**100.0%**	**1.26 [0.85, 1.86]**
Total events	32		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						

Problem solving versus antidepressant for dysthymia

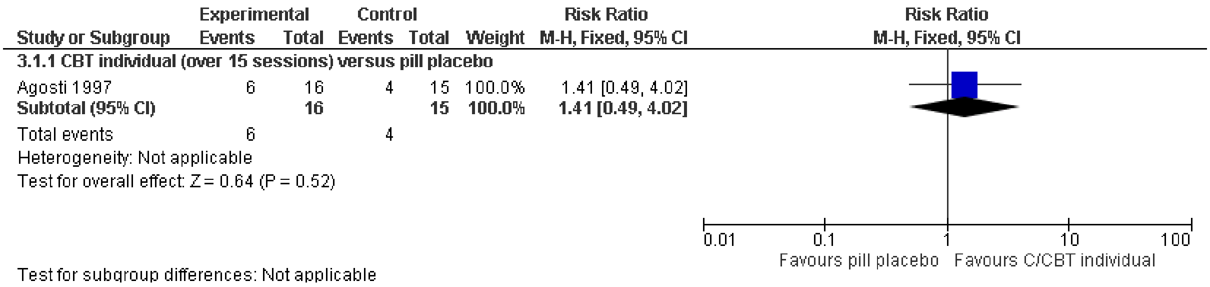


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Problem solving versus paroxetine						
Williams 2000	32	63	26	57	100.0%	1.11 [0.77, 1.62]
Subtotal (95% CI)		**63**		**57**	**100.0%**	**1.11 [0.77, 1.62]**
Total events	32		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						

Test for subgroup differences: Not applicable

Cognitive and cognitive behavioural therapies versus pill placebo for chronic depressive symptoms

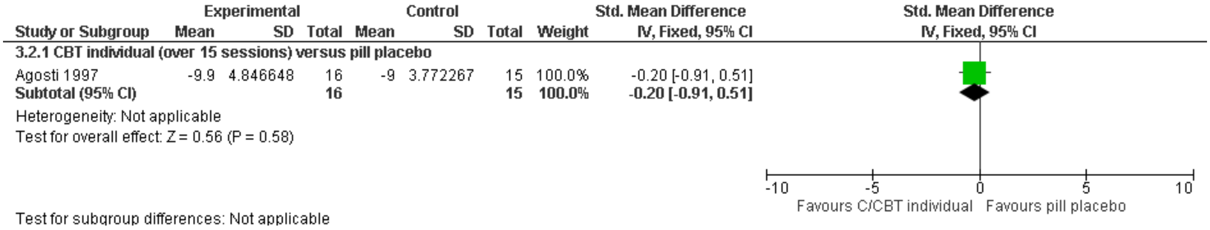
Remission (<7 on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 CBT individual (over 15 sessions) versus pill placebo						
Agosti 1997	6	16	4	15	100.0%	1.41 [0.49, 4.02]
Subtotal (95% CI)		**16**		**15**	**100.0%**	**1.41 [0.49, 4.02]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours pill placebo
Favours C/CBT individual

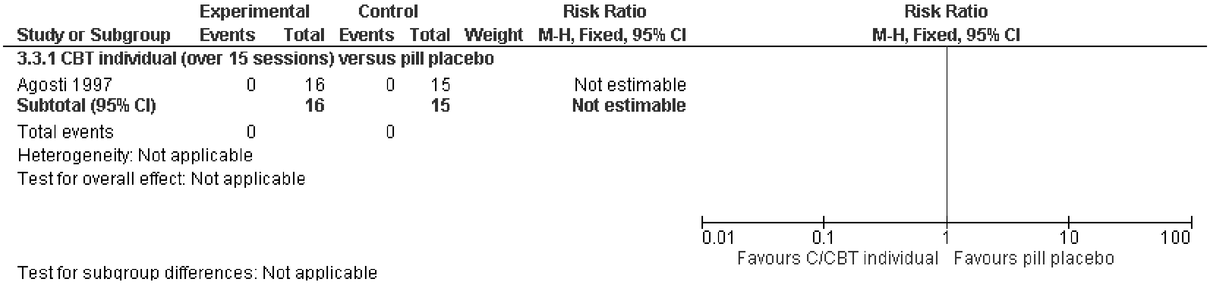
Depression symptomatology (HAM-D change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.2.1 CBT individual (over 15 sessions) versus pill placebo								
Agosti 1997	-9.9	4.846648	16	-9	3.772267	15	100.0%	-0.20 [-0.91, 0.51]
Subtotal (95% CI)			**16**			**15**	**100.0%**	**-0.20 [-0.91, 0.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.58)								
Test for subgroup differences: Not applicable								

Std. Mean Difference
IV, Fixed, 95% CI
-10
-5
0
5
10
Favours C/CBT individual
Favours pill placebo

Discontinuation for any reason

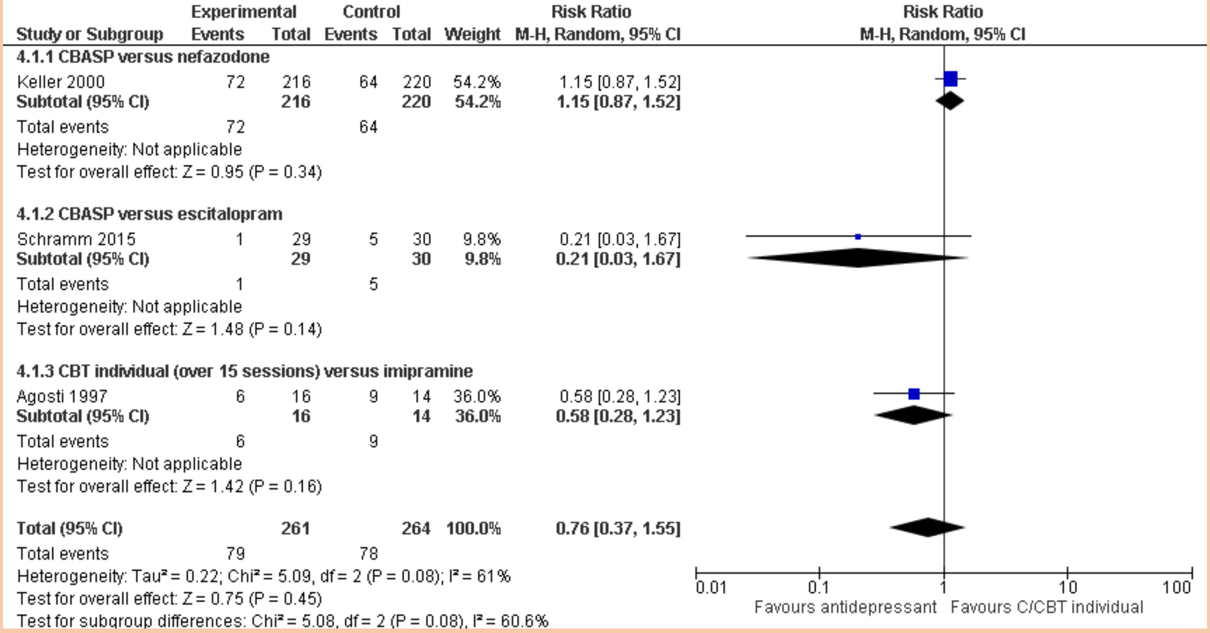


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 CBT individual (over 15 sessions) versus pill placebo						
Agosti 1997	0	16	0	15		Not estimable
Subtotal (95% CI)		**16**		**15**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours C/CBT individual
Favours pill placebo

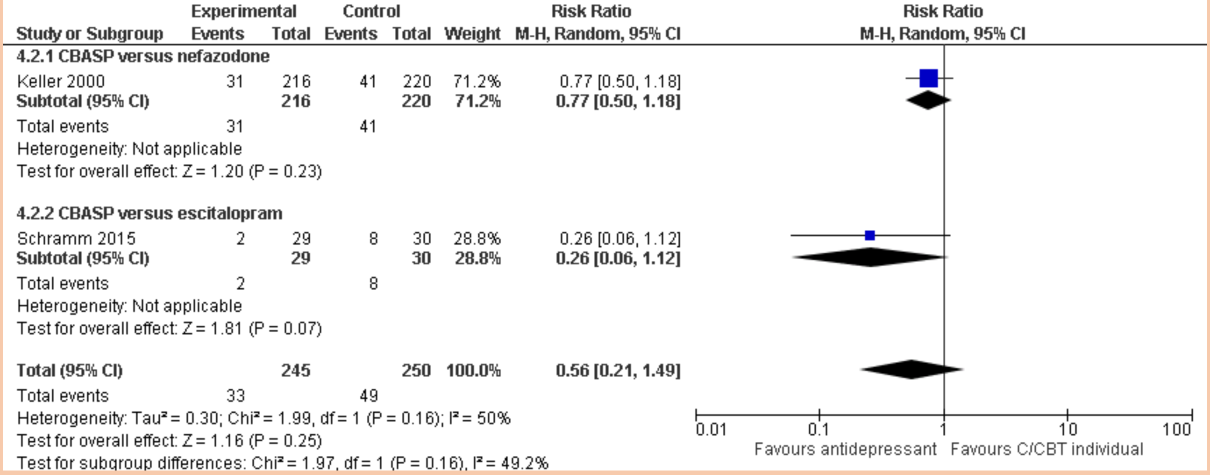
Cognitive and cognitive behavioural therapies versus antidepressants for chronic depressive symptoms

Remission (≤8/<7 on HAM-D/≤9 on MADRS)



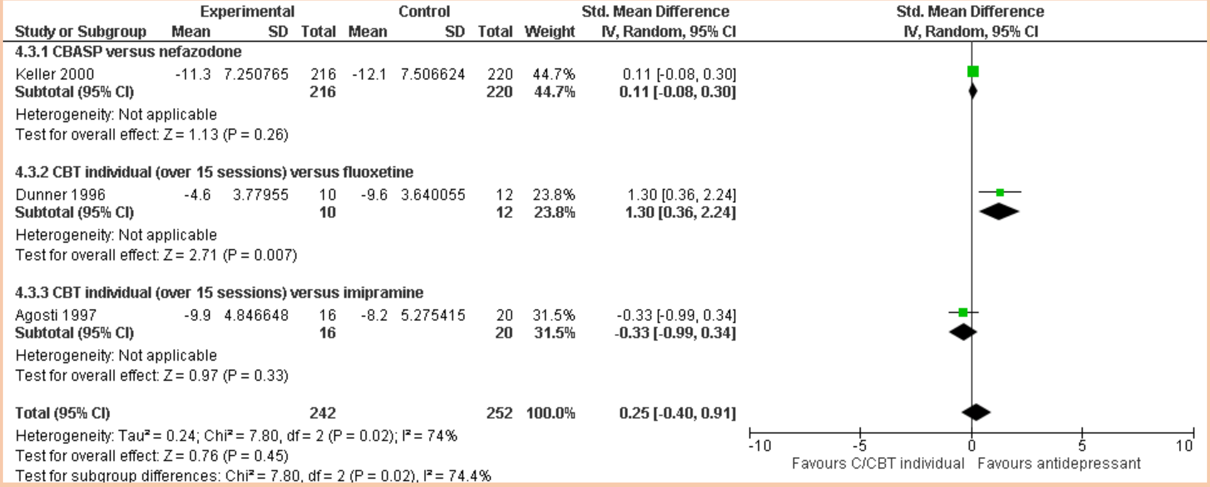
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 CBASP versus nefazodone						
Keller 2000	72	216	64	220	54.2%	1.15 [0.87, 1.52]
Subtotal (95% CI)		**216**		**220**	**54.2%**	**1.15 [0.87, 1.52]**
Total events	72		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
4.1.2 CBASP versus escitalopram						
Schramm 2015	1	29	5	30	9.8%	0.21 [0.03, 1.67]
Subtotal (95% CI)		**29**		**30**	**9.8%**	**0.21 [0.03, 1.67]**
Total events	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
4.1.3 CBT individual (over 15 sessions) versus imipramine						
Agosti 1997	6	16	9	14	36.0%	0.58 [0.28, 1.23]
Subtotal (95% CI)		**16**		**14**	**36.0%**	**0.58 [0.28, 1.23]**
Total events	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
Total (95% CI)		**261**		**264**	**100.0%**	**0.76 [0.37, 1.55]**
Total events	79		78			
Heterogeneity: Tau^2 = 0.22; Chi^2 = 5.09, df = 2 (P = 0.08); I^2 = 61%						
Test for overall effect: Z = 0.75 (P = 0.45)						
Test for subgroup differences: Chi^2 = 5.08, df = 2 (P = 0.08), I^2 = 60.6%						

Response (≥50% improvement on HAM-D & HAMD score 8-15 [response without remission]/≥50% improvement on MADRS)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 CBASP versus nefazodone						
Keller 2000	31	216	41	220	71.2%	0.77 [0.50, 1.18]
Subtotal (95% CI)		**216**		**220**	**71.2%**	**0.77 [0.50, 1.18]**
Total events	31		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
4.2.2 CBASP versus escitalopram						
Schramm 2015	2	29	8	30	28.8%	0.26 [0.06, 1.12]
Subtotal (95% CI)		**29**		**30**	**28.8%**	**0.26 [0.06, 1.12]**
Total events	2		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
Total (95% CI)		**245**		**250**	**100.0%**	**0.56 [0.21, 1.49]**
Total events	33		49			
Heterogeneity: Tau^2 = 0.30; Chi^2 = 1.99, df = 1 (P = 0.16); I^2 = 50%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Chi^2 = 1.97, df = 1 (P = 0.16), I^2 = 49.2%						

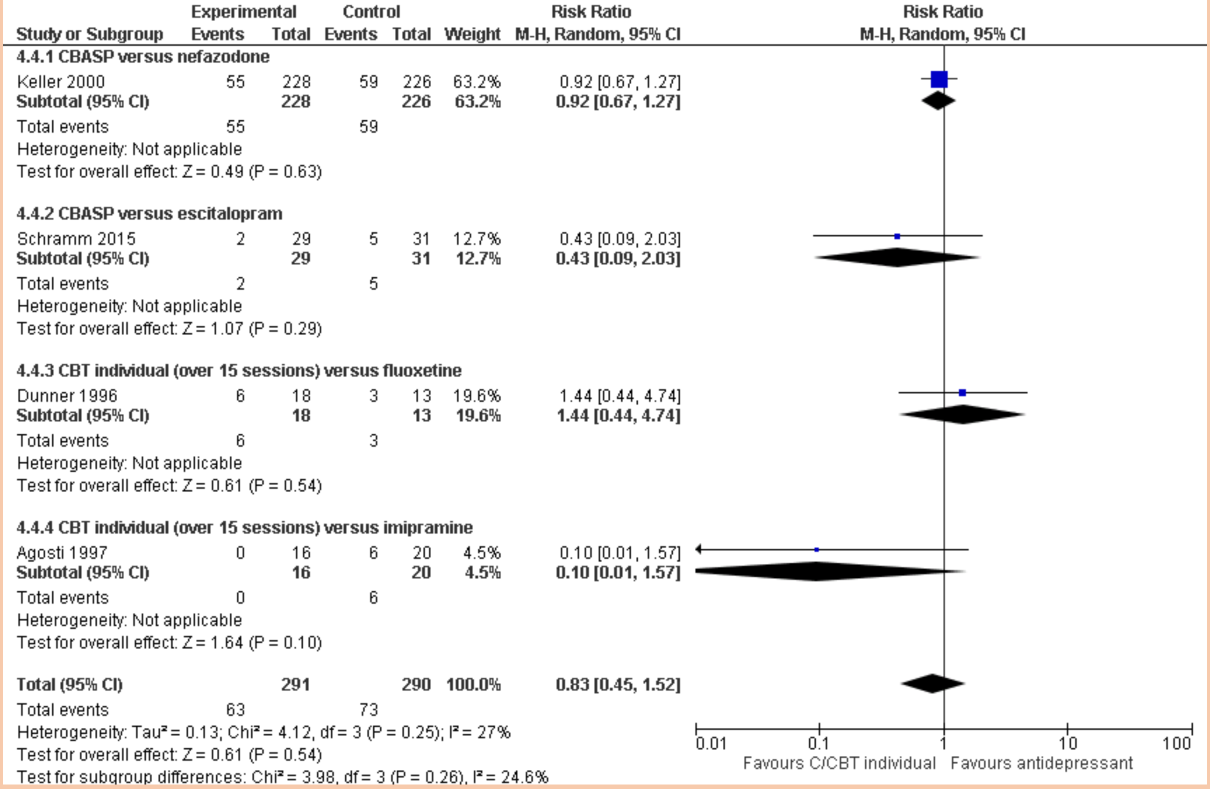
Depression symptomatology (HAMD change score)



	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
4.3.1 CBASP versus nefazodone								
Keller 2000	-11.3	7.250765	216	-12.1	7.506624	220	44.7%	0.11 [-0.08, 0.30]
Subtotal (95% CI)			**216**			**220**	**44.7%**	**0.11 [-0.08, 0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.13 (P = 0.26)								
4.3.2 CBT individual (over 15 sessions) versus fluoxetine								
Dunner 1996	-4.6	3.77955	10	-9.6	3.640055	12	23.8%	1.30 [0.36, 2.24]
Subtotal (95% CI)			**10**			**12**	**23.8%**	**1.30 [0.36, 2.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.71 (P = 0.007)								
4.3.3 CBT individual (over 15 sessions) versus imipramine								
Agosti 1997	-9.9	4.846648	16	-8.2	5.275415	20	31.5%	-0.33 [-0.99, 0.34]
Subtotal (95% CI)			**16**			**20**	**31.5%**	**-0.33 [-0.99, 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.97 (P = 0.33)								
Total (95% CI)			**242**			**252**	**100.0%**	**0.25 [-0.40, 0.91]**

Heterogeneity: $\text{Tau}^2 = 0.24$; $\text{Chi}^2 = 7.80$, df = 2 (P = 0.02); $I^2 = 74\%$
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: $\text{Chi}^2 = 7.80$, df = 2 (P = 0.02), $I^2 = 74.4\%$

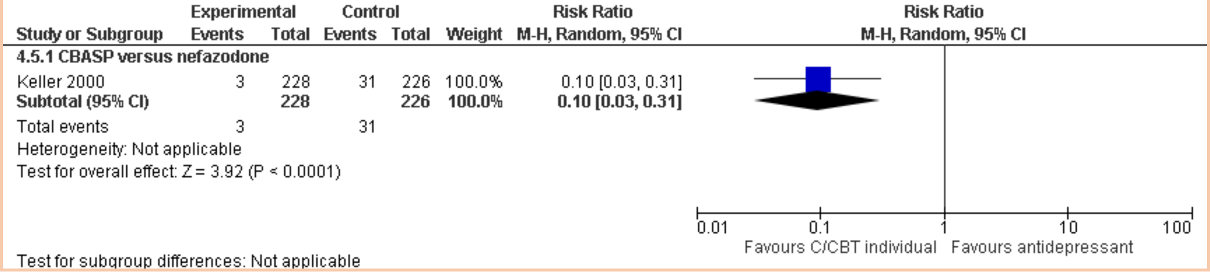
Discontinuation for any reason



	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
4.4.1 CBASP versus nefazodone						
Keller 2000	55	228	59	226	63.2%	0.92 [0.67, 1.27]
Subtotal (95% CI)		**228**		**226**	**63.2%**	**0.92 [0.67, 1.27]**
Total events	55		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
4.4.2 CBASP versus escitalopram						
Schramm 2015	2	29	5	31	12.7%	0.43 [0.09, 2.03]
Subtotal (95% CI)		**29**		**31**	**12.7%**	**0.43 [0.09, 2.03]**
Total events	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
4.4.3 CBT individual (over 15 sessions) versus fluoxetine						
Dunner 1996	6	18	3	13	19.6%	1.44 [0.44, 4.74]
Subtotal (95% CI)		**18**		**13**	**19.6%**	**1.44 [0.44, 4.74]**
Total events	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
4.4.4 CBT individual (over 15 sessions) versus imipramine						
Agosti 1997	0	16	6	20	4.5%	0.10 [0.01, 1.57]
Subtotal (95% CI)		**16**		**20**	**4.5%**	**0.10 [0.01, 1.57]**
Total events	0		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
Total (95% CI)		**291**		**290**	**100.0%**	**0.83 [0.45, 1.52]**
Total events	63		73			

Heterogeneity: $\text{Tau}^2 = 0.13$; $\text{Chi}^2 = 4.12$, df = 3 (P = 0.25); $I^2 = 27\%$
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: $\text{Chi}^2 = 3.98$, df = 3 (P = 0.26), $I^2 = 24.6\%$

Discontinuation due to adverse events

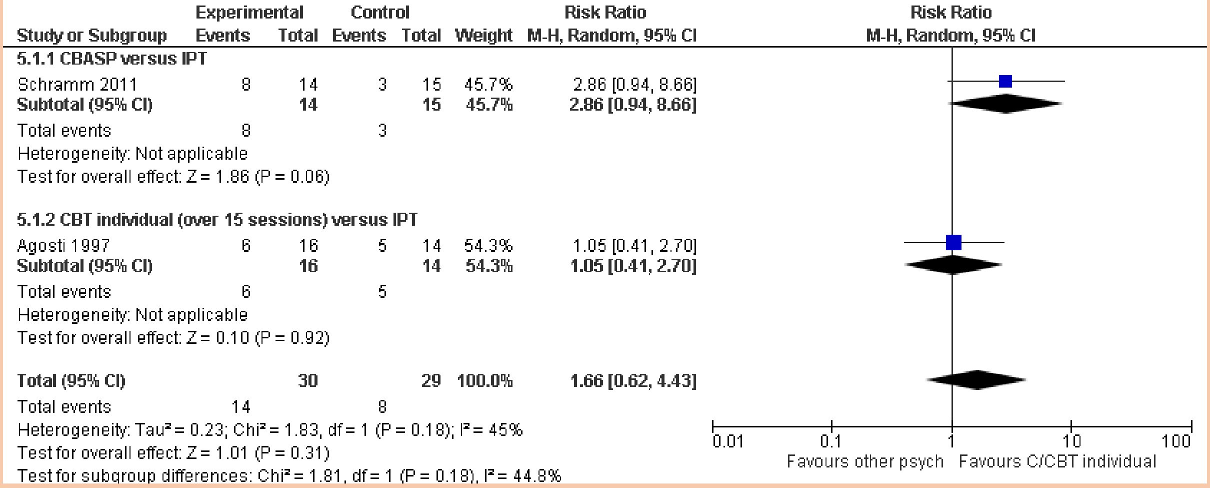


	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
4.5.1 CBASP versus nefazodone						
Keller 2000	3	228	31	226	100.0%	0.10 [0.03, 0.31]
Subtotal (95% CI)		**228**		**226**	**100.0%**	**0.10 [0.03, 0.31]**
Total events	3		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.92 (P < 0.0001)						

Test for subgroup differences: Not applicable

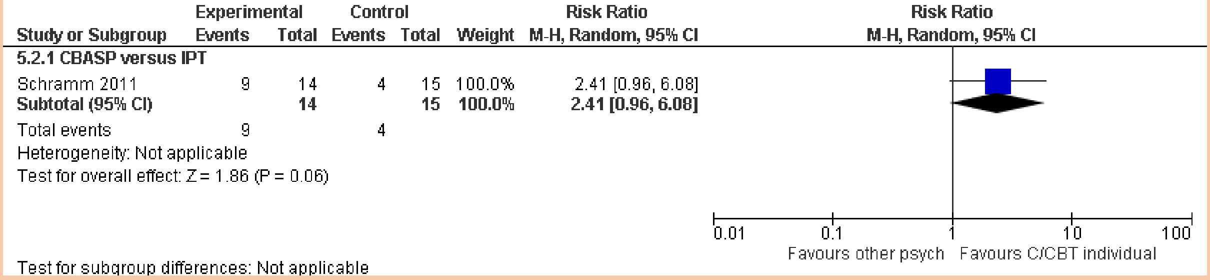
CBASP versus other psychological intervention for chronic depressive symptoms

Remission (score ≤8 on HAM-D)



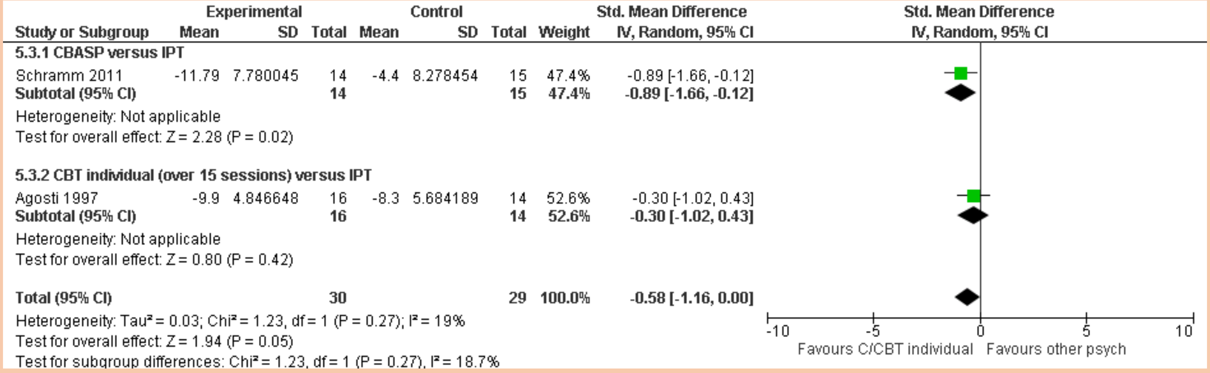
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 CBASP versus IPT						
Schramm 2011	8	14	3	15	45.7%	2.86 [0.94, 8.66]
Subtotal (95% CI)		**14**		**15**	**45.7%**	**2.86 [0.94, 8.66]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
5.1.2 CBT individual (over 15 sessions) versus IPT						
Agosti 1997	6	16	5	14	54.3%	1.05 [0.41, 2.70]
Subtotal (95% CI)		**16**		**14**	**54.3%**	**1.05 [0.41, 2.70]**
Total events	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**30**		**29**	**100.0%**	**1.66 [0.62, 4.43]**
Total events	14		8			
Heterogeneity: Tau² = 0.23; Chi² = 1.83, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 1.81, df = 1 (P = 0.18), I² = 44.8%						

Response (≥50% improvement on HAMD & HAMD score≤15/≥50% improvement on HAMD)



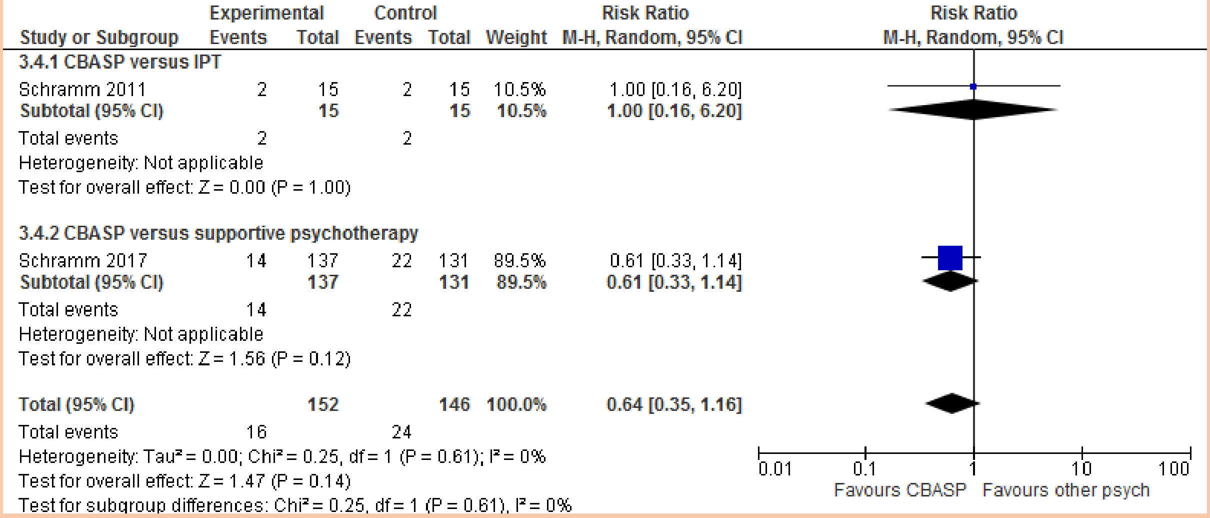
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 CBASP versus IPT						
Schramm 2011	9	14	4	15	100.0%	2.41 [0.96, 6.08]
Subtotal (95% CI)		**14**		**15**	**100.0%**	**2.41 [0.96, 6.08]**
Total events	9		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: Not applicable						

Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.3.1 CBASP versus IPT								
Schramm 2011	-11.79	7.780045	14	-4.4	8.278454	15	47.4%	-0.89 [-1.66, -0.12]
Subtotal (95% CI)			**14**			**15**	**47.4%**	**-0.89 [-1.66, -0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28 (P = 0.02)								
5.3.2 CBT individual (over 15 sessions) versus IPT								
Agosti 1997	-9.9	4.846648	16	-8.3	5.684189	14	52.6%	-0.30 [-1.02, 0.43]
Subtotal (95% CI)			**16**			**14**	**52.6%**	**-0.30 [-1.02, 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.80 (P = 0.42)								
Total (95% CI)			**30**			**29**	**100.0%**	**-0.58 [-1.16, 0.00]**
Heterogeneity: Tau² = 0.03; Chi² = 1.23, df = 1 (P = 0.27); I² = 19%								
Test for overall effect: Z = 1.94 (P = 0.05)								
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.7%								

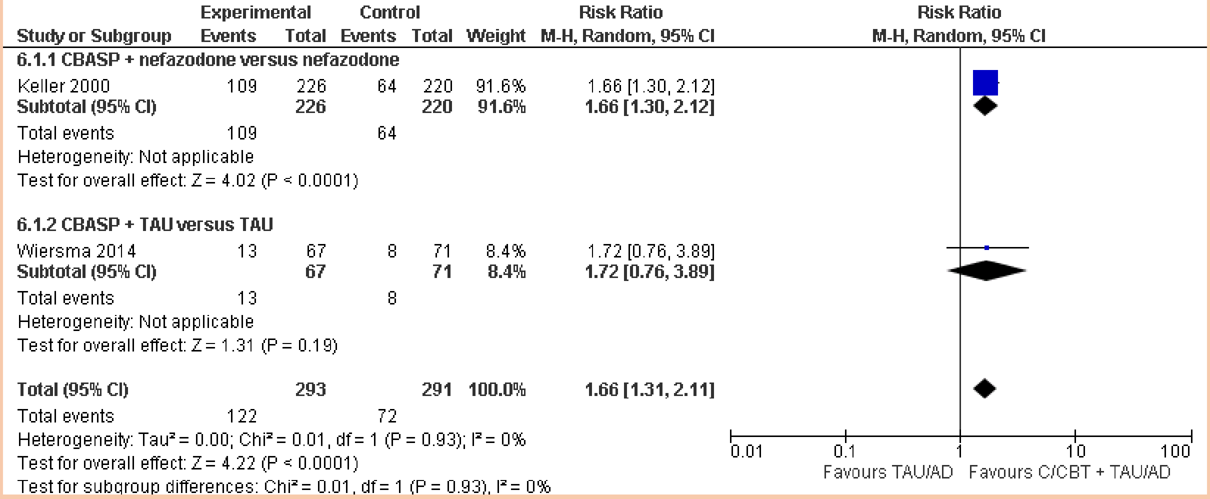
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 CBASP versus IPT						
Schramm 2011	2	15	2	15	10.5%	1.00 [0.16, 6.20]
Subtotal (95% CI)		**15**		**15**	**10.5%**	**1.00 [0.16, 6.20]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
3.4.2 CBASP versus supportive psychotherapy						
Schramm 2017	14	137	22	131	89.5%	0.61 [0.33, 1.14]
Subtotal (95% CI)		**137**		**131**	**89.5%**	**0.61 [0.33, 1.14]**
Total events	14		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)		**152**		**146**	**100.0%**	**0.64 [0.35, 1.16]**
Total events	16		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.61), I² = 0%						

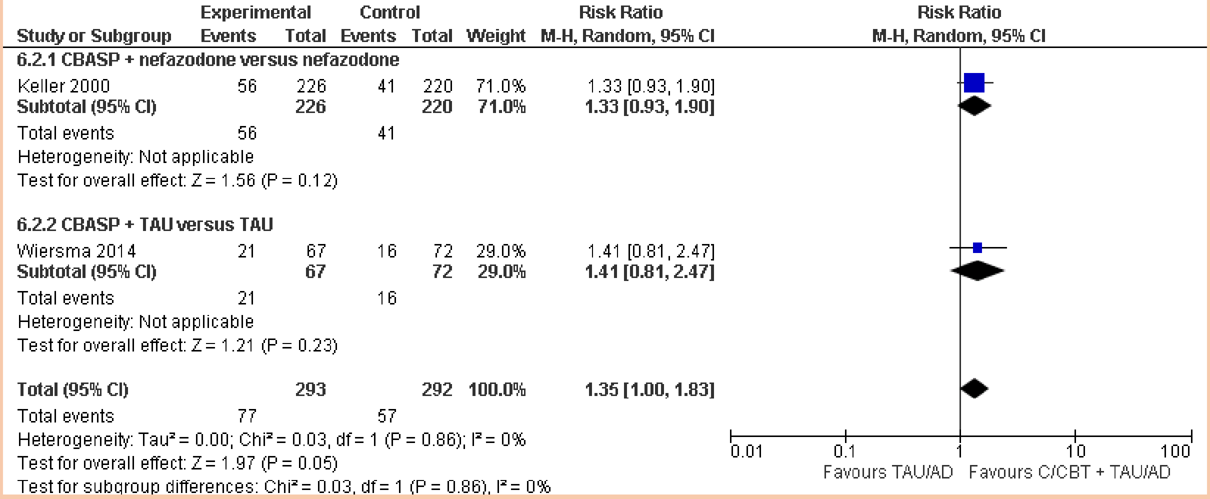
Cognitive and cognitive behavioural therapies + TAU/AD versus TAU/AD-only for chronic depressive symptoms

Remission (≤8 HAM-D/ ≤13 on IDS)



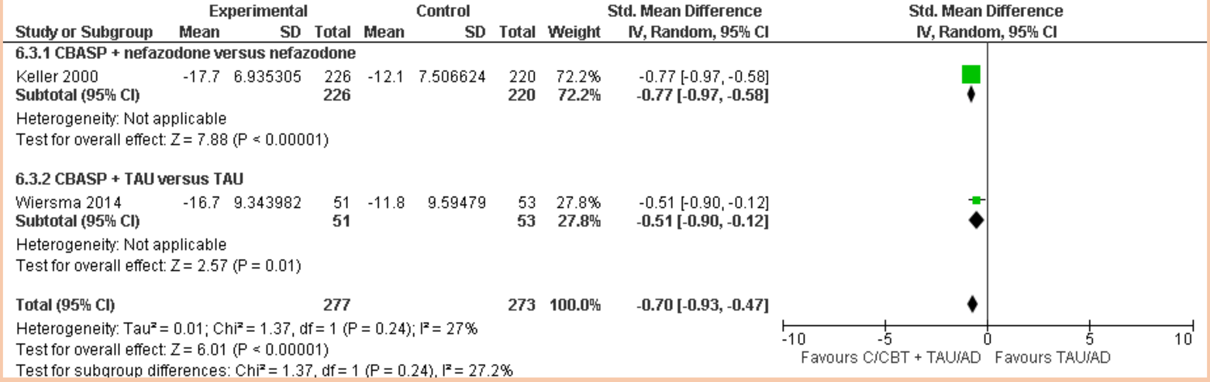
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 CBASP + nefazodone versus nefazodone						
Keller 2000	109	226	64	220	91.6%	1.66 [1.30, 2.12]
Subtotal (95% CI)		**226**		**220**	**91.6%**	**1.66 [1.30, 2.12]**
Total events	109		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.02 (P < 0.0001)						
6.1.2 CBASP + TAU versus TAU						
Wiersma 2014	13	67	8	71	8.4%	1.72 [0.76, 3.89]
Subtotal (95% CI)		**67**		**71**	**8.4%**	**1.72 [0.76, 3.89]**
Total events	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**293**		**291**	**100.0%**	**1.66 [1.31, 2.11]**
Total events	122		72			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 4.22 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						

Response (≥50% improvement on HAMD & HAMD score 8-15 [response without remission]/≥50% improvement on IDS)



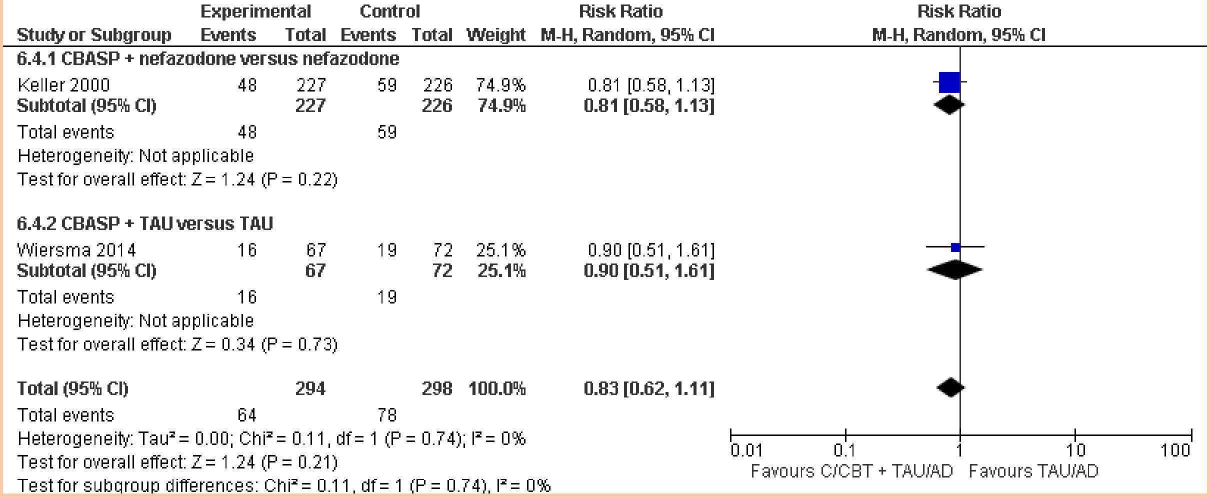
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 CBASP + nefazodone versus nefazodone						
Keller 2000	56	226	41	220	71.0%	1.33 [0.93, 1.90]
Subtotal (95% CI)		**226**		**220**	**71.0%**	**1.33 [0.93, 1.90]**
Total events	56		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						
6.2.2 CBASP + TAU versus TAU						
Wiersma 2014	21	67	16	72	29.0%	1.41 [0.81, 2.47]
Subtotal (95% CI)		**67**		**72**	**29.0%**	**1.41 [0.81, 2.47]**
Total events	21		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
Total (95% CI)		**293**		**292**	**100.0%**	**1.35 [1.00, 1.83]**
Total events	77		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						

Depression symptomatology (HAMD/IDS change score)



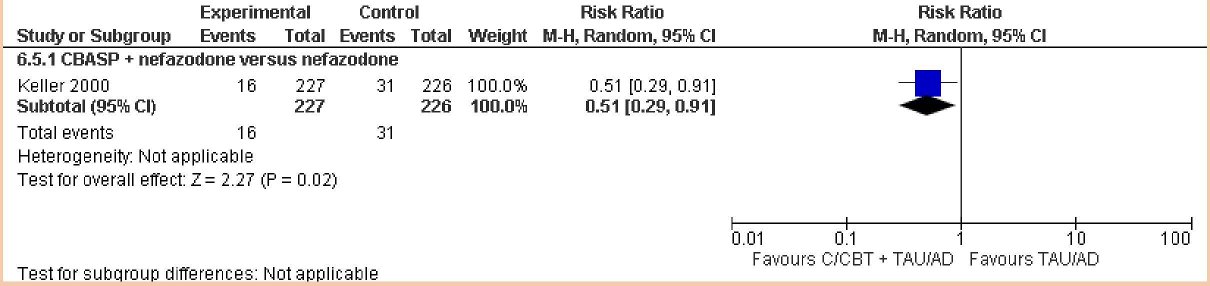
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
6.3.1 CBASP + nefazodone versus nefazodone								
Keller 2000	-17.7	6.935305	226	-12.1	7.506624	220	72.2%	-0.77 [-0.97, -0.58]
Subtotal (95% CI)			**226**			**220**	**72.2%**	**-0.77 [-0.97, -0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.88 (P < 0.00001)								
6.3.2 CBASP + TAU versus TAU								
Wiersma 2014	-16.7	9.343982	51	-11.8	9.59479	53	27.8%	-0.51 [-0.90, -0.12]
Subtotal (95% CI)			**51**			**53**	**27.8%**	**-0.51 [-0.90, -0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.57 (P = 0.01)								
Total (95% CI)			**277**			**273**	**100.0%**	**-0.70 [-0.93, -0.47]**
Heterogeneity: Tau² = 0.01; Chi² = 1.37, df = 1 (P = 0.24); I² = 27%								
Test for overall effect: Z = 6.01 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.37, df = 1 (P = 0.24), I² = 27.2%								

Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 CBASP + nefazodone versus nefazodone						
Keller 2000	48	227	59	226	74.9%	0.81 [0.58, 1.13]
Subtotal (95% CI)		**227**		**226**	**74.9%**	**0.81 [0.58, 1.13]**
Total events	48		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
6.4.2 CBASP + TAU versus TAU						
Wiersma 2014	16	67	19	72	25.1%	0.90 [0.51, 1.61]
Subtotal (95% CI)		**67**		**72**	**25.1%**	**0.90 [0.51, 1.61]**
Total events	16		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)		**294**		**298**	**100.0%**	**0.83 [0.62, 1.11]**
Total events	64		78			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						

Discontinuation due to adverse events



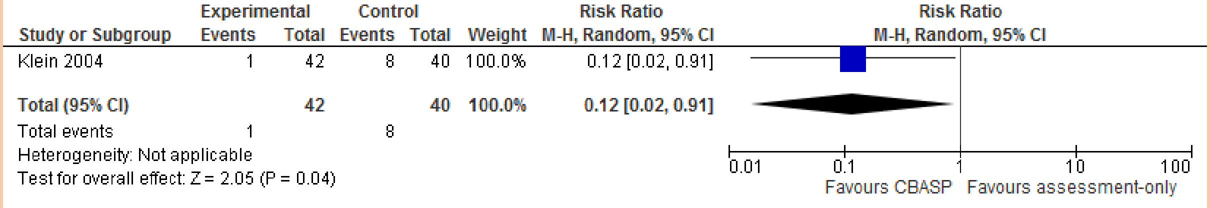
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 CBASP + nefazodone versus nefazodone						
Keller 2000	16	227	31	226	100.0%	0.51 [0.29, 0.91]
Subtotal (95% CI)		**227**		**226**	**100.0%**	**0.51 [0.29, 0.91]**
Total events	16		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)

Test for subgroup differences: Not applicable

CBASP (maintenance treatment) versus assessment-only for relapse prevention in chronic depressive symptoms

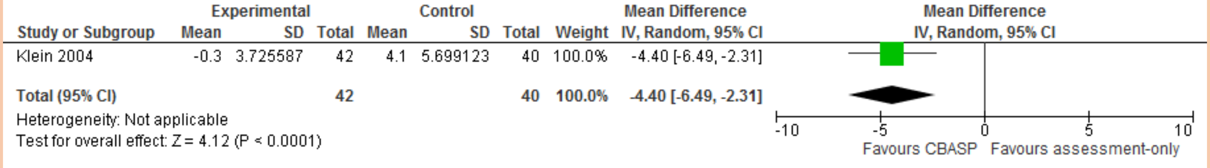
Relapse (score ≥16 on HAM-D on 2 consecutive visits & DSM-IV MDD diagnosis)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Klein 2004	1	42	8	40	100.0%	0.12 [0.02, 0.91]
Total (95% CI)		**42**		**40**	**100.0%**	**0.12 [0.02, 0.91]**
Total events	1		8			

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

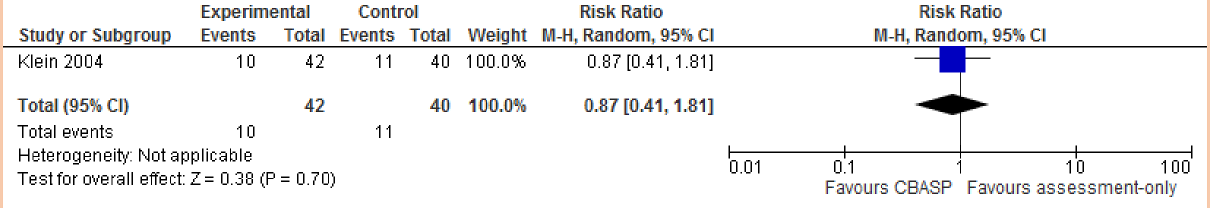
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Klein 2004	-0.3	3.725587	42	4.1	5.699123	40	100.0%	-4.40 [-6.49, -2.31]
Total (95% CI)			**42**			**40**	**100.0%**	**-4.40 [-6.49, -2.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.12 (P < 0.0001)

Discontinuation for any reason

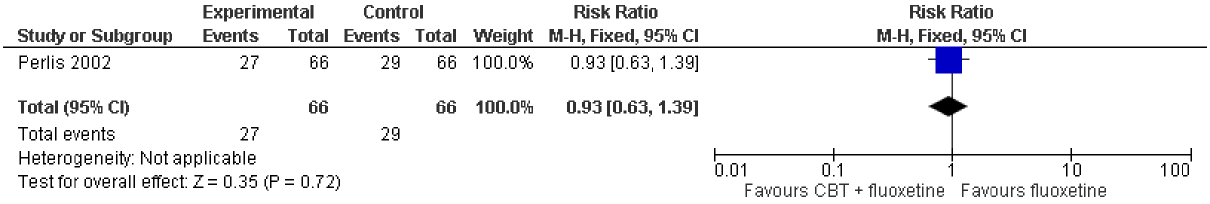


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Klein 2004	10	42	11	40	100.0%	0.87 [0.41, 1.81]
Total (95% CI)		**42**		**40**	**100.0%**	**0.87 [0.41, 1.81]**
Total events	10		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

CBT + fluoxetine (dose increase) versus fluoxetine (dose increase) for relapse prevention in chronic depressive symptoms

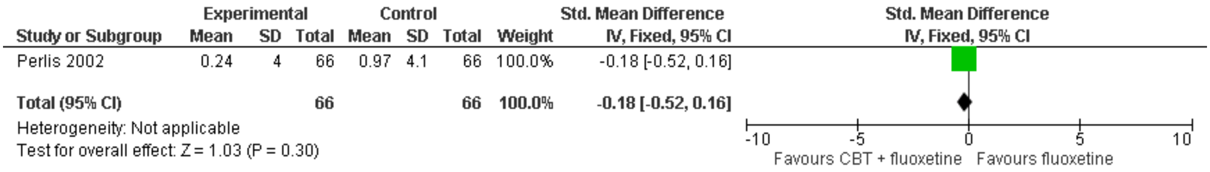
Relapse (≥15 on HAM-D on 2 consecutive visits or DSR-III-R MDD)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Perlis 2002	27	66	29	66	100.0%	0.93 [0.63, 1.39]
Total (95% CI)		**66**		**66**	**100.0%**	**0.93 [0.63, 1.39]**
Total events	27		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)

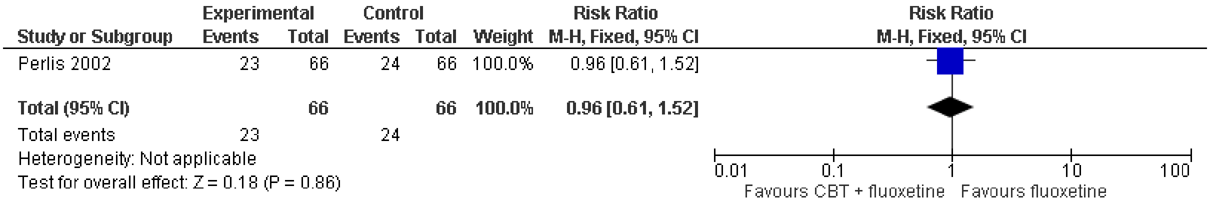
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Perlis 2002	0.24	4	66	0.97	4.1	66	100.0%	-0.18 [-0.52, 0.16]
Total (95% CI)			**66**			**66**	**100.0%**	**-0.18 [-0.52, 0.16]**

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

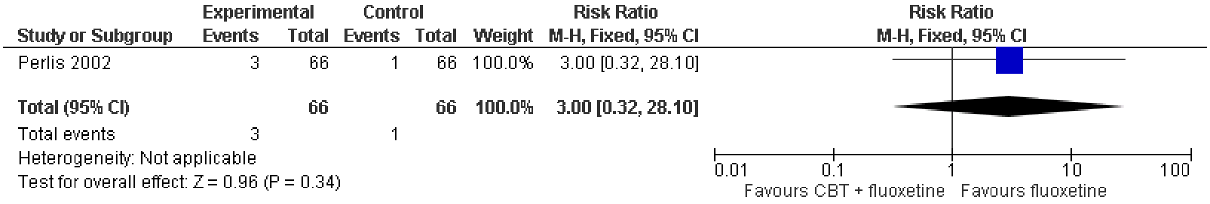
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Perlis 2002	23	66	24	66	100.0%	0.96 [0.61, 1.52]
Total (95% CI)		**66**		**66**	**100.0%**	**0.96 [0.61, 1.52]**
Total events	23		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

Discontinuation due to adverse events

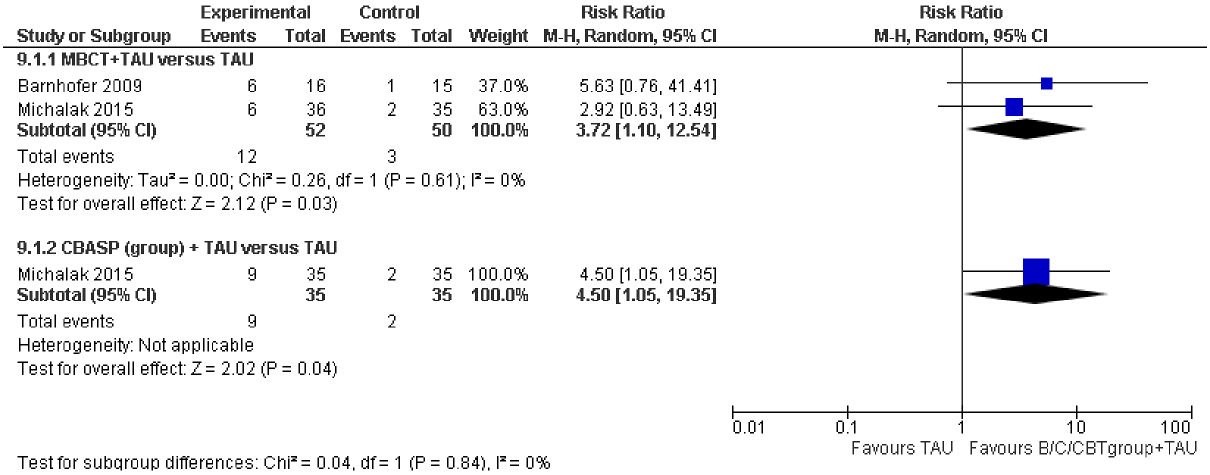


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Perlis 2002	3	66	1	66	100.0%	3.00 [0.32, 28.10]
Total (95% CI)		**66**		**66**	**100.0%**	**3.00 [0.32, 28.10]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

Behavioural, cognitive, or CBT groups + TAU/AD versus TAU/AD only for chronic depressive symptoms

Remission (≤13 on BDI-II & ≥ 50% improvement on BDI-II/<7 on HAMD)



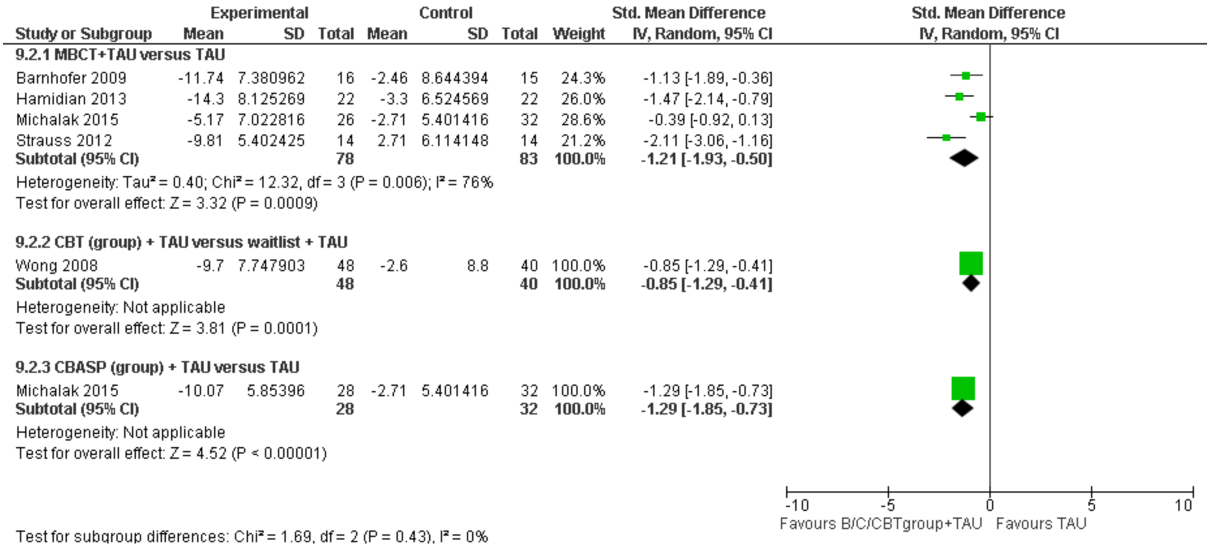
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 MBCT+TAU versus TAU						
Barnhofer 2009	6	16	1	15	37.0%	5.63 [0.76, 41.41]
Michalak 2015	6	36	2	35	63.0%	2.92 [0.63, 13.49]
Subtotal (95% CI)		**52**		**50**	**100.0%**	**3.72 [1.10, 12.54]**
Total events	12		3			
9.1.2 CBASP (group) + TAU versus TAU						
Michalak 2015	9	35	2	35	100.0%	4.50 [1.05, 19.35]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**4.50 [1.05, 19.35]**
Total events	9		2			

9.1.1: Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)

9.1.2: Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)

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

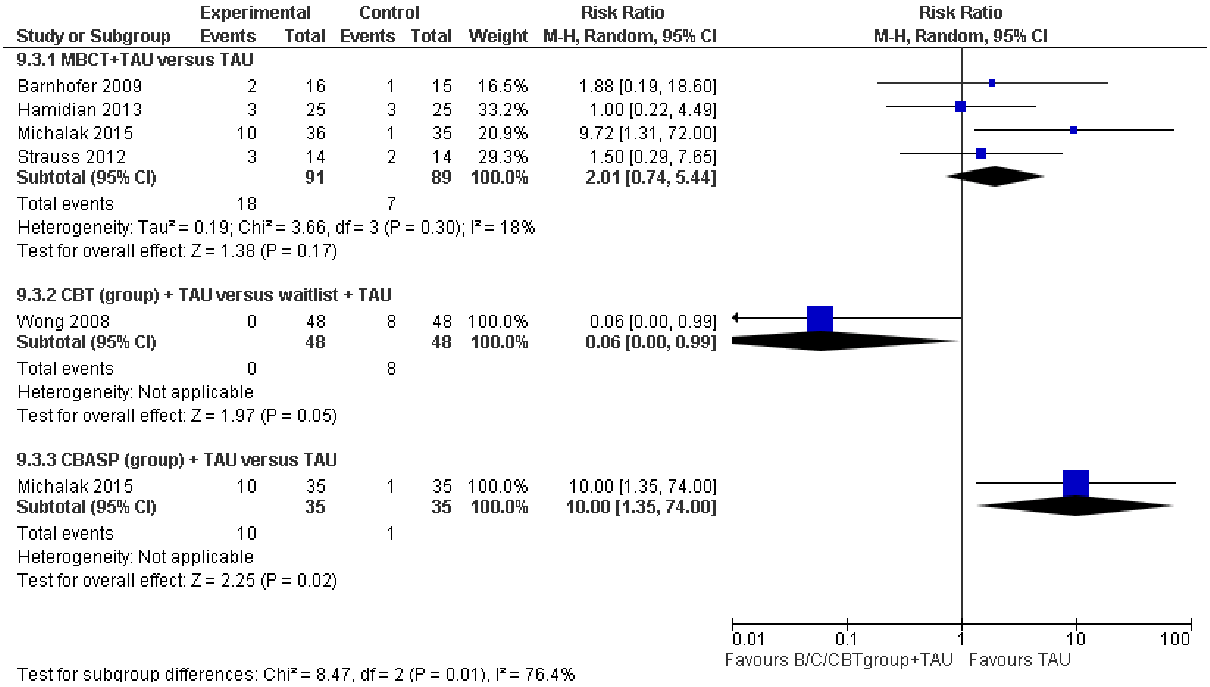
Depression symptomatology (BDI/BDI-II /HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
9.2.1 MBCT+TAU versus TAU								
Barnhofer 2009	-11.74	7.380962	16	-2.46	8.644394	15	24.3%	-1.13 [-1.89, -0.36]
Hamidian 2013	-14.3	8.125269	22	-3.3	6.524569	22	26.0%	-1.47 [-2.14, -0.79]
Michalak 2015	-5.17	7.022816	26	-2.71	5.401416	32	28.6%	-0.39 [-0.92, 0.13]
Strauss 2012	-9.81	5.402425	14	2.71	6.114148	14	21.2%	-2.11 [-3.06, -1.16]
Subtotal (95% CI)			**78**			**83**	**100.0%**	**-1.21 [-1.93, -0.50]**
Heterogeneity: Tau² = 0.40; Chi² = 12.32, df = 3 (P = 0.006); I² = 76%								
Test for overall effect: Z = 3.32 (P = 0.0009)								
9.2.2 CBT (group) + TAU versus waitlist + TAU								
Wong 2008	-9.7	7.747903	48	-2.6	8.8	40	100.0%	-0.85 [-1.29, -0.41]
Subtotal (95% CI)			**48**			**40**	**100.0%**	**-0.85 [-1.29, -0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.81 (P = 0.0001)								
9.2.3 CBASP (group) + TAU versus TAU								
Michalak 2015	-10.07	5.85396	28	-2.71	5.401416	32	100.0%	-1.29 [-1.85, -0.73]
Subtotal (95% CI)			**28**			**32**	**100.0%**	**-1.29 [-1.85, -0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.52 (P < 0.00001)								

Test for subgroup differences: Chi² = 1.69, df = 2 (P = 0.43), I² = 0%

Discontinuation for any reason

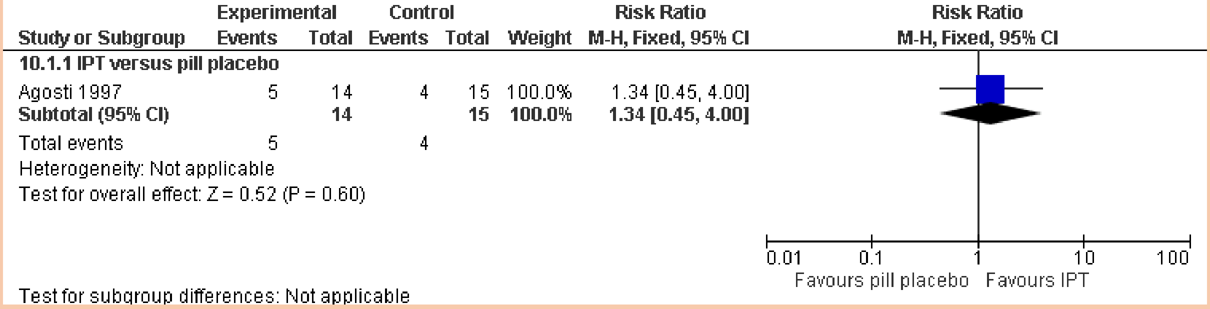


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.3.1 MBCT+TAU versus TAU						
Barnhofer 2009	2	16	1	15	16.5%	1.88 [0.19, 18.60]
Hamidian 2013	3	25	3	25	33.2%	1.00 [0.22, 4.49]
Michalak 2015	10	36	1	35	20.9%	9.72 [1.31, 72.00]
Strauss 2012	3	14	2	14	29.3%	1.50 [0.29, 7.65]
Subtotal (95% CI)		**91**		**89**	**100.0%**	**2.01 [0.74, 5.44]**
Total events	18		7			
Heterogeneity: Tau² = 0.19; Chi² = 3.66, df = 3 (P = 0.30); I² = 18%						
Test for overall effect: Z = 1.38 (P = 0.17)						
9.3.2 CBT (group) + TAU versus waitlist + TAU						
Wong 2008	0	48	8	48	100.0%	0.06 [0.00, 0.99]
Subtotal (95% CI)		**48**		**48**	**100.0%**	**0.06 [0.00, 0.99]**
Total events	0		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
9.3.3 CBASP (group) + TAU versus TAU						
Michalak 2015	10	35	1	35	100.0%	10.00 [1.35, 74.00]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**10.00 [1.35, 74.00]**
Total events	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						

Test for subgroup differences: Chi² = 8.47, df = 2 (P = 0.01), I² = 76.4%

IPT versus pill placebo for chronic depressive symptoms

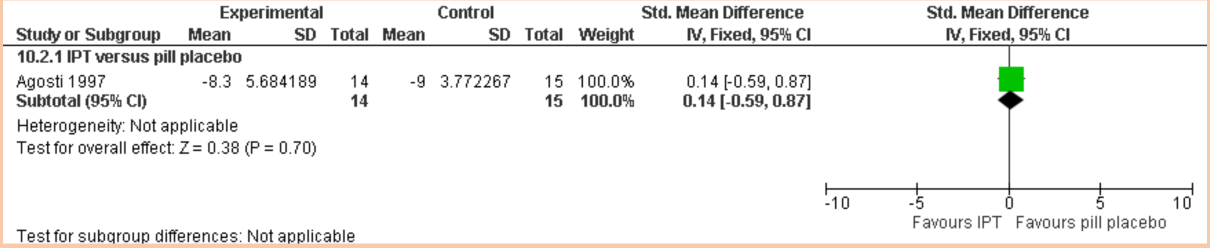
Remission (HAM-D <7)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 IPT versus pill placebo						
Agosti 1997	5	14	4	15	100.0%	1.34 [0.45, 4.00]
Subtotal (95% CI)		**14**		**15**	**100.0%**	**1.34 [0.45, 4.00]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						

Test for subgroup differences: Not applicable

Depression symptomatology (HAM-D change score)

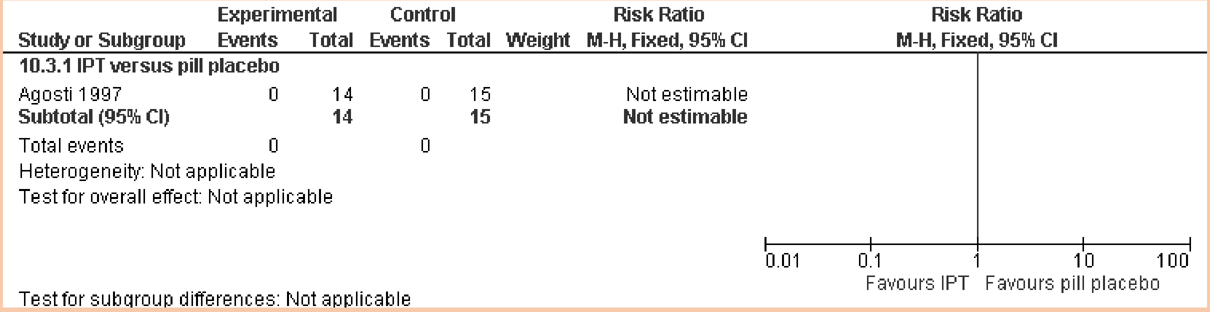


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
10.2.1 IPT versus pill placebo								
Agosti 1997	-8.3	5.684189	14	-9	3.772267	15	100.0%	0.14 [-0.59, 0.87]
Subtotal (95% CI)			**14**			**15**	**100.0%**	**0.14 [-0.59, 0.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable

Discontinuation for any reason



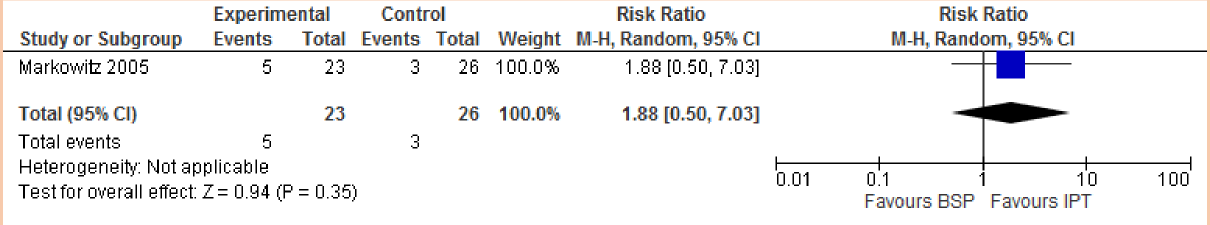
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.3.1 IPT versus pill placebo						
Agosti 1997	0	14	0	15		Not estimable
Subtotal (95% CI)		**14**		**15**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Test for subgroup differences: Not applicable

IPT versus brief supportive psychotherapy (BSP) for chronic depressive symptoms

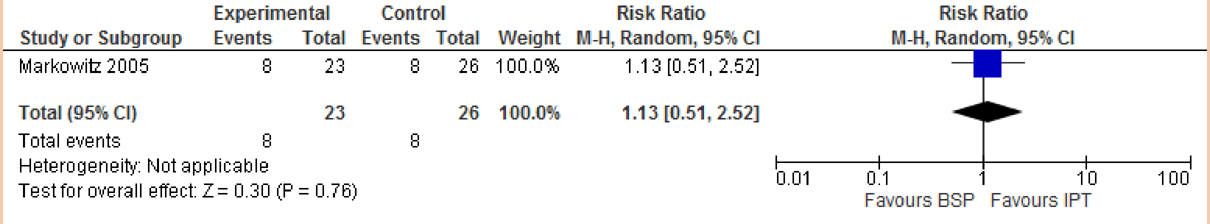
Remission (score <7 on HAM-D & >50% improvement on HAMD & GAF score>70)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	5	23	3	26	100.0%	1.88 [0.50, 7.03]
Total (95% CI)		**23**		**26**	**100.0%**	**1.88 [0.50, 7.03]**
Total events	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

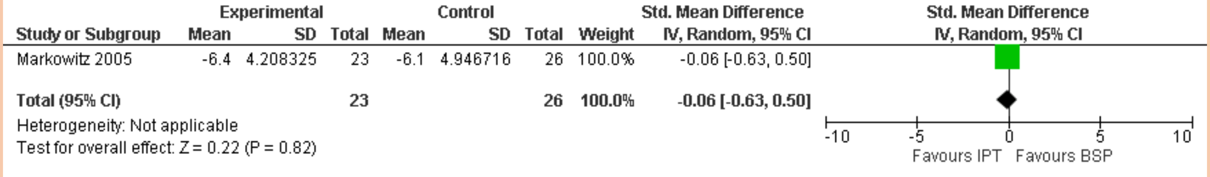
Response (≥50% improvement on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	8	23	8	26	100.0%	1.13 [0.51, 2.52]
Total (95% CI)		**23**		**26**	**100.0%**	**1.13 [0.51, 2.52]**
Total events	8		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)

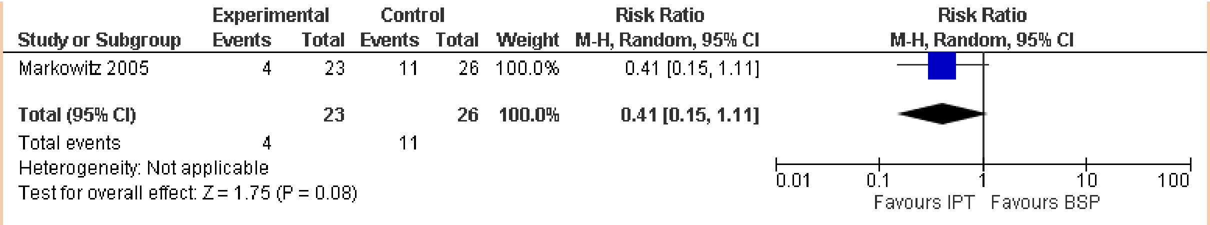
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Markowitz 2005	-6.4	4.208325	23	-6.1	4.946716	26	100.0%	-0.06 [-0.63, 0.50]
Total (95% CI)			**23**			**26**	**100.0%**	**-0.06 [-0.63, 0.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)

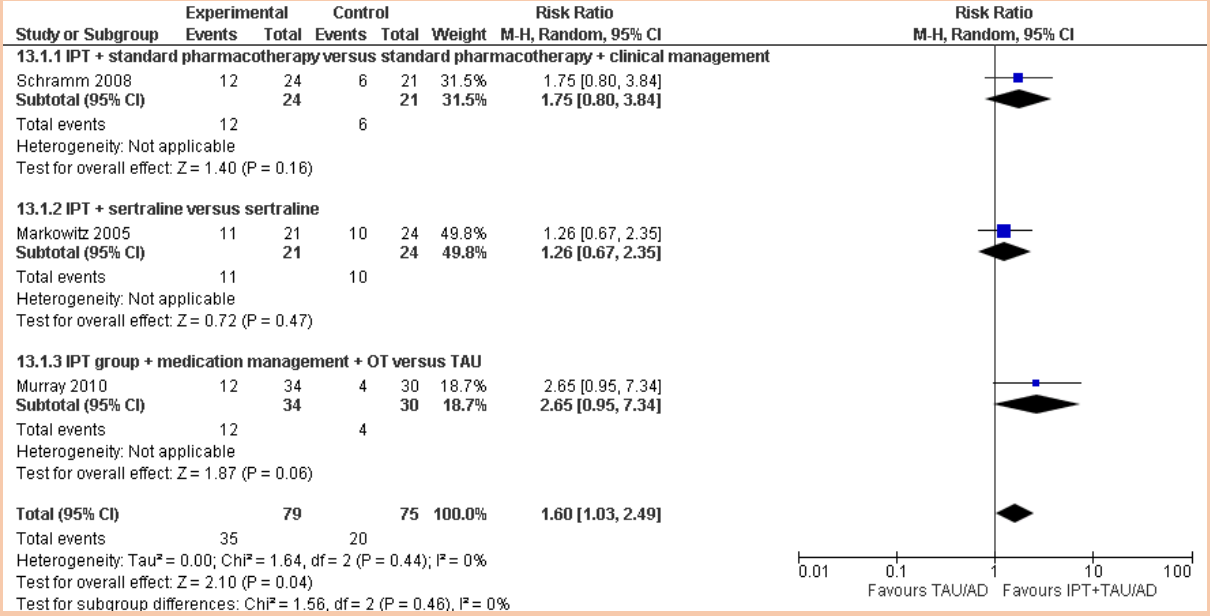
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	4	23	11	26	100.0%	0.41 [0.15, 1.11]
Total (95% CI)		**23**		**26**	**100.0%**	**0.41 [0.15, 1.11]**
Total events	4		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						

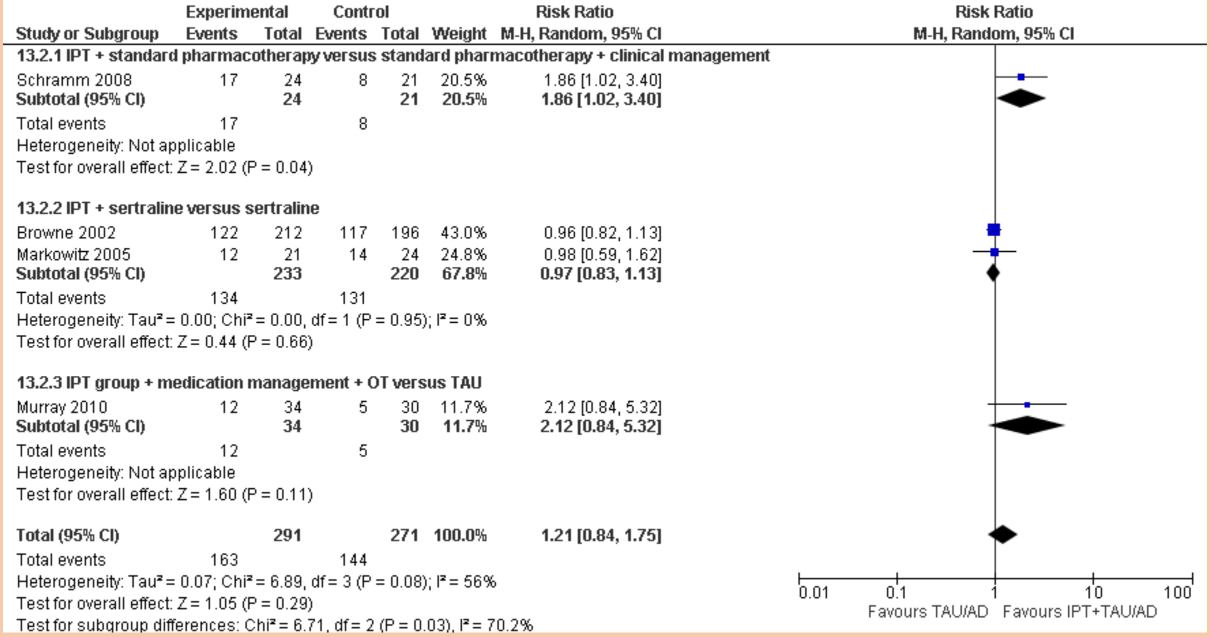
IPT + TAU/AD versus TAU/AD-only for chronic depressive symptoms

Remission (score ≤7 on HAM-D/score <7 on HAM-D & >50% improvement on HAMD & GAF score>70)



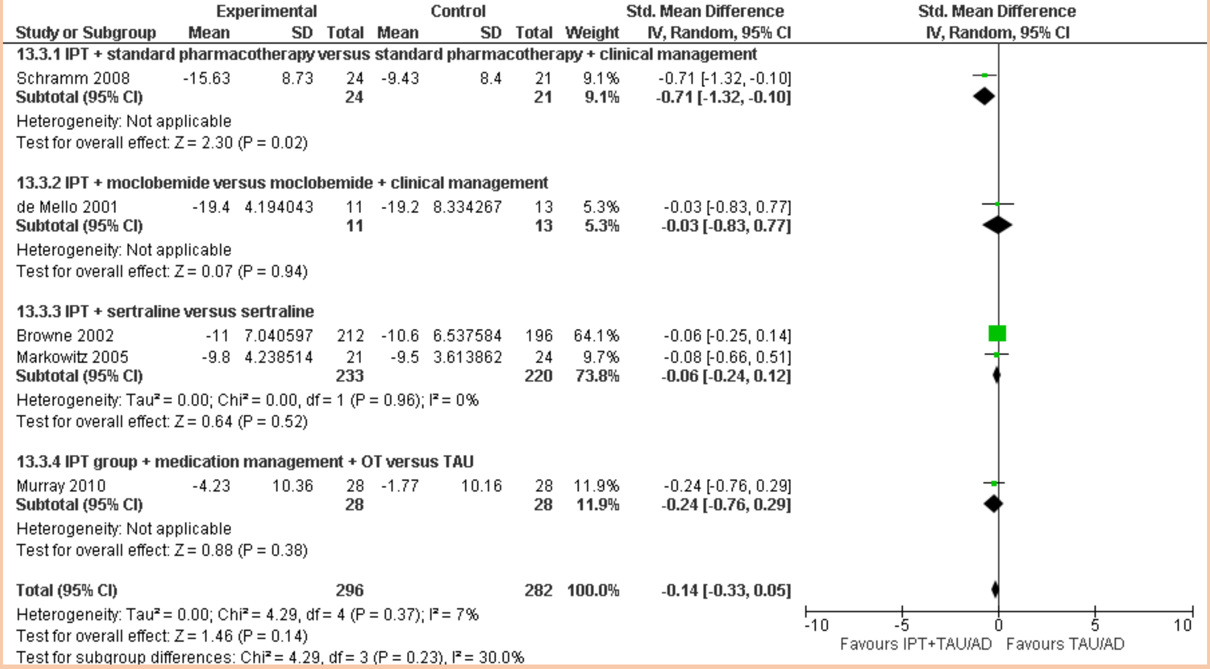
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 IPT + standard pharmacotherapy versus standard pharmacotherapy + clinical management						
Schramm 2008	12	24	6	21	31.5%	1.75 [0.80, 3.84]
Subtotal (95% CI)		**24**		**21**	**31.5%**	**1.75 [0.80, 3.84]**
Total events	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
13.1.2 IPT + sertraline versus sertraline						
Markowitz 2005	11	21	10	24	49.8%	1.26 [0.67, 2.35]
Subtotal (95% CI)		**21**		**24**	**49.8%**	**1.26 [0.67, 2.35]**
Total events	11		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
13.1.3 IPT group + medication management + OT versus TAU						
Murray 2010	12	34	4	30	18.7%	2.65 [0.95, 7.34]
Subtotal (95% CI)		**34**		**30**	**18.7%**	**2.65 [0.95, 7.34]**
Total events	12		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
Total (95% CI)		**79**		**75**	**100.0%**	**1.60 [1.03, 2.49]**
Total events	35		20			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.64, df = 2 (P = 0.44); I^2 = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
Test for subgroup differences: Chi^2 = 1.56, df = 2 (P = 0.46), I^2 = 0%						

Response (≥50% improvement on HAM-D/≥40% improvement on MADRS)



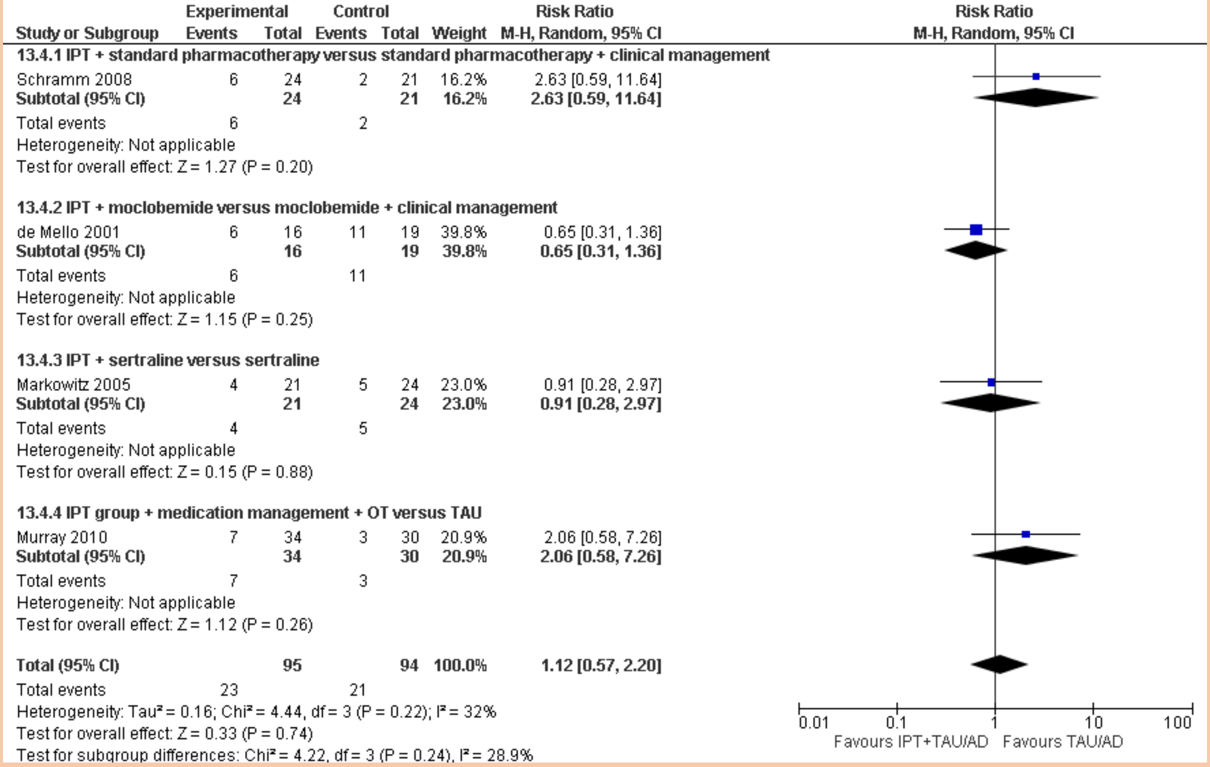
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.2.1 IPT + standard pharmacotherapy versus standard pharmacotherapy + clinical management						
Schramm 2008	17	24	8	21	20.5%	1.86 [1.02, 3.40]
Subtotal (95% CI)		**24**		**21**	**20.5%**	**1.86 [1.02, 3.40]**
Total events	17		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
13.2.2 IPT + sertraline versus sertraline						
Browne 2002	122	212	117	196	43.0%	0.96 [0.82, 1.13]
Markowitz 2005	12	21	14	24	24.8%	0.98 [0.59, 1.62]
Subtotal (95% CI)		**233**		**220**	**67.8%**	**0.97 [0.83, 1.13]**
Total events	134		131			
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
13.2.3 IPT group + medication management + OT versus TAU						
Murray 2010	12	34	5	30	11.7%	2.12 [0.84, 5.32]
Subtotal (95% CI)		**34**		**30**	**11.7%**	**2.12 [0.84, 5.32]**
Total events	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						
Total (95% CI)		**291**		**271**	**100.0%**	**1.21 [0.84, 1.75]**
Total events	163		144			
Heterogeneity: Tau^2 = 0.07; Chi^2 = 6.89, df = 3 (P = 0.08); I^2 = 56%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: Chi^2 = 6.71, df = 2 (P = 0.03), I^2 = 70.2%						

Depression symptomatology (HAMD/MADRS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
13.3.1 IPT + standard pharmacotherapy versus standard pharmacotherapy + clinical management								
Schramm 2008	-15.63	8.73	24	-9.43	8.4	21	9.1%	-0.71 [-1.32, -0.10]
Subtotal (95% CI)			**24**			**21**	**9.1%**	**-0.71 [-1.32, -0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.30 (P = 0.02)								
13.3.2 IPT + moclobemide versus moclobemide + clinical management								
de Mello 2001	-19.4	4.194043	11	-19.2	8.334267	13	5.3%	-0.03 [-0.83, 0.77]
Subtotal (95% CI)			**11**			**13**	**5.3%**	**-0.03 [-0.83, 0.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.94)								
13.3.3 IPT + sertraline versus sertraline								
Browne 2002	-11	7.040597	212	-10.6	6.537584	196	64.1%	-0.06 [-0.25, 0.14]
Markowitz 2005	-9.8	4.238514	21	-9.5	3.613862	24	9.7%	-0.08 [-0.66, 0.51]
Subtotal (95% CI)			**233**			**220**	**73.8%**	**-0.06 [-0.24, 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%								
Test for overall effect: Z = 0.64 (P = 0.52)								
13.3.4 IPT group + medication management + OT versus TAU								
Murray 2010	-4.23	10.36	28	-1.77	10.16	28	11.9%	-0.24 [-0.76, 0.29]
Subtotal (95% CI)			**28**			**28**	**11.9%**	**-0.24 [-0.76, 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.88 (P = 0.38)								
Total (95% CI)			**296**			**282**	**100.0%**	**-0.14 [-0.33, 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 4.29, df = 4 (P = 0.37); I² = 7%								
Test for overall effect: Z = 1.46 (P = 0.14)								
Test for subgroup differences: Chi² = 4.29, df = 3 (P = 0.23), I² = 30.0%								

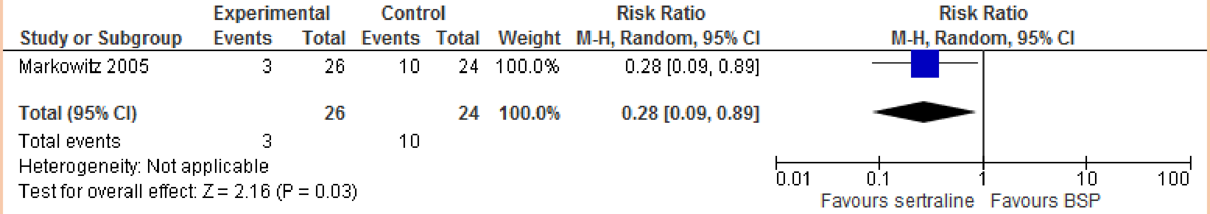
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.4.1 IPT + standard pharmacotherapy versus standard pharmacotherapy + clinical management						
Schramm 2008	6	24	2	21	16.2%	2.63 [0.59, 11.64]
Subtotal (95% CI)		**24**		**21**	**16.2%**	**2.63 [0.59, 11.64]**
Total events	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
13.4.2 IPT + moclobemide versus moclobemide + clinical management						
de Mello 2001	6	16	11	19	39.8%	0.65 [0.31, 1.36]
Subtotal (95% CI)		**16**		**19**	**39.8%**	**0.65 [0.31, 1.36]**
Total events	6		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
13.4.3 IPT + sertraline versus sertraline						
Markowitz 2005	4	21	5	24	23.0%	0.91 [0.28, 2.97]
Subtotal (95% CI)		**21**		**24**	**23.0%**	**0.91 [0.28, 2.97]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
13.4.4 IPT group + medication management + OT versus TAU						
Murray 2010	7	34	3	30	20.9%	2.06 [0.58, 7.26]
Subtotal (95% CI)		**34**		**30**	**20.9%**	**2.06 [0.58, 7.26]**
Total events	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**95**		**94**	**100.0%**	**1.12 [0.57, 2.20]**
Total events	23		21			
Heterogeneity: Tau² = 0.16; Chi² = 4.44, df = 3 (P = 0.22); I² = 32%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Chi² = 4.22, df = 3 (P = 0.24), I² = 28.9%						

Brief supportive psychotherapy (BSP) versus sertraline for chronic depressive symptoms

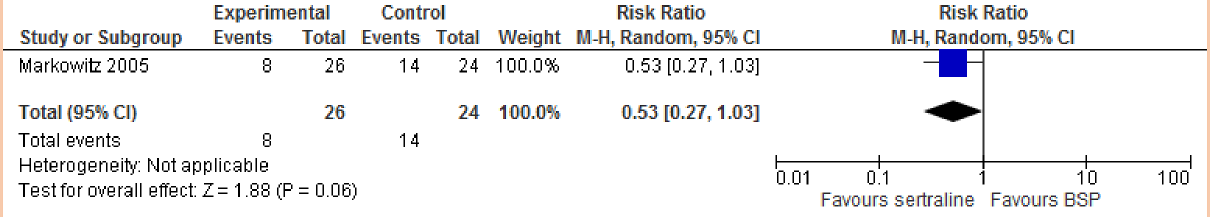
Remission (score <7 on HAM-D & >50% improvement on HAMD & GAF score>70)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	3	26	10	24	100.0%	0.28 [0.09, 0.89]
Total (95% CI)		**26**		**24**	**100.0%**	**0.28 [0.09, 0.89]**
Total events	3		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.16 (P = 0.03)

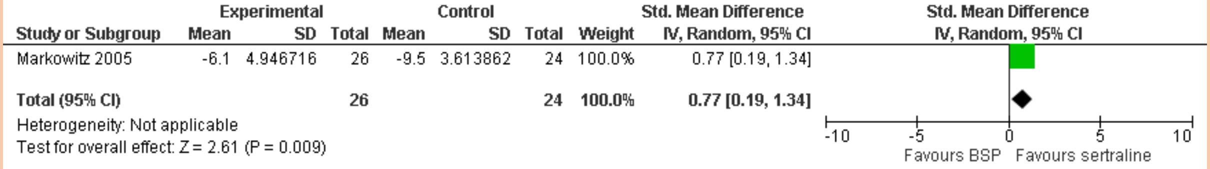
Response (≥50% improvement on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	8	26	14	24	100.0%	0.53 [0.27, 1.03]
Total (95% CI)		**26**		**24**	**100.0%**	**0.53 [0.27, 1.03]**
Total events	8		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)

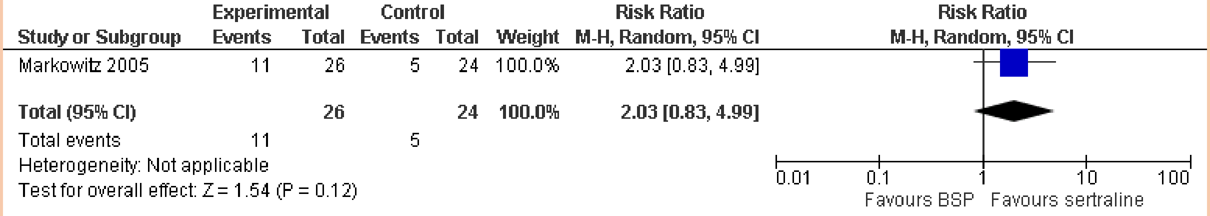
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Markowitz 2005	-6.1	4.946716	26	-9.5	3.613862	24	100.0%	0.77 [0.19, 1.34]
Total (95% CI)			**26**			**24**	**100.0%**	**0.77 [0.19, 1.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)

Discontinuation for any reason

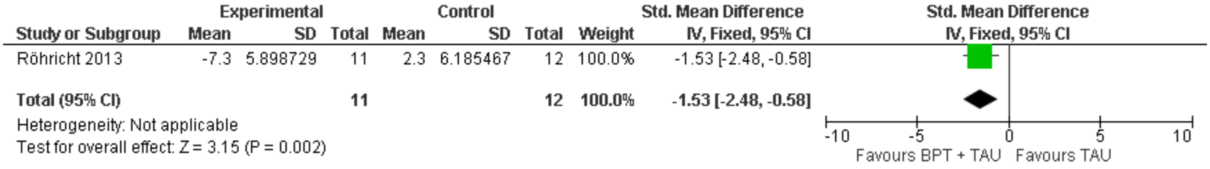


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	11	26	5	24	100.0%	2.03 [0.83, 4.99]
Total (95% CI)		**26**		**24**	**100.0%**	**2.03 [0.83, 4.99]**
Total events	11		5			

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

Body psychotherapy (BPT) + TAU versus TAU for chronic depressive symptoms

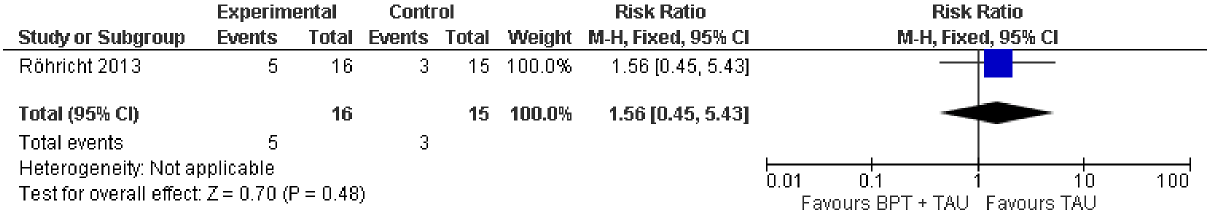
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Röhricht 2013	-7.3	5.898729	11	2.3	6.185467	12	100.0%	-1.53 [-2.48, -0.58]
Total (95% CI)			**11**			**12**	**100.0%**	**-1.53 [-2.48, -0.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.15 (P = 0.002)

Discontinuation for any reason

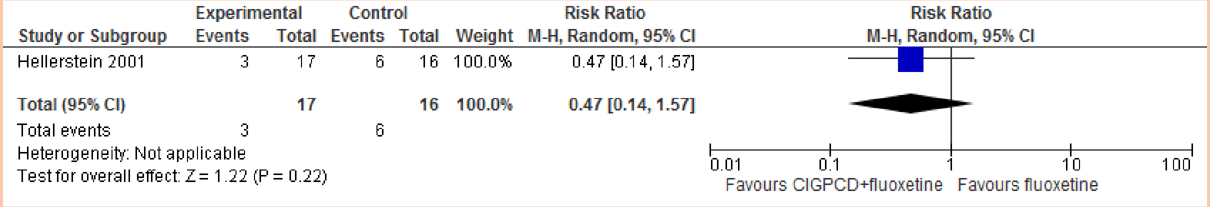


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Röhricht 2013	5	16	3	15	100.0%	1.56 [0.45, 5.43]
Total (95% CI)		**16**		**15**	**100.0%**	**1.56 [0.45, 5.43]**
Total events	5		3			

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

Cognitive-Interpersonal Group Psychotherapy for Chronic Depression (CIGP-CD) + fluoxetine versus fluoxetine (maintenance treatment) for relapse prevention in dysthymia

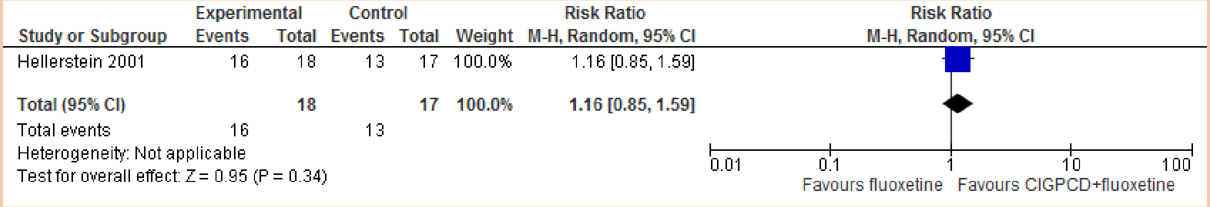
Relapse (score >0 on item #1 (depressed mood) on HAM-D OR meeting DSM-IV criteria for a diagnosis of dysthymia)



	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Hellerstein 2001	3	17	6	16	100.0%	0.47 [0.14, 1.57]
Total (95% CI)		**17**		**16**	**100.0%**	**0.47 [0.14, 1.57]**
Total events	3		6			

Heterogeneity: Not applicable
Test for overall effect: $Z = 1.22$ ($P = 0.22$)

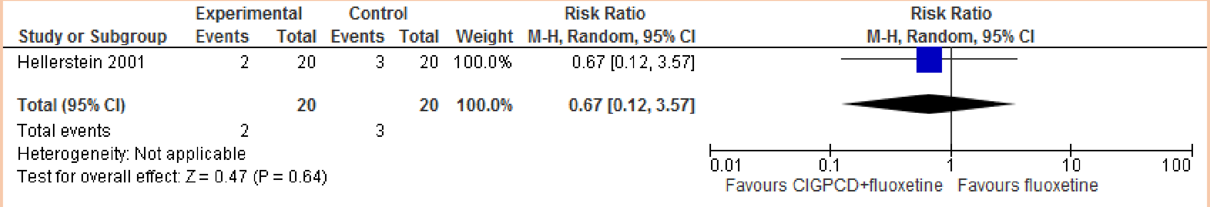
Response (≥50% improvement on HAM-D & much/very much improved on CGI-I)



	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Hellerstein 2001	16	18	13	17	100.0%	1.16 [0.85, 1.59]
Total (95% CI)		**18**		**17**	**100.0%**	**1.16 [0.85, 1.59]**
Total events	16		13			

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.95$ ($P = 0.34$)

Discontinuation for any reason

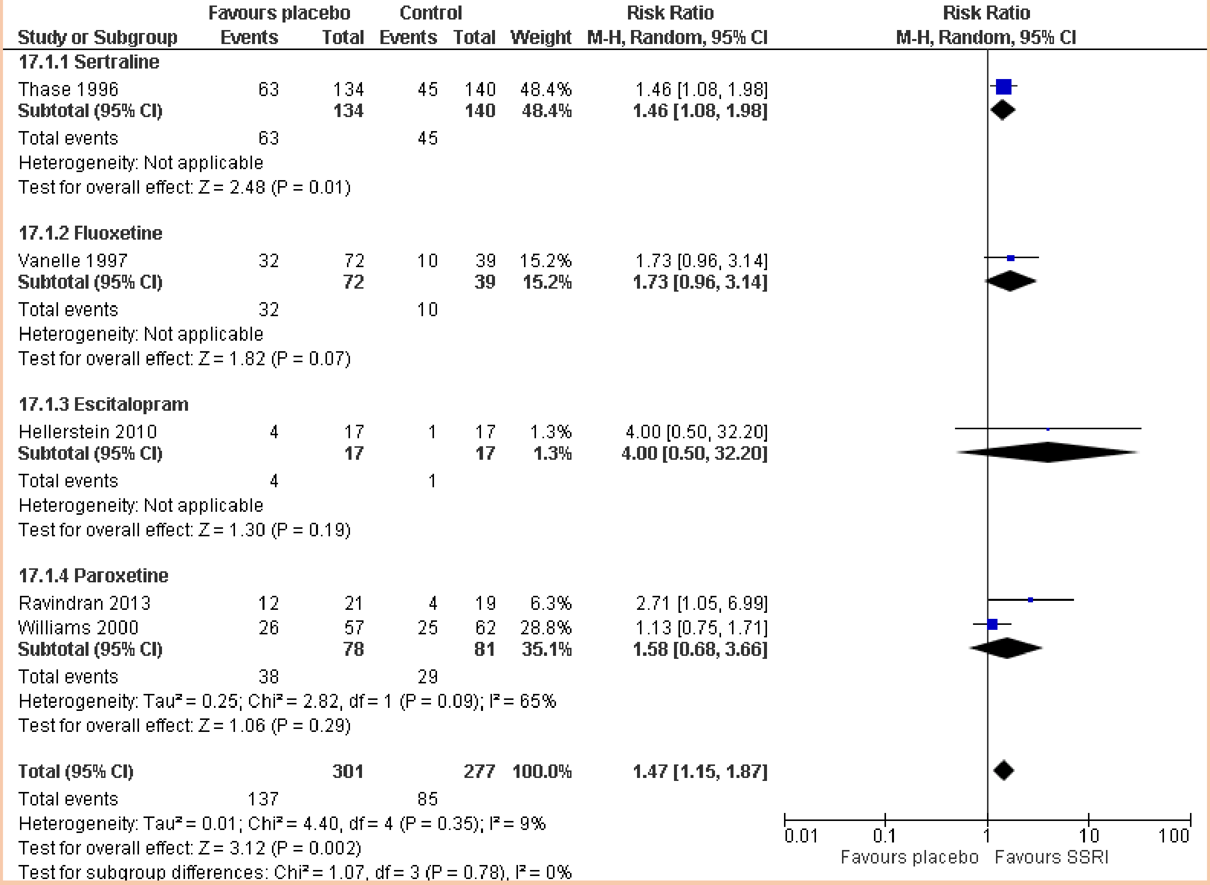


	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Hellerstein 2001	2	20	3	20	100.0%	0.67 [0.12, 3.57]
Total (95% CI)		**20**		**20**	**100.0%**	**0.67 [0.12, 3.57]**
Total events	2		3			

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

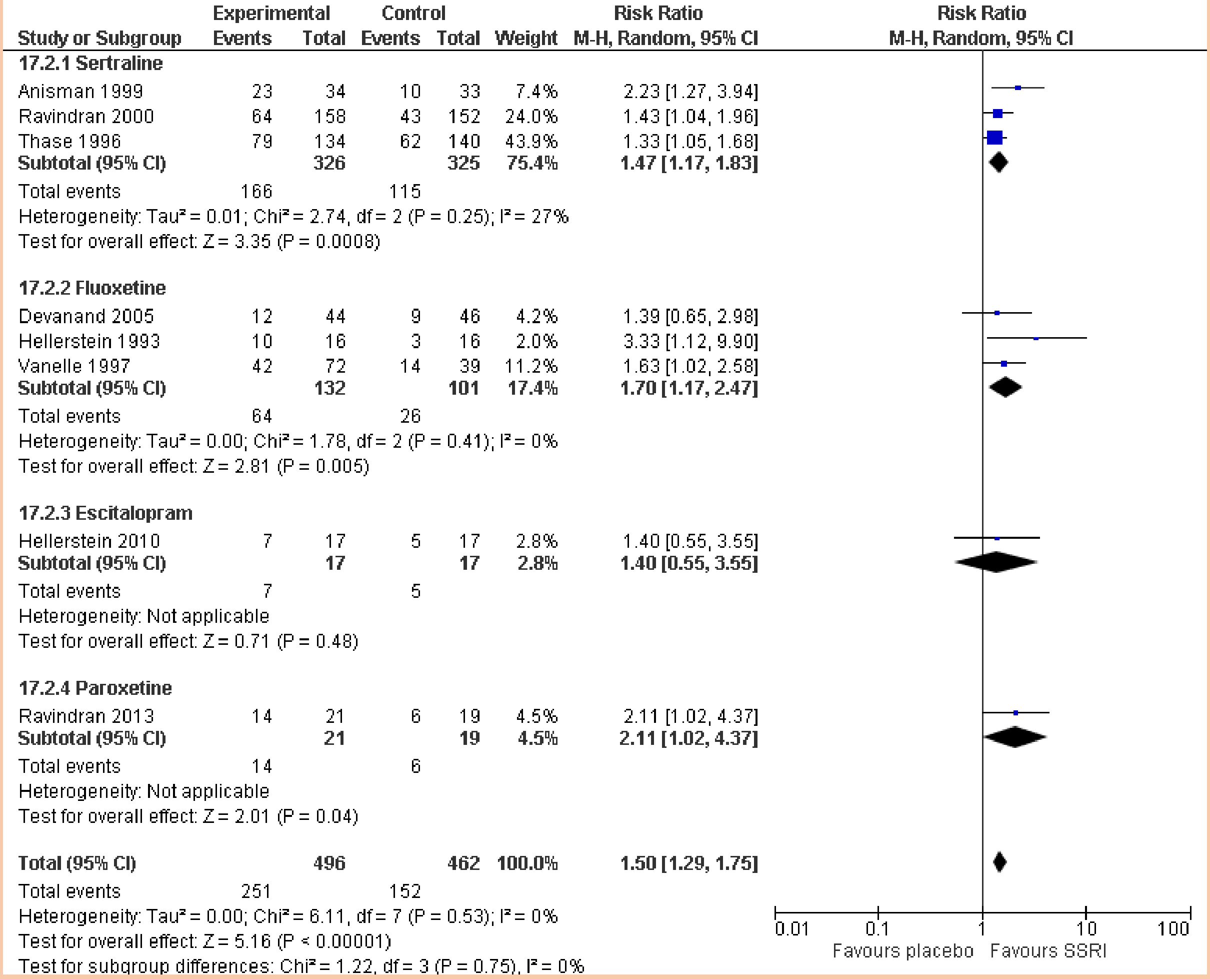
SSRIs versus placebo for chronic depressive symptoms

Remission (score ≤4/<7/≤8 on HAM-D/≤4 on HAM-D & HAMD item # 1 [depressed mood] score=0)



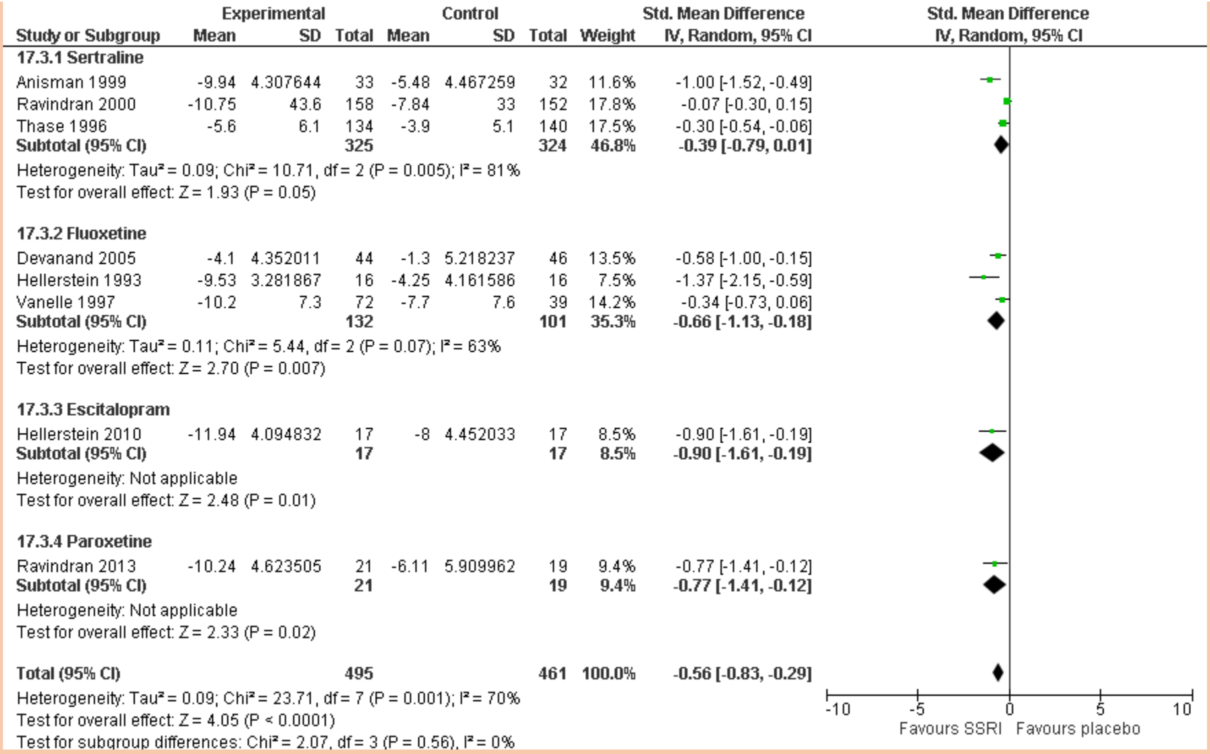
	Favours placebo		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
17.1.1 Sertraline						
Thase 1996	63	134	45	140	48.4%	1.46 [1.08, 1.98]
Subtotal (95% CI)		**134**		**140**	**48.4%**	**1.46 [1.08, 1.98]**
Total events	63		45			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.48 (P = 0.01)						
17.1.2 Fluoxetine						
Vanelle 1997	32	72	10	39	15.2%	1.73 [0.96, 3.14]
Subtotal (95% CI)		**72**		**39**	**15.2%**	**1.73 [0.96, 3.14]**
Total events	32		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
17.1.3 Escitalopram						
Hellerstein 2010	4	17	1	17	1.3%	4.00 [0.50, 32.20]
Subtotal (95% CI)		**17**		**17**	**1.3%**	**4.00 [0.50, 32.20]**
Total events	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
17.1.4 Paroxetine						
Ravindran 2013	12	21	4	19	6.3%	2.71 [1.05, 6.99]
Williams 2000	26	57	25	62	28.8%	1.13 [0.75, 1.71]
Subtotal (95% CI)		**78**		**81**	**35.1%**	**1.58 [0.68, 3.66]**
Total events	38		29			
Heterogeneity: Tau² = 0.25; Chi² = 2.82, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**301**		**277**	**100.0%**	**1.47 [1.15, 1.87]**
Total events	137		85			
Heterogeneity: Tau² = 0.01; Chi² = 4.40, df = 4 (P = 0.35); I² = 9%						
Test for overall effect: Z = 3.12 (P = 0.002)						
Test for subgroup differences: Chi² = 1.07, df = 3 (P = 0.78), I² = 0%						

Response (≥50% improvement on HAMD & HAMD score≤10/≥50% improvement on HAMD &/or much/very much improved on CGI-I)



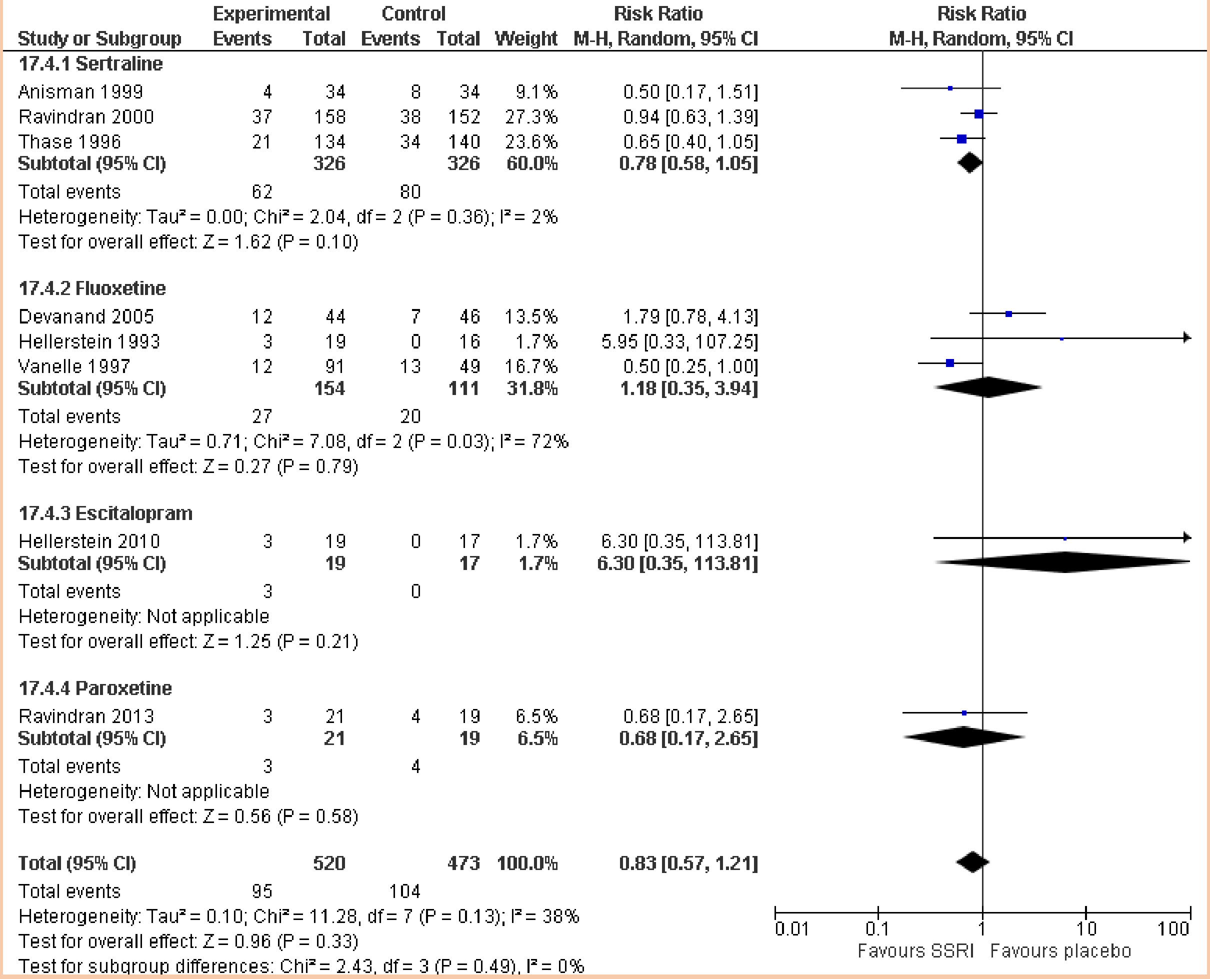
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.2.1 Sertraline						
Anisman 1999	23	34	10	33	7.4%	2.23 [1.27, 3.94]
Ravindran 2000	64	158	43	152	24.0%	1.43 [1.04, 1.96]
Thase 1996	79	134	62	140	43.9%	1.33 [1.05, 1.68]
Subtotal (95% CI)		**326**		**325**	**75.4%**	**1.47 [1.17, 1.83]**
Total events	166		115			
Heterogeneity: Tau² = 0.01; Chi² = 2.74, df = 2 (P = 0.25); I² = 27%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
17.2.2 Fluoxetine						
Devanand 2005	12	44	9	46	4.2%	1.39 [0.65, 2.98]
Hellerstein 1993	10	16	3	16	2.0%	3.33 [1.12, 9.90]
Vanelle 1997	42	72	14	39	11.2%	1.63 [1.02, 2.58]
Subtotal (95% CI)		**132**		**101**	**17.4%**	**1.70 [1.17, 2.47]**
Total events	64		26			
Heterogeneity: Tau² = 0.00; Chi² = 1.78, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.81 (P = 0.005)						
17.2.3 Escitalopram						
Hellerstein 2010	7	17	5	17	2.8%	1.40 [0.55, 3.55]
Subtotal (95% CI)		**17**		**17**	**2.8%**	**1.40 [0.55, 3.55]**
Total events	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
17.2.4 Paroxetine						
Ravindran 2013	14	21	6	19	4.5%	2.11 [1.02, 4.37]
Subtotal (95% CI)		**21**		**19**	**4.5%**	**2.11 [1.02, 4.37]**
Total events	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
Total (95% CI)		**496**		**462**	**100.0%**	**1.50 [1.29, 1.75]**
Total events	251		152			
Heterogeneity: Tau² = 0.00; Chi² = 6.11, df = 7 (P = 0.53); I² = 0%						
Test for overall effect: Z = 5.16 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.22, df = 3 (P = 0.75), I² = 0%						

Depression symptomatology (HAMD change score)



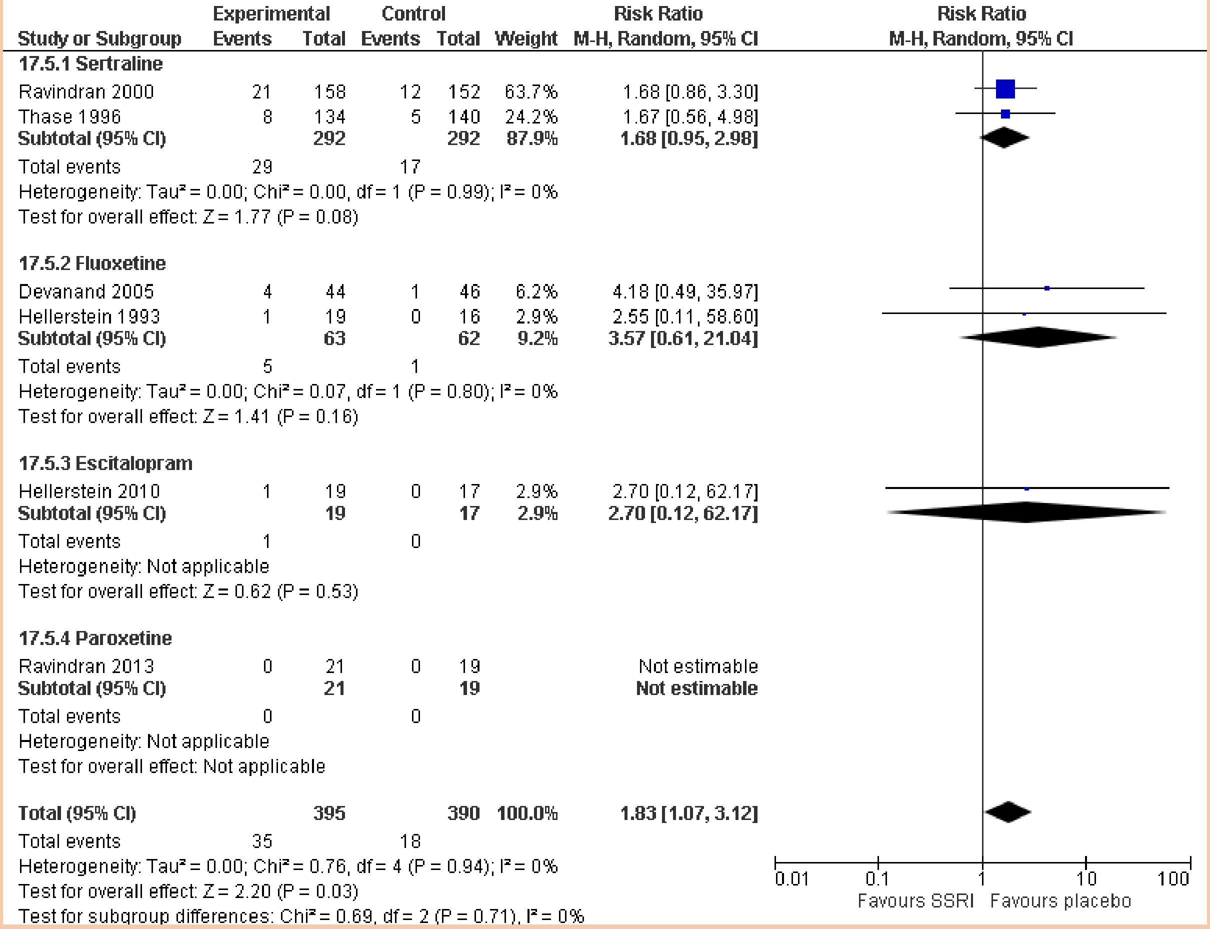
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
17.3.1 Sertraline								
Anisman 1999	-9.94	4.307644	33	-5.48	4.467259	32	11.6%	-1.00 [-1.52, -0.49]
Ravindran 2000	-10.75	43.6	158	-7.84	33	152	17.8%	-0.07 [-0.30, 0.15]
Thase 1996	-5.6	6.1	134	-3.9	5.1	140	17.5%	-0.30 [-0.54, -0.06]
Subtotal (95% CI)			**325**			**324**	**46.8%**	**-0.39 [-0.79, 0.01]**
Heterogeneity: Tau² = 0.09; Chi² = 10.71, df = 2 (P = 0.005); I² = 81%								
Test for overall effect: Z = 1.93 (P = 0.05)								
17.3.2 Fluoxetine								
Devanand 2005	-4.1	4.352011	44	-1.3	5.218237	46	13.5%	-0.58 [-1.00, -0.15]
Hellerstein 1993	-9.53	3.281867	16	-4.25	4.161586	16	7.5%	-1.37 [-2.15, -0.59]
Vanelle 1997	-10.2	7.3	72	-7.7	7.6	39	14.2%	-0.34 [-0.73, 0.06]
Subtotal (95% CI)			**132**			**101**	**35.3%**	**-0.66 [-1.13, -0.18]**
Heterogeneity: Tau² = 0.11; Chi² = 5.44, df = 2 (P = 0.07); I² = 63%								
Test for overall effect: Z = 2.70 (P = 0.007)								
17.3.3 Escitalopram								
Hellerstein 2010	-11.94	4.094832	17	-8	4.452033	17	8.5%	-0.90 [-1.61, -0.19]
Subtotal (95% CI)			**17**			**17**	**8.5%**	**-0.90 [-1.61, -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.48 (P = 0.01)								
17.3.4 Paroxetine								
Ravindran 2013	-10.24	4.623505	21	-6.11	5.909962	19	9.4%	-0.77 [-1.41, -0.12]
Subtotal (95% CI)			**21**			**19**	**9.4%**	**-0.77 [-1.41, -0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.33 (P = 0.02)								
Total (95% CI)			**495**			**461**	**100.0%**	**-0.56 [-0.83, -0.29]**
Heterogeneity: Tau² = 0.09; Chi² = 23.71, df = 7 (P = 0.001); I² = 70%								
Test for overall effect: Z = 4.05 (P < 0.0001)								
Test for subgroup differences: Chi² = 2.07, df = 3 (P = 0.56), I² = 0%								

Discontinuation for any reason (including adverse events)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.4.1 Sertraline						
Anisman 1999	4	34	8	34	9.1%	0.50 [0.17, 1.51]
Ravindran 2000	37	158	38	152	27.3%	0.94 [0.63, 1.39]
Thase 1996	21	134	34	140	23.6%	0.65 [0.40, 1.05]
Subtotal (95% CI)		**326**		**326**	**60.0%**	**0.78 [0.58, 1.05]**
Total events	62		80			
Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 2 (P = 0.36); I² = 2%						
Test for overall effect: Z = 1.62 (P = 0.10)						
17.4.2 Fluoxetine						
Devanand 2005	12	44	7	46	13.5%	1.79 [0.78, 4.13]
Hellerstein 1993	3	19	0	16	1.7%	5.95 [0.33, 107.25]
Vanelle 1997	12	91	13	49	16.7%	0.50 [0.25, 1.00]
Subtotal (95% CI)		**154**		**111**	**31.8%**	**1.18 [0.35, 3.94]**
Total events	27		20			
Heterogeneity: Tau² = 0.71; Chi² = 7.08, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 0.27 (P = 0.79)						
17.4.3 Escitalopram						
Hellerstein 2010	3	19	0	17	1.7%	6.30 [0.35, 113.81]
Subtotal (95% CI)		**19**		**17**	**1.7%**	**6.30 [0.35, 113.81]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
17.4.4 Paroxetine						
Ravindran 2013	3	21	4	19	6.5%	0.68 [0.17, 2.65]
Subtotal (95% CI)		**21**		**19**	**6.5%**	**0.68 [0.17, 2.65]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
Total (95% CI)		**520**		**473**	**100.0%**	**0.83 [0.57, 1.21]**
Total events	95		104			
Heterogeneity: Tau² = 0.10; Chi² = 11.28, df = 7 (P = 0.13); I² = 38%						
Test for overall effect: Z = 0.96 (P = 0.33)						
Test for subgroup differences: Chi² = 2.43, df = 3 (P = 0.49), I² = 0%						

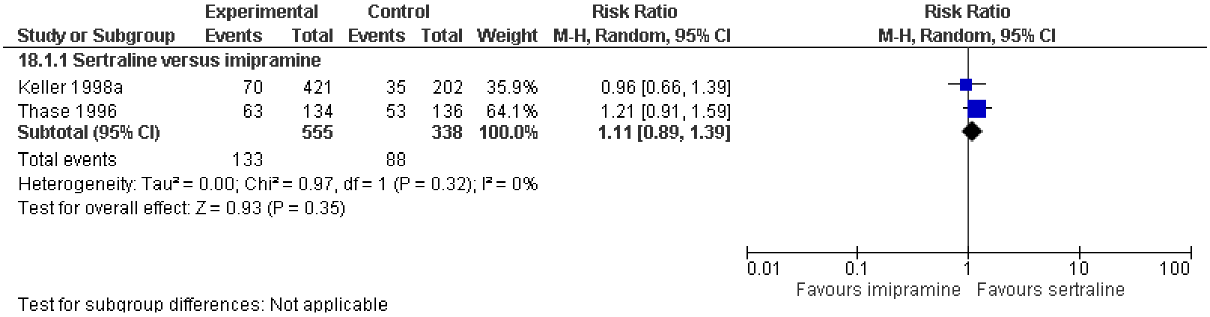
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.5.1 Sertraline						
Ravindran 2000	21	158	12	152	63.7%	1.68 [0.86, 3.30]
Thase 1996	8	134	5	140	24.2%	1.67 [0.56, 4.98]
Subtotal (95% CI)		**292**		**292**	**87.9%**	**1.68 [0.95, 2.98]**
Total events	29		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
17.5.2 Fluoxetine						
Devanand 2005	4	44	1	46	6.2%	4.18 [0.49, 35.97]
Hellerstein 1993	1	19	0	16	2.9%	2.55 [0.11, 58.60]
Subtotal (95% CI)		**63**		**62**	**9.2%**	**3.57 [0.61, 21.04]**
Total events	5		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
17.5.3 Escitalopram						
Hellerstein 2010	1	19	0	17	2.9%	2.70 [0.12, 62.17]
Subtotal (95% CI)		**19**		**17**	**2.9%**	**2.70 [0.12, 62.17]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
17.5.4 Paroxetine						
Ravindran 2013	0	21	0	19		Not estimable
Subtotal (95% CI)		**21**		**19**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**395**		**390**	**100.0%**	**1.83 [1.07, 3.12]**
Total events	35		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%						

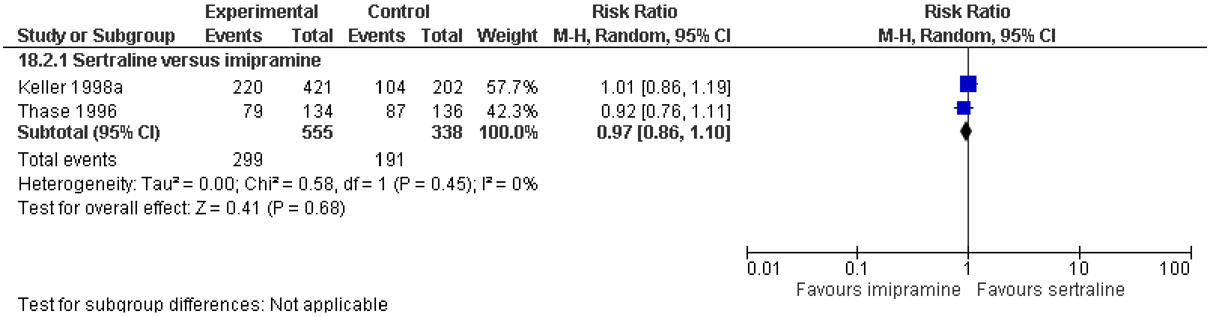
SSRI versus TCA for chronic depressive symptoms

Remission (score ≤ 7 on HAM-D & much/very much improved on CGI-I/≤4 on HAM-D)



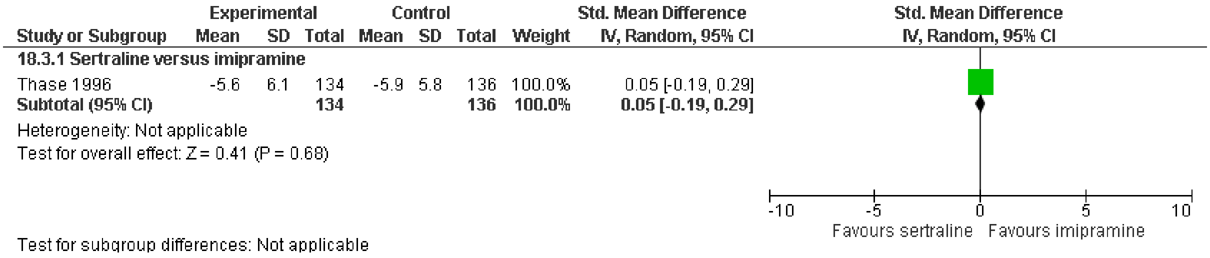
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.1.1 Sertraline versus imipramine						
Keller 1998a	70	421	35	202	35.9%	0.96 [0.66, 1.39]
Thase 1996	63	134	53	136	64.1%	1.21 [0.91, 1.59]
Subtotal (95% CI)		**555**		**338**	**100.0%**	**1.11 [0.89, 1.39]**
Total events	133		88			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
Test for subgroup differences: Not applicable						

Response (≥50% on HAM-D & much/very much improved on CGI-I/≤4 on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.2.1 Sertraline versus imipramine						
Keller 1998a	220	421	104	202	57.7%	1.01 [0.86, 1.19]
Thase 1996	79	134	87	136	42.3%	0.92 [0.76, 1.11]
Subtotal (95% CI)		**555**		**338**	**100.0%**	**0.97 [0.86, 1.10]**
Total events	299		191			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Test for subgroup differences: Not applicable						

Depression symptomatology (HAM-D change score)



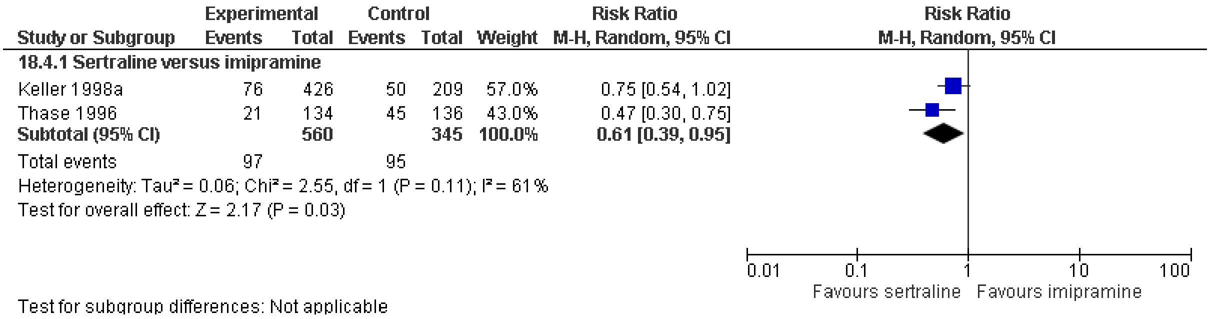
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
18.3.1 Sertraline versus imipramine								
Thase 1996	-5.6	6.1	134	-5.9	5.8	136	100.0%	0.05 [-0.19, 0.29]
Subtotal (95% CI)			**134**			**136**	**100.0%**	**0.05 [-0.19, 0.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Std. Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours sertraline
Favours imipramine

Discontinuation for any reason (including adverse events)



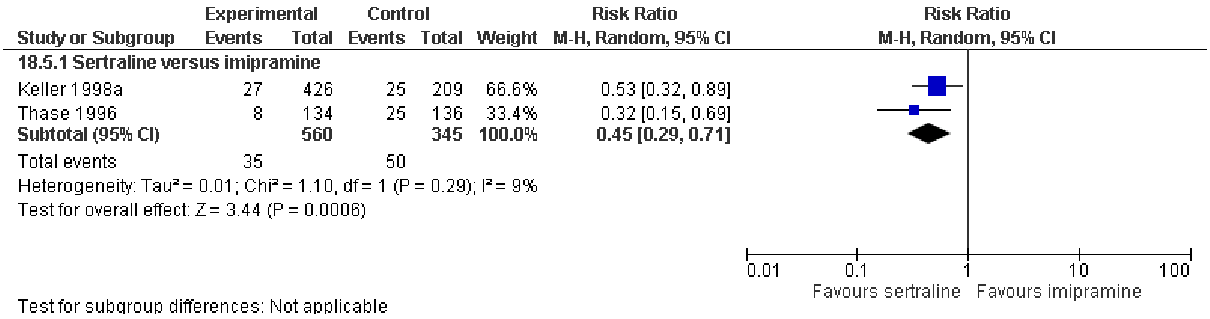
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.4.1 Sertraline versus imipramine						
Keller 1998a	76	426	50	209	57.0%	0.75 [0.54, 1.02]
Thase 1996	21	134	45	136	43.0%	0.47 [0.30, 0.75]
Subtotal (95% CI)		**560**		**345**	**100.0%**	**0.61 [0.39, 0.95]**
Total events	97		95			

Heterogeneity: Tau² = 0.06; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 2.17 (P = 0.03)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours sertraline
Favours imipramine

Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
18.5.1 Sertraline versus imipramine						
Keller 1998a	27	426	25	209	66.6%	0.53 [0.32, 0.89]
Thase 1996	8	134	25	136	33.4%	0.32 [0.15, 0.69]
Subtotal (95% CI)		**560**		**345**	**100.0%**	**0.45 [0.29, 0.71]**
Total events	35		50			

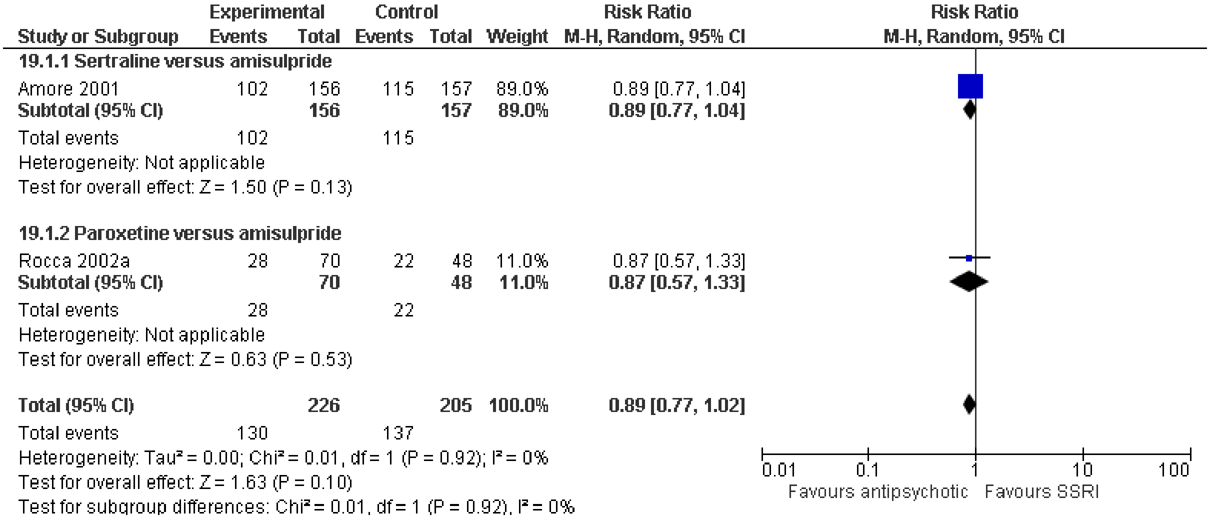
Heterogeneity: Tau² = 0.01; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%
Test for overall effect: Z = 3.44 (P = 0.0006)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours sertraline
Favours imipramine

SSRI versus antipsychotic for dysthymia or double depression

Remission (</≤7 on HAM-D)

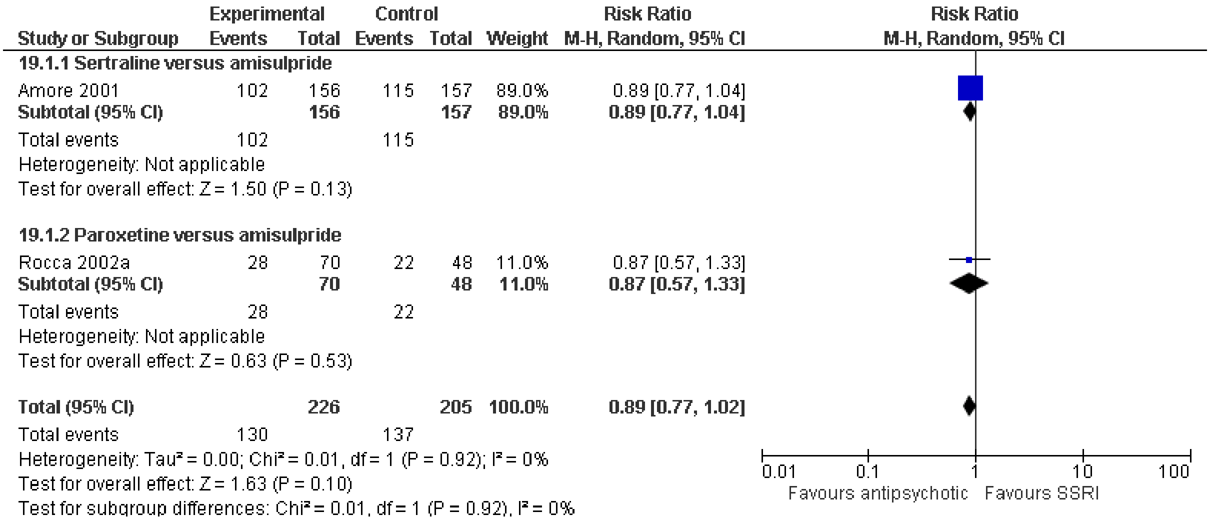


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
19.1.1 Sertraline versus amisulpride						
Amore 2001	102	156	115	157	89.0%	0.89 [0.77, 1.04]
Subtotal (95% CI)		**156**		**157**	**89.0%**	**0.89 [0.77, 1.04]**
Total events	102		115			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
19.1.2 Paroxetine versus amisulpride						
Rocca 2002a	28	70	22	48	11.0%	0.87 [0.57, 1.33]
Subtotal (95% CI)		**70**		**48**	**11.0%**	**0.87 [0.57, 1.33]**
Total events	28		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**226**		**205**	**100.0%**	**0.89 [0.77, 1.02]**
Total events	130		137			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%

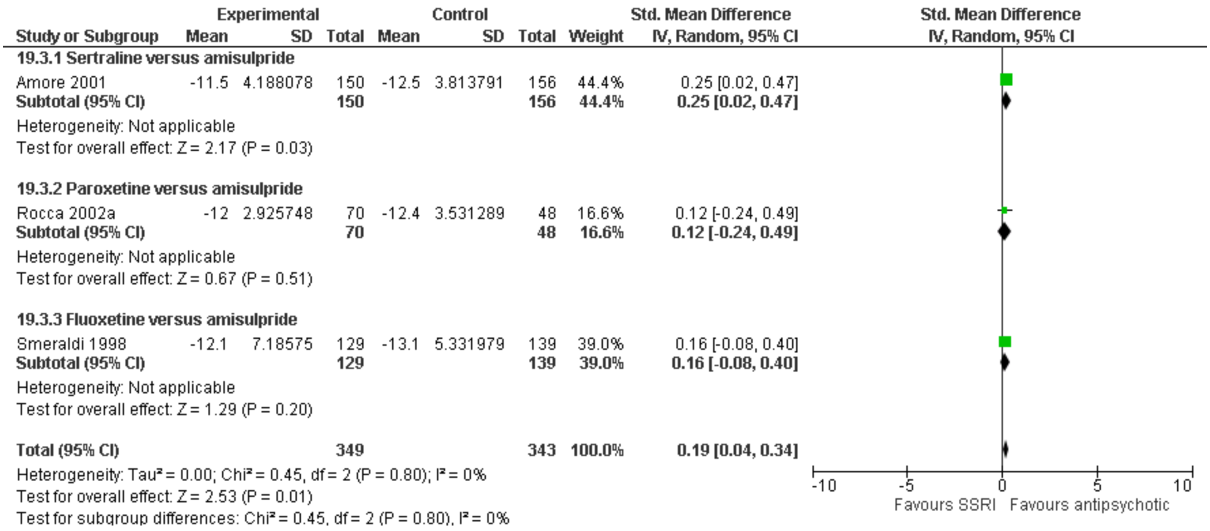
Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours antipsychotic
Favours SSRI

Response (≥50% improvement on HAMD/MADR)



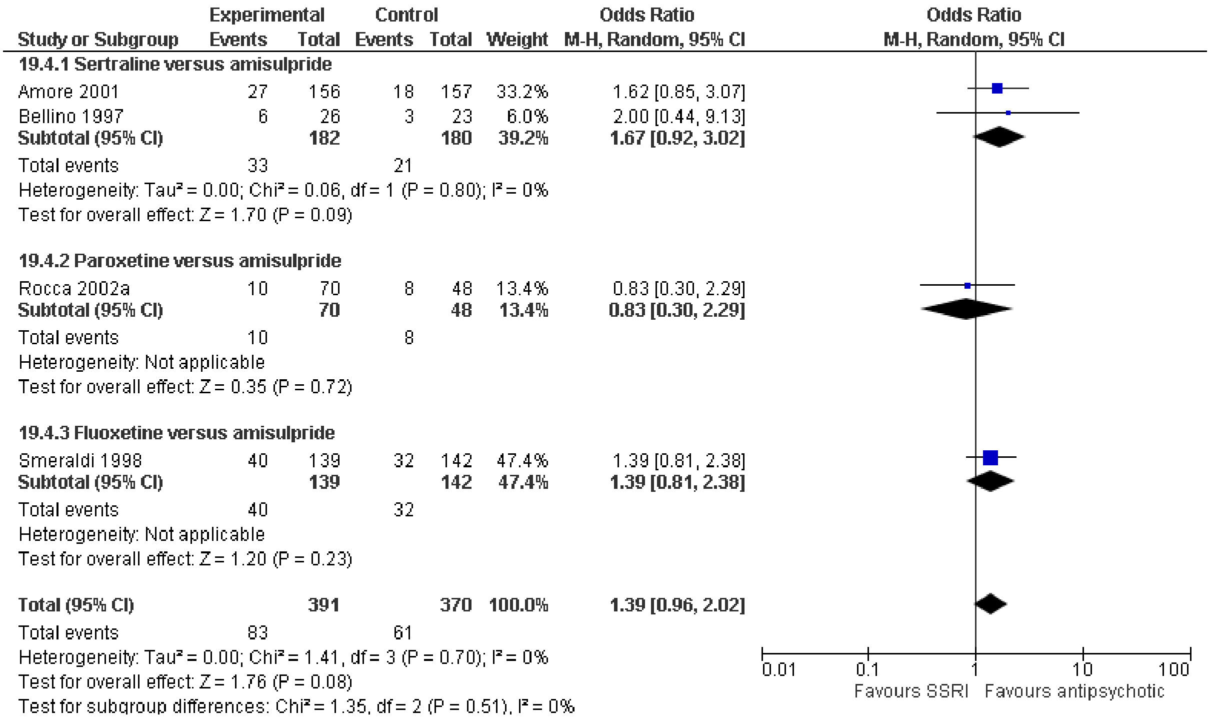
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
19.1.1 Sertraline versus amisulpride						
Amore 2001	102	156	115	157	89.0%	0.89 [0.77, 1.04]
Subtotal (95% CI)		**156**		**157**	**89.0%**	**0.89 [0.77, 1.04]**
Total events	102		115			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
19.1.2 Paroxetine versus amisulpride						
Rocca 2002a	28	70	22	48	11.0%	0.87 [0.57, 1.33]
Subtotal (95% CI)		**70**		**48**	**11.0%**	**0.87 [0.57, 1.33]**
Total events	28		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**226**		**205**	**100.0%**	**0.89 [0.77, 1.02]**
Total events	130		137			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

Depression symptomatology (HAMD/MADRS change score)



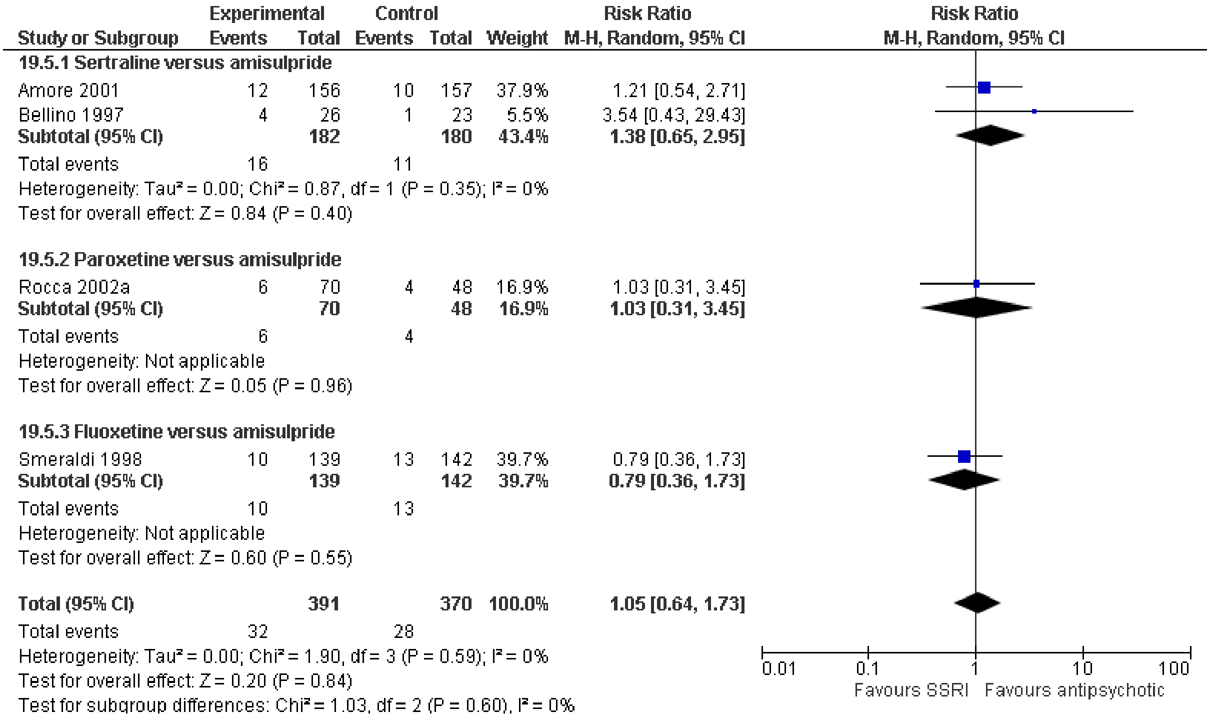
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
19.3.1 Sertraline versus amisulpride								
Amore 2001	-11.5	4.188078	150	-12.5	3.813791	156	44.4%	0.25 [0.02, 0.47]
Subtotal (95% CI)			**150**			**156**	**44.4%**	**0.25 [0.02, 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.17 (P = 0.03)								
19.3.2 Paroxetine versus amisulpride								
Rocca 2002a	-12	2.925748	70	-12.4	3.531289	48	16.6%	0.12 [-0.24, 0.49]
Subtotal (95% CI)			**70**			**48**	**16.6%**	**0.12 [-0.24, 0.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.51)								
19.3.3 Fluoxetine versus amisulpride								
Smeraldi 1998	-12.1	7.18575	129	-13.1	5.331979	139	39.0%	0.16 [-0.08, 0.40]
Subtotal (95% CI)			**129**			**139**	**39.0%**	**0.16 [-0.08, 0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
Total (95% CI)			**349**			**343**	**100.0%**	**0.19 [0.04, 0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%								
Test for overall effect: Z = 2.53 (P = 0.01)								
Test for subgroup differences: Chi² = 0.45, df = 2 (P = 0.80), I² = 0%								

Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
19.4.1 Sertraline versus amisulpride						
Amore 2001	27	156	18	157	33.2%	1.62 [0.85, 3.07]
Bellino 1997	6	26	3	23	6.0%	2.00 [0.44, 9.13]
Subtotal (95% CI)		**182**		**180**	**39.2%**	**1.67 [0.92, 3.02]**
Total events	33		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
19.4.2 Paroxetine versus amisulpride						
Rocca 2002a	10	70	8	48	13.4%	0.83 [0.30, 2.29]
Subtotal (95% CI)		**70**		**48**	**13.4%**	**0.83 [0.30, 2.29]**
Total events	10		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						
19.4.3 Fluoxetine versus amisulpride						
Smeraldi 1998	40	139	32	142	47.4%	1.39 [0.81, 2.38]
Subtotal (95% CI)		**139**		**142**	**47.4%**	**1.39 [0.81, 2.38]**
Total events	40		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
Total (95% CI)		**391**		**370**	**100.0%**	**1.39 [0.96, 2.02]**
Total events	83		61			
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 1.35, df = 2 (P = 0.51), I² = 0%						

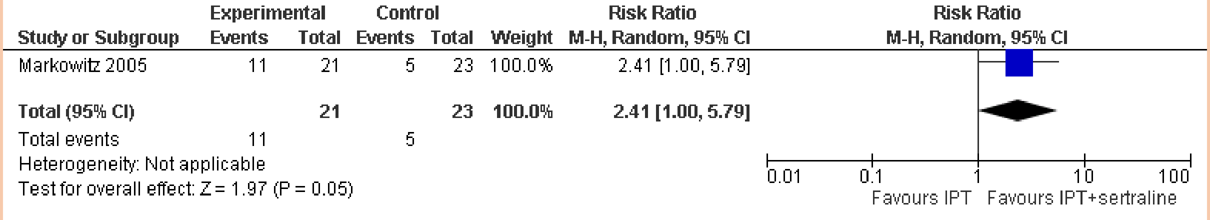
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
19.5.1 Sertraline versus amisulpride						
Amore 2001	12	156	10	157	37.9%	1.21 [0.54, 2.71]
Bellino 1997	4	26	1	23	5.5%	3.54 [0.43, 29.43]
Subtotal (95% CI)		**182**		**180**	**43.4%**	**1.38 [0.65, 2.95]**
Total events	16		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
19.5.2 Paroxetine versus amisulpride						
Rocca 2002a	6	70	4	48	16.9%	1.03 [0.31, 3.45]
Subtotal (95% CI)		**70**		**48**	**16.9%**	**1.03 [0.31, 3.45]**
Total events	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
19.5.3 Fluoxetine versus amisulpride						
Smeraldi 1998	10	139	13	142	39.7%	0.79 [0.36, 1.73]
Subtotal (95% CI)		**139**		**142**	**39.7%**	**0.79 [0.36, 1.73]**
Total events	10		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**391**		**370**	**100.0%**	**1.05 [0.64, 1.73]**
Total events	32		28			
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 1.03, df = 2 (P = 0.60), I² = 0%						

Sertraline versus IPT versus IPT- only for dysthymia

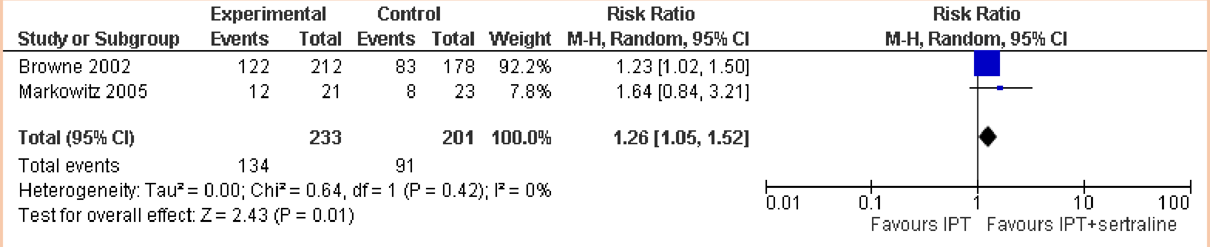
Remission (score <7 on HAM-D & > 50% improvement on HAMD & GAF score> 70)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	11	21	5	23	100.0%	2.41 [1.00, 5.79]
Total (95% CI)		**21**		**23**	**100.0%**	**2.41 [1.00, 5.79]**
Total events	11		5			

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

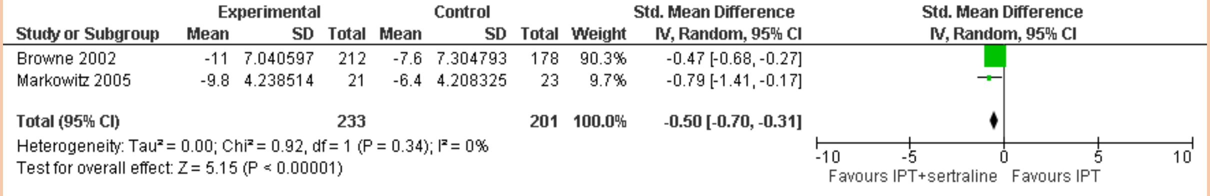
Response (≥40% improvement on MADRS/≥ 50% improvement on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Browne 2002	122	212	83	178	92.2%	1.23 [1.02, 1.50]
Markowitz 2005	12	21	8	23	7.8%	1.64 [0.84, 3.21]
Total (95% CI)		**233**		**201**	**100.0%**	**1.26 [1.05, 1.52]**
Total events	134		91			

Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.01)

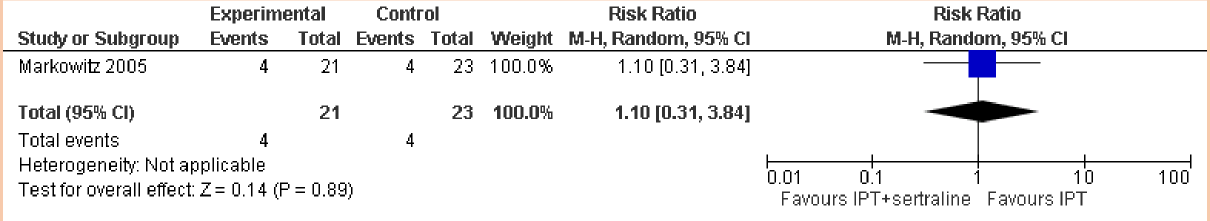
Depression symptomatology (MADRS/HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Browne 2002	-11	7.040597	212	-7.6	7.304793	178	90.3%	-0.47 [-0.68, -0.27]
Markowitz 2005	-9.8	4.238514	21	-6.4	4.208325	23	9.7%	-0.79 [-1.41, -0.17]
Total (95% CI)			**233**			**201**	**100.0%**	**-0.50 [-0.70, -0.31]**

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 5.15 (P < 0.00001)

Discontinuation for any reason (including adverse events)

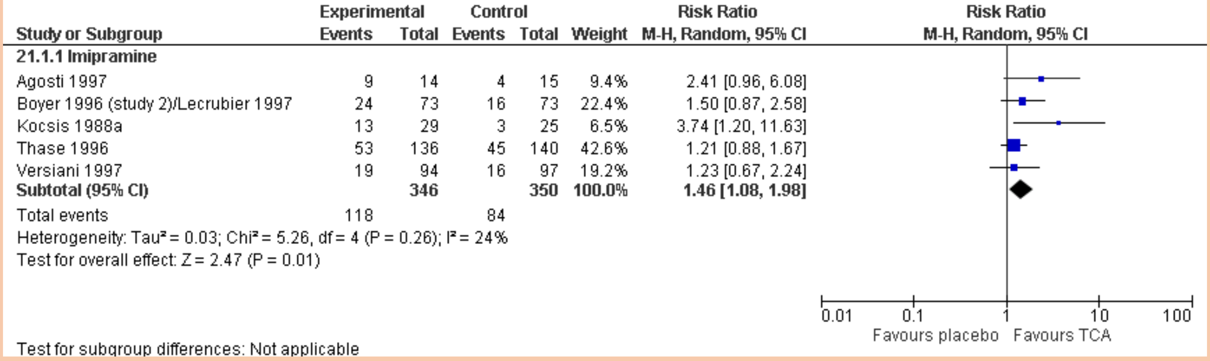


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Markowitz 2005	4	21	4	23	100.0%	1.10 [0.31, 3.84]
Total (95% CI)		**21**		**23**	**100.0%**	**1.10 [0.31, 3.84]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)

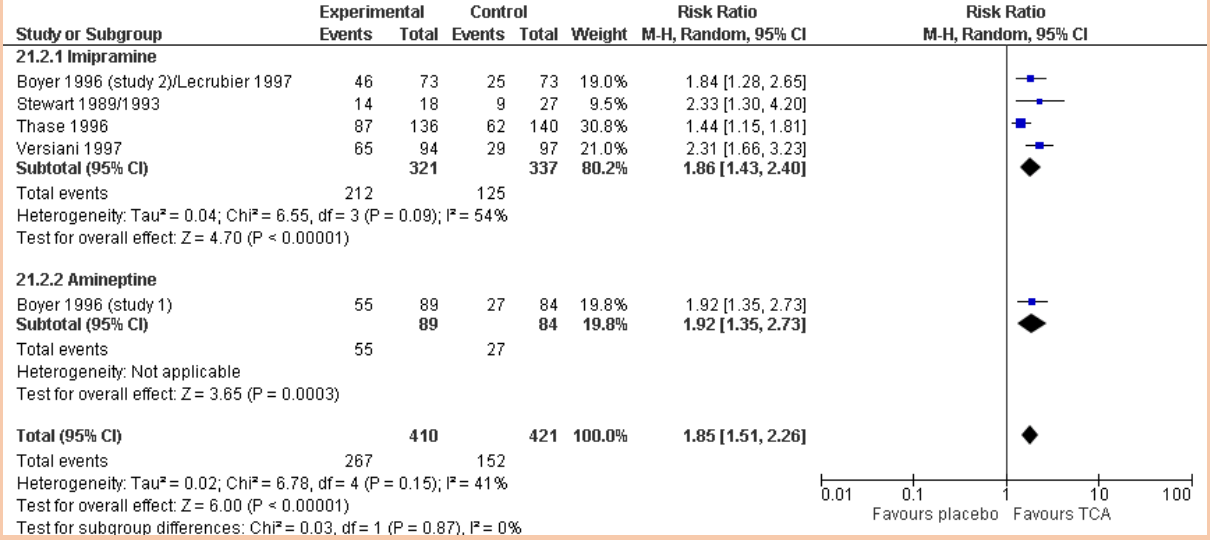
TCAs versus placebo for chronic depressive symptoms

Remission (score ≤4 on HAM-D/≤6 on HAM-D & ≥10-point improvement on GAS & no longer meet DSM-III criteria for dysthymia/<8 on MADRS)



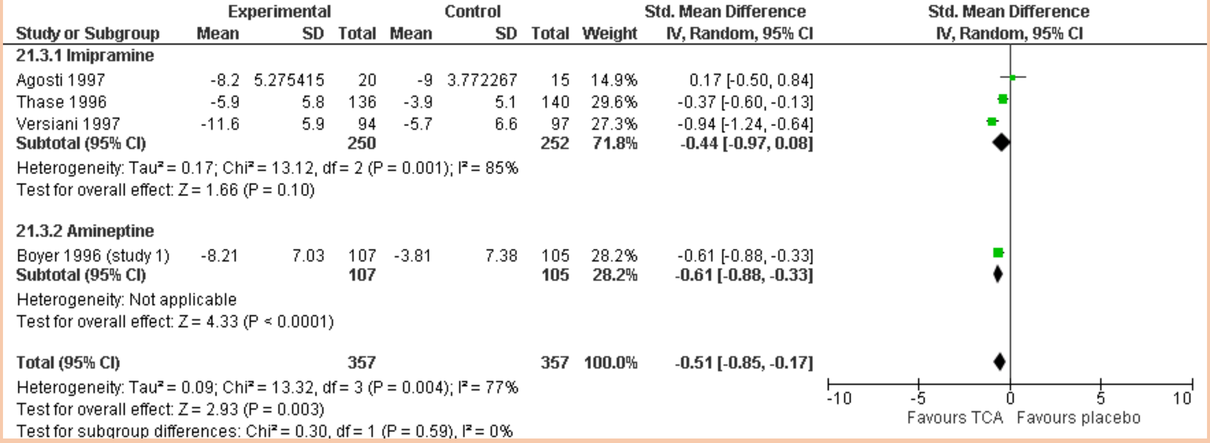
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 Imipramine						
Agosti 1997	9	14	4	15	9.4%	2.41 [0.96, 6.08]
Boyer 1996 (study 2)/Lecrubier 1997	24	73	16	73	22.4%	1.50 [0.87, 2.58]
Kocsis 1988a	13	29	3	25	6.5%	3.74 [1.20, 11.63]
Thase 1996	53	136	45	140	42.6%	1.21 [0.88, 1.67]
Versiani 1997	19	94	16	97	19.2%	1.23 [0.67, 2.24]
Subtotal (95% CI)		**346**		**350**	**100.0%**	**1.46 [1.08, 1.98]**
Total events	118		84			
Heterogeneity: Tau² = 0.03; Chi² = 5.26, df = 4 (P = 0.26); I² = 24%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Not applicable						

Response (CGI-I score 1-2 [much/very much improved]/≥50% improvement on HAM-D)



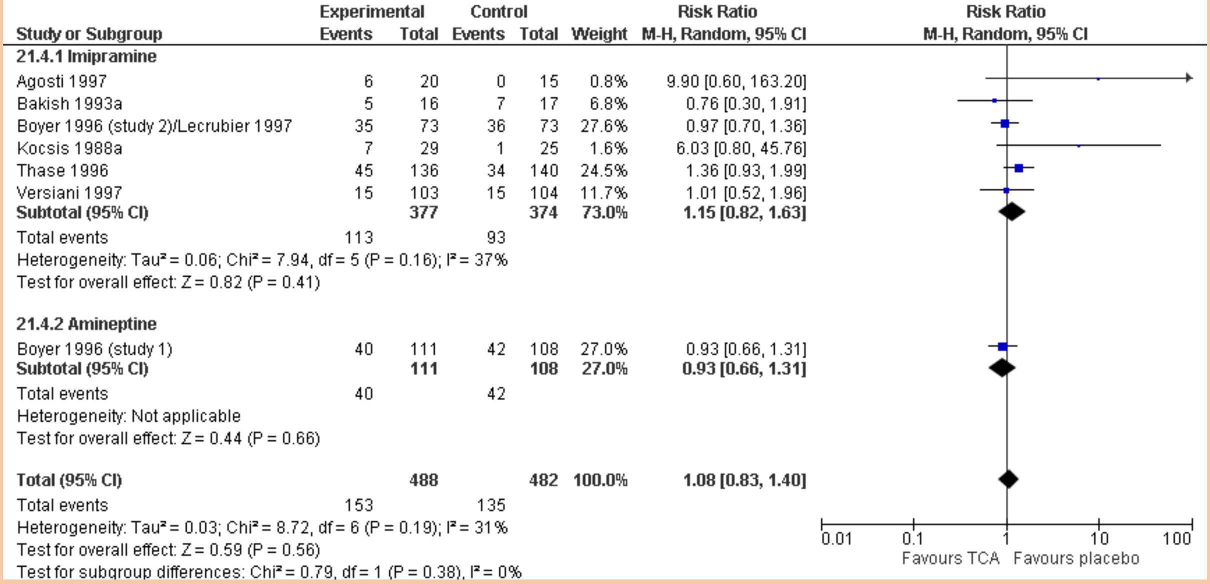
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.2.1 Imipramine						
Boyer 1996 (study 2)/Lecrubier 1997	46	73	25	73	19.0%	1.84 [1.28, 2.65]
Stewart 1989/1993	14	18	9	27	9.5%	2.33 [1.30, 4.20]
Thase 1996	87	136	62	140	30.8%	1.44 [1.15, 1.81]
Versiani 1997	65	94	29	97	21.0%	2.31 [1.66, 3.23]
Subtotal (95% CI)		**321**		**337**	**80.2%**	**1.86 [1.43, 2.40]**
Total events	212		125			
Heterogeneity: Tau² = 0.04; Chi² = 6.55, df = 3 (P = 0.09); I² = 54%						
Test for overall effect: Z = 4.70 (P < 0.00001)						
21.2.2 Amineptine						
Boyer 1996 (study 1)	55	89	27	84	19.8%	1.92 [1.35, 2.73]
Subtotal (95% CI)		**89**		**84**	**19.8%**	**1.92 [1.35, 2.73]**
Total events	55		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Total (95% CI)		**410**		**421**	**100.0%**	**1.85 [1.51, 2.26]**
Total events	267		152			
Heterogeneity: Tau² = 0.02; Chi² = 6.78, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 6.00 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						

Depression symptomatology (HAMD/MADRS change score)



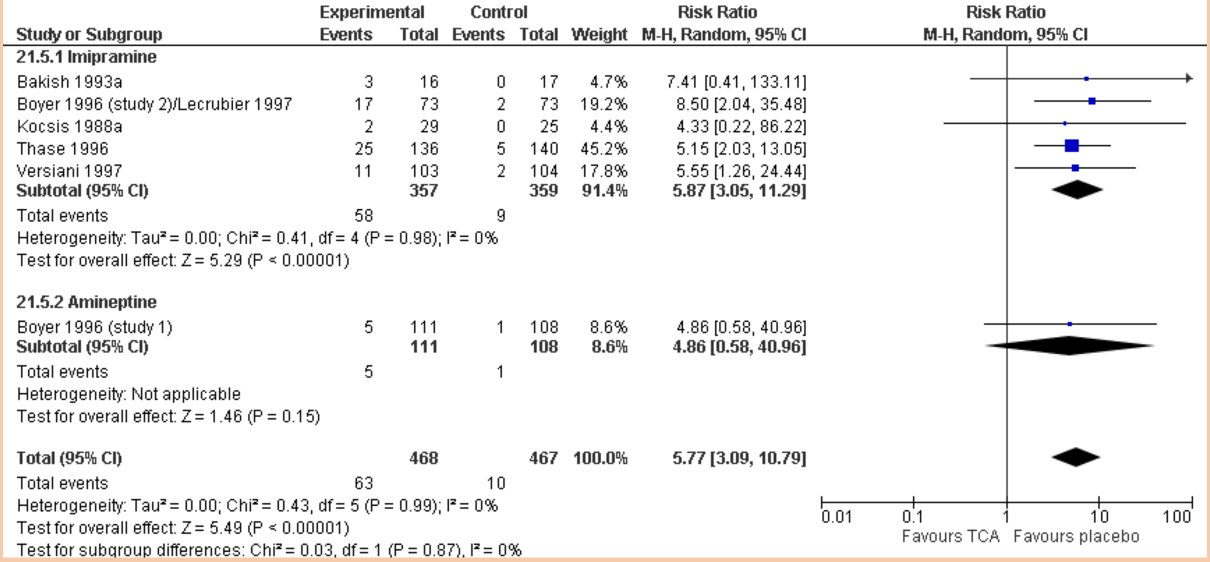
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
21.3.1 Imipramine								
Agosti 1997	-8.2	5.275415	20	-9	3.772267	15	14.9%	0.17 [-0.50, 0.84]
Thase 1996	-5.9	5.8	136	-3.9	5.1	140	29.6%	-0.37 [-0.60, -0.13]
Versiani 1997	-11.6	5.9	94	-5.7	6.6	97	27.3%	-0.94 [-1.24, -0.64]
Subtotal (95% CI)			**250**			**252**	**71.8%**	**-0.44 [-0.97, 0.08]**
Heterogeneity: Tau² = 0.17; Chi² = 13.12, df = 2 (P = 0.001); I² = 85%								
Test for overall effect: Z = 1.66 (P = 0.10)								
21.3.2 Amineptine								
Boyer 1996 (study 1)	-8.21	7.03	107	-3.81	7.38	105	28.2%	-0.61 [-0.88, -0.33]
Subtotal (95% CI)			**107**			**105**	**28.2%**	**-0.61 [-0.88, -0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.33 (P < 0.0001)								
Total (95% CI)			**357**			**357**	**100.0%**	**-0.51 [-0.85, -0.17]**
Heterogeneity: Tau² = 0.09; Chi² = 13.32, df = 3 (P = 0.004); I² = 77%								
Test for overall effect: Z = 2.93 (P = 0.003)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%								

Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.4.1 Imipramine						
Agosti 1997	6	20	0	15	0.8%	9.90 [0.60, 163.20]
Bakish 1993a	5	16	7	17	6.8%	0.76 [0.30, 1.91]
Boyer 1996 (study 2)/Lecrubier 1997	35	73	36	73	27.6%	0.97 [0.70, 1.36]
Kocsis 1988a	7	29	1	25	1.6%	6.03 [0.80, 45.76]
Thase 1996	45	136	34	140	24.5%	1.36 [0.93, 1.99]
Versiani 1997	15	103	15	104	11.7%	1.01 [0.52, 1.96]
Subtotal (95% CI)		**377**		**374**	**73.0%**	**1.15 [0.82, 1.63]**
Total events	113		93			
Heterogeneity: Tau² = 0.06; Chi² = 7.94, df = 5 (P = 0.16); I² = 37%						
Test for overall effect: Z = 0.82 (P = 0.41)						
21.4.2 Amineptine						
Boyer 1996 (study 1)	40	111	42	108	27.0%	0.93 [0.66, 1.31]
Subtotal (95% CI)		**111**		**108**	**27.0%**	**0.93 [0.66, 1.31]**
Total events	40		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**488**		**482**	**100.0%**	**1.08 [0.83, 1.40]**
Total events	153		135			
Heterogeneity: Tau² = 0.03; Chi² = 8.72, df = 6 (P = 0.19); I² = 31%						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Chi² = 0.79, df = 1 (P = 0.38), I² = 0%						

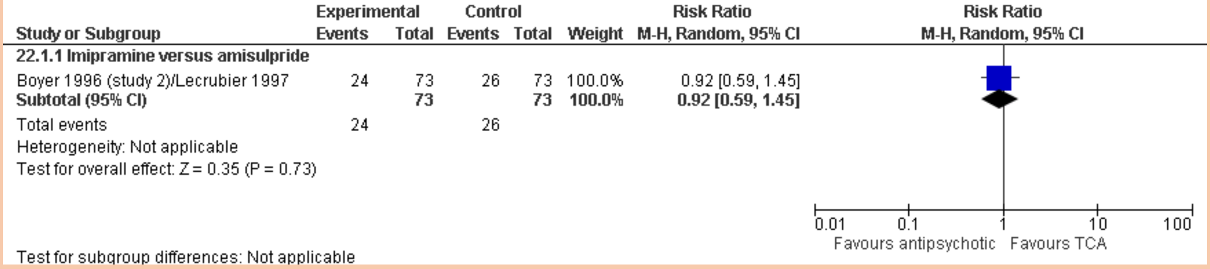
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.5.1 Imipramine						
Bakish 1993a	3	16	0	17	4.7%	7.41 [0.41, 133.11]
Boyer 1996 (study 2)/Lecrubier 1997	17	73	2	73	19.2%	8.50 [2.04, 35.48]
Kocsis 1988a	2	29	0	25	4.4%	4.33 [0.22, 86.22]
Thase 1996	25	136	5	140	45.2%	5.15 [2.03, 13.05]
Versiani 1997	11	103	2	104	17.8%	5.55 [1.26, 24.44]
Subtotal (95% CI)		**357**		**359**	**91.4%**	**5.87 [3.05, 11.29]**
Total events	58		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 5.29 (P < 0.00001)						
21.5.2 Amineptine						
Boyer 1996 (study 1)	5	111	1	108	8.6%	4.86 [0.58, 40.96]
Subtotal (95% CI)		**111**		**108**	**8.6%**	**4.86 [0.58, 40.96]**
Total events	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.15)						
Total (95% CI)		**468**		**467**	**100.0%**	**5.77 [3.09, 10.79]**
Total events	63		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 5 (P = 0.99); I² = 0%						
Test for overall effect: Z = 5.49 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						

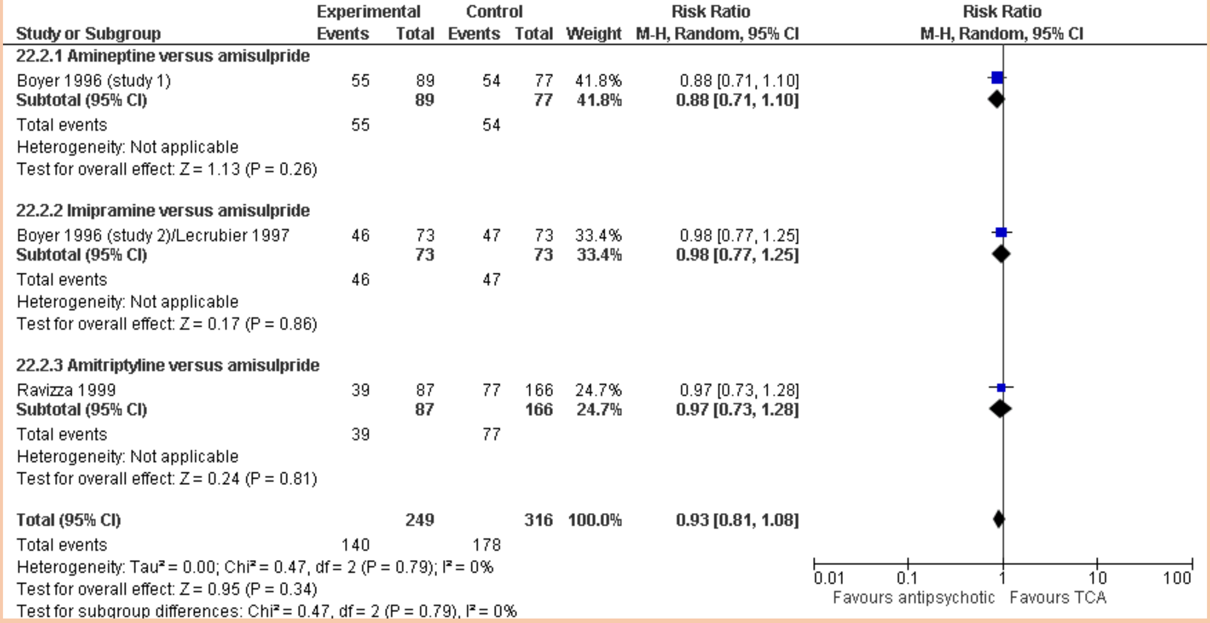
TCA versus antipsychotic for chronic depressive symptoms

Remission (<8 on MADRS)



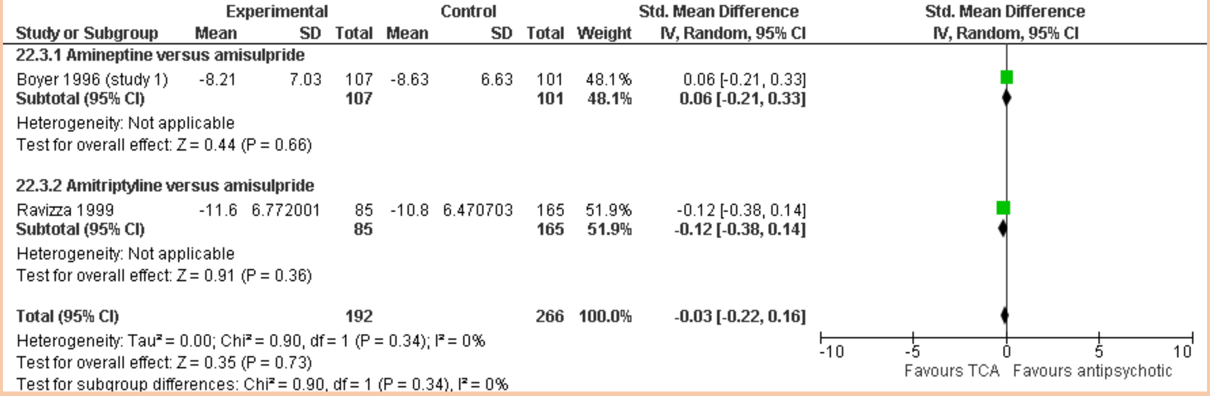
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.1.1 Imipramine versus amisulpride						
Boyer 1996 (study 2)/Lecrubier 1997	24	73	26	73	100.0%	0.92 [0.59, 1.45]
Subtotal (95% CI)		**73**		**73**	**100.0%**	**0.92 [0.59, 1.45]**
Total events	24		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
Test for subgroup differences: Not applicable						

Response (MADRS ≥ 50% improvement & CGI-I score 1-2 [much/very much improved])



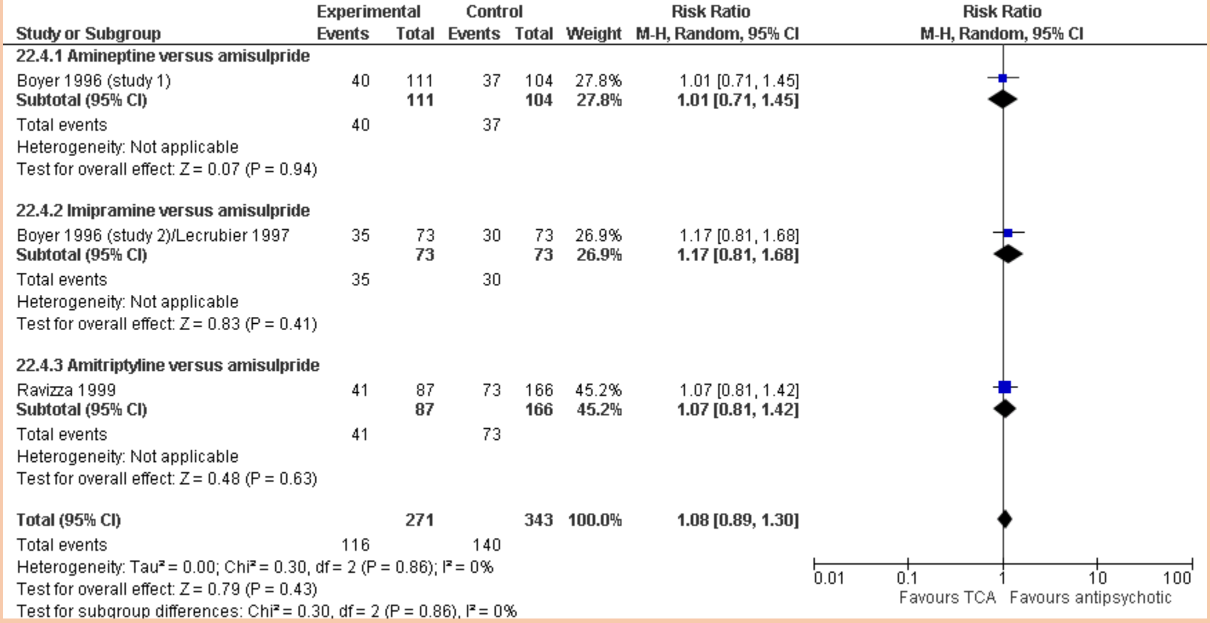
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.2.1 Amineptine versus amisulpride						
Boyer 1996 (study 1)	55	89	54	77	41.8%	0.88 [0.71, 1.10]
Subtotal (95% CI)		**89**		**77**	**41.8%**	**0.88 [0.71, 1.10]**
Total events	55		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
22.2.2 Imipramine versus amisulpride						
Boyer 1996 (study 2)/Lecrubier 1997	46	73	47	73	33.4%	0.98 [0.77, 1.25]
Subtotal (95% CI)		**73**		**73**	**33.4%**	**0.98 [0.77, 1.25]**
Total events	46		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.86)						
22.2.3 Amitriptyline versus amisulpride						
Ravizza 1999	39	87	77	166	24.7%	0.97 [0.73, 1.28]
Subtotal (95% CI)		**87**		**166**	**24.7%**	**0.97 [0.73, 1.28]**
Total events	39		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**249**		**316**	**100.0%**	**0.93 [0.81, 1.08]**
Total events	140		178			
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Test for subgroup differences: Chi² = 0.47, df = 2 (P = 0.79), I² = 0%						

Depression symptomatology (MADRS change score)



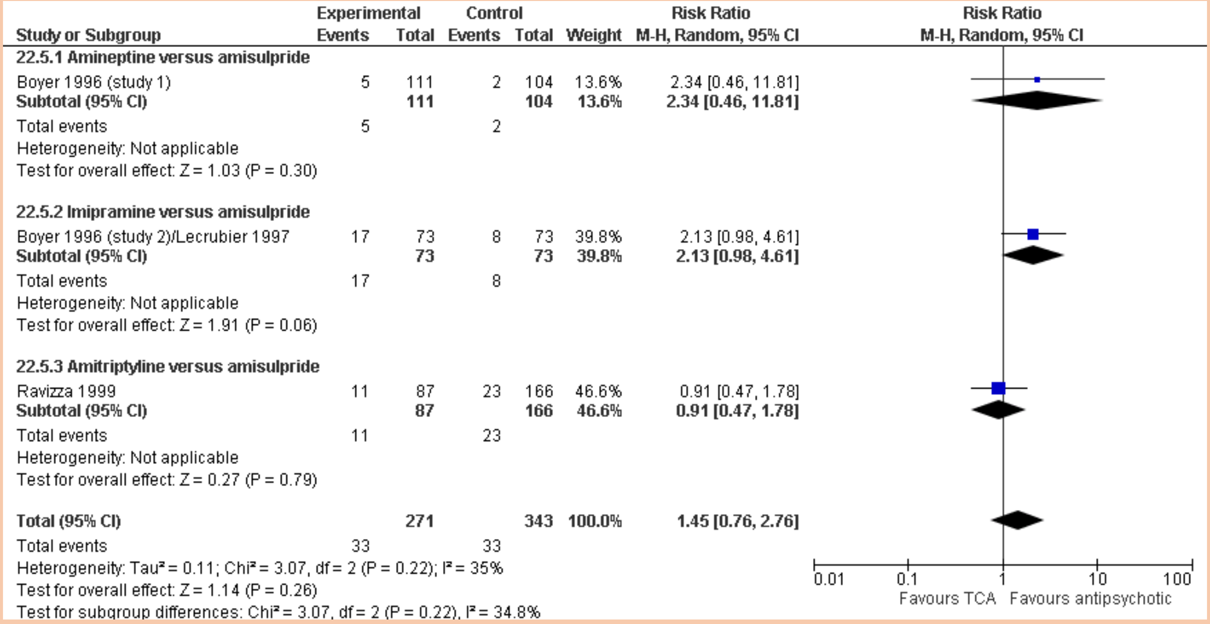
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
22.3.1 Amineptine versus amisulpride								
Boyer 1996 (study 1)	-8.21	7.03	107	-8.63	6.63	101	48.1%	0.06 [-0.21, 0.33]
Subtotal (95% CI)			**107**			**101**	**48.1%**	**0.06 [-0.21, 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.44 (P = 0.66)								
22.3.2 Amitriptyline versus amisulpride								
Ravizza 1999	-11.6	6.772001	85	-10.8	6.470703	165	51.9%	-0.12 [-0.38, 0.14]
Subtotal (95% CI)			**85**			**165**	**51.9%**	**-0.12 [-0.38, 0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
Total (95% CI)			**192**			**266**	**100.0%**	**-0.03 [-0.22, 0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%								

Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.4.1 Amineptine versus amisulpride						
Boyer 1996 (study 1)	40	111	37	104	27.8%	1.01 [0.71, 1.45]
Subtotal (95% CI)		**111**		**104**	**27.8%**	**1.01 [0.71, 1.45]**
Total events	40		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
22.4.2 Imipramine versus amisulpride						
Boyer 1996 (study 2)/Lecrubier 1997	35	73	30	73	26.9%	1.17 [0.81, 1.68]
Subtotal (95% CI)		**73**		**73**	**26.9%**	**1.17 [0.81, 1.68]**
Total events	35		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
22.4.3 Amitriptyline versus amisulpride						
Ravizza 1999	41	87	73	166	45.2%	1.07 [0.81, 1.42]
Subtotal (95% CI)		**87**		**166**	**45.2%**	**1.07 [0.81, 1.42]**
Total events	41		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**271**		**343**	**100.0%**	**1.08 [0.89, 1.30]**
Total events	116		140			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Chi² = 0.30, df = 2 (P = 0.86), I² = 0%						

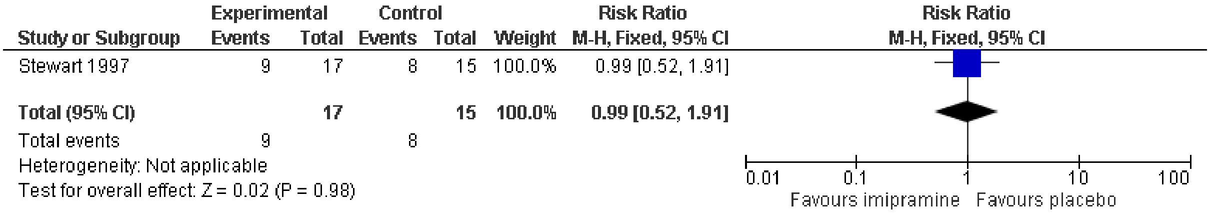
Discontinuation due to adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.5.1 Amineptine versus amisulpride						
Boyer 1996 (study 1)	5	111	2	104	13.6%	2.34 [0.46, 11.81]
Subtotal (95% CI)		**111**		**104**	**13.6%**	**2.34 [0.46, 11.81]**
Total events	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
22.5.2 Imipramine versus amisulpride						
Boyer 1996 (study 2)/Lecrubier 1997	17	73	8	73	39.8%	2.13 [0.98, 4.61]
Subtotal (95% CI)		**73**		**73**	**39.8%**	**2.13 [0.98, 4.61]**
Total events	17		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.91 (P = 0.06)						
22.5.3 Amitriptyline versus amisulpride						
Ravizza 1999	11	87	23	166	46.6%	0.91 [0.47, 1.78]
Subtotal (95% CI)		**87**		**166**	**46.6%**	**0.91 [0.47, 1.78]**
Total events	11		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**271**		**343**	**100.0%**	**1.45 [0.76, 2.76]**
Total events	33		33			
Heterogeneity: Tau² = 0.11; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 1.14 (P = 0.26)						
Test for subgroup differences: Chi² = 3.07, df = 2 (P = 0.22), I² = 34.8%						

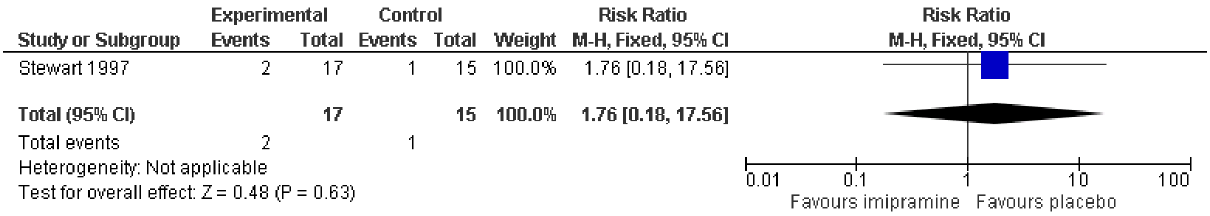
Maintenance imipramine versus placebo for relapse prevention in chronic depressive symptoms

Relapse (≥3 on CGI-I on 2 consecutive weeks)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stewart 1997	9	17	8	15	100.0%	0.99 [0.52, 1.91]
Total (95% CI)		**17**		**15**	**100.0%**	**0.99 [0.52, 1.91]**
Total events	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						

Discontinuation for any reason

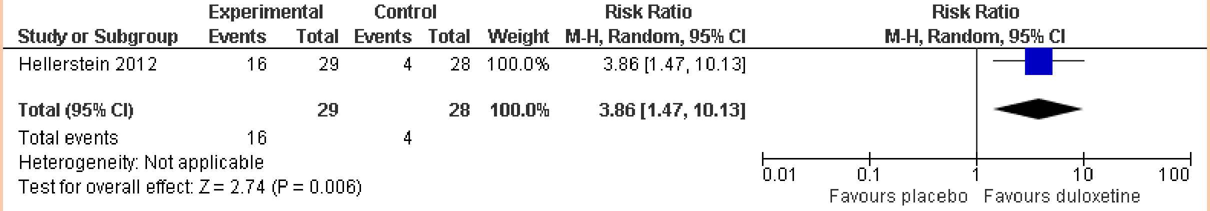


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stewart 1997	2	17	1	15	100.0%	1.76 [0.18, 17.56]
Total (95% CI)		**17**		**15**	**100.0%**	**1.76 [0.18, 17.56]**
Total events	2		1			

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

Duloxetine versus placebo for non-major chronic depressive symptoms

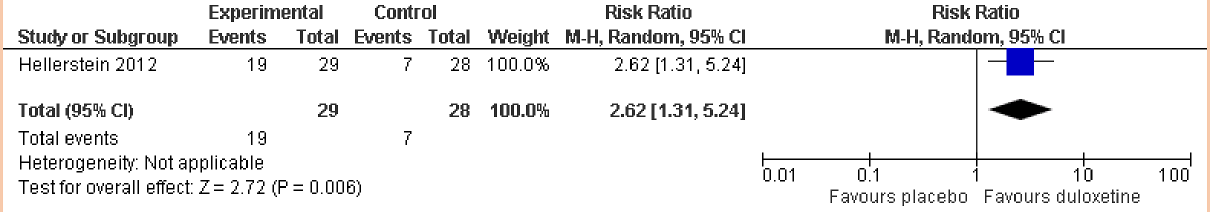
Remission (≤4 on HAM-D & HAM-D item # 1 [depressed mood] score=0)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hellerstein 2012	16	29	4	28	100.0%	3.86 [1.47, 10.13]
Total (95% CI)		**29**		**28**	**100.0%**	**3.86 [1.47, 10.13]**
Total events	16		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.74 (P = 0.006)

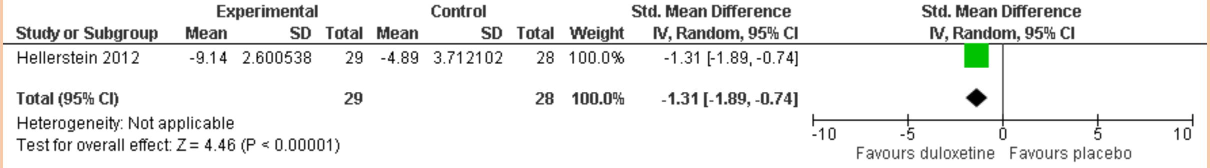
Response (≥50% improvement on HAM-D & much/very much improved on CGI-I [score 1-2])



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hellerstein 2012	19	29	7	28	100.0%	2.62 [1.31, 5.24]
Total (95% CI)		**29**		**28**	**100.0%**	**2.62 [1.31, 5.24]**
Total events	19		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.72 (P = 0.006)

Depression symptomatology (HAMD change score)

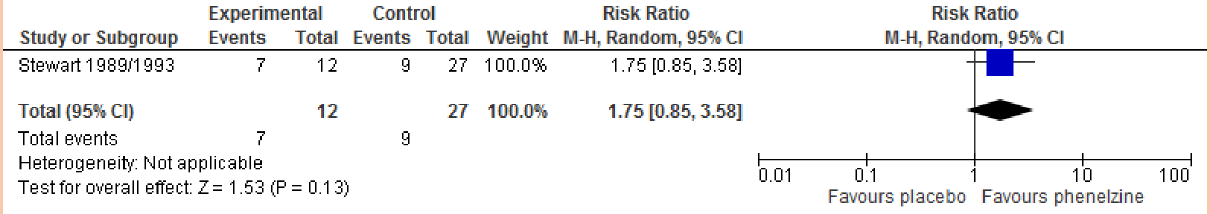


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hellerstein 2012	-9.14	2.600538	29	-4.89	3.712102	28	100.0%	-1.31 [-1.89, -0.74]
Total (95% CI)			**29**			**28**	**100.0%**	**-1.31 [-1.89, -0.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.46 (P < 0.00001)

Phenelzine versus placebo for chronic depressive symptoms

Response (CGI-I score 1-2 [much/very much improved])

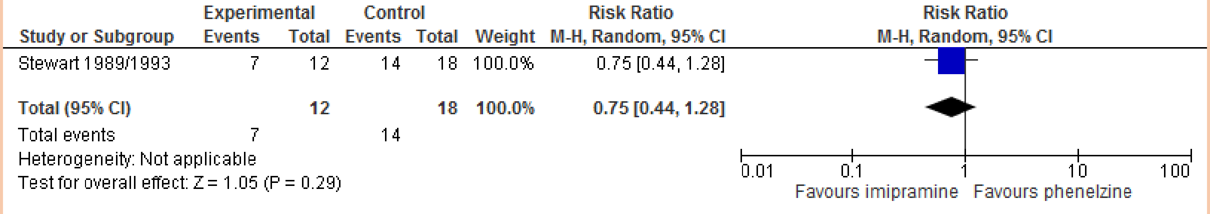


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Stewart 1989/1993	7	12	9	27	100.0%	1.75 [0.85, 3.58]
Total (95% CI)		**12**		**27**	**100.0%**	**1.75 [0.85, 3.58]**
Total events	7		9			

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

Phenelzine versus imipramine for dysthymia

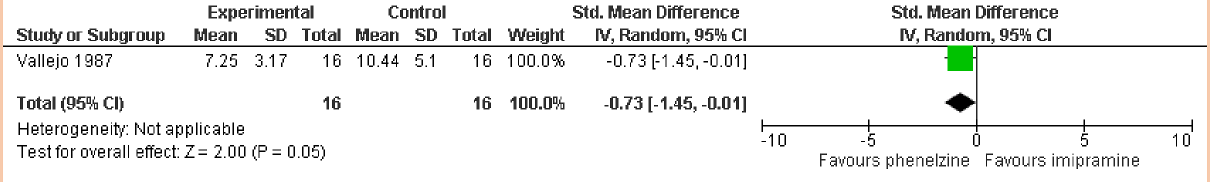
Response (CGI-I score 1-2 [much/very much improved])



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Stewart 1989/1993	7	12	14	18	100.0%	0.75 [0.44, 1.28]
Total (95% CI)		**12**		**18**	**100.0%**	**0.75 [0.44, 1.28]**
Total events	7		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

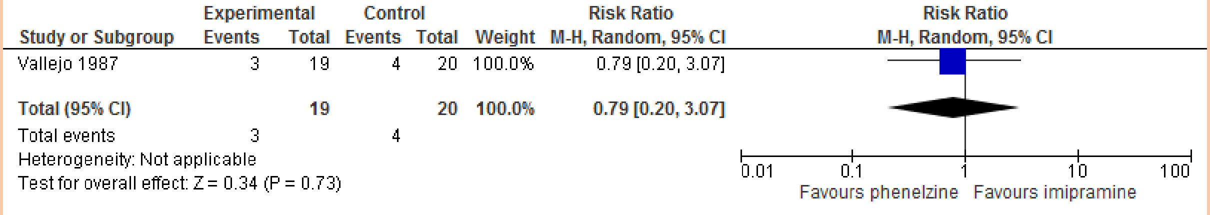
Depression symptomatology (HAMD endpoint)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Vallejo 1987	7.25	3.17	16	10.44	5.1	16	100.0%	-0.73 [-1.45, -0.01]
Total (95% CI)			**16**			**16**	**100.0%**	**-0.73 [-1.45, -0.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)

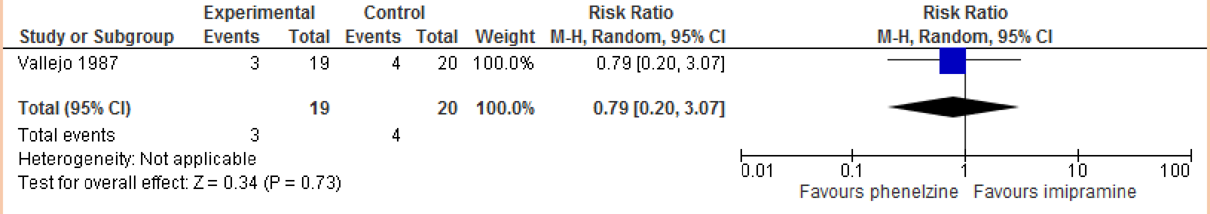
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Vallejo 1987	3	19	4	20	100.0%	0.79 [0.20, 3.07]
Total (95% CI)		**19**		**20**	**100.0%**	**0.79 [0.20, 3.07]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

Discontinuation due to adverse events

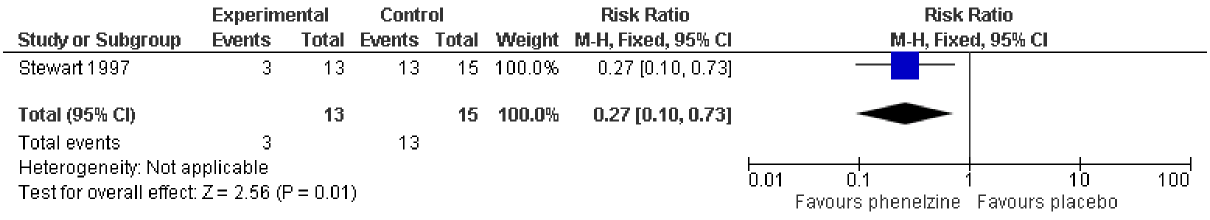


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Vallejo 1987	3	19	4	20	100.0%	0.79 [0.20, 3.07]
Total (95% CI)		**19**		**20**	**100.0%**	**0.79 [0.20, 3.07]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

Maintenance phenelzine versus placebo for relapse prevention in chronic depressive symptoms

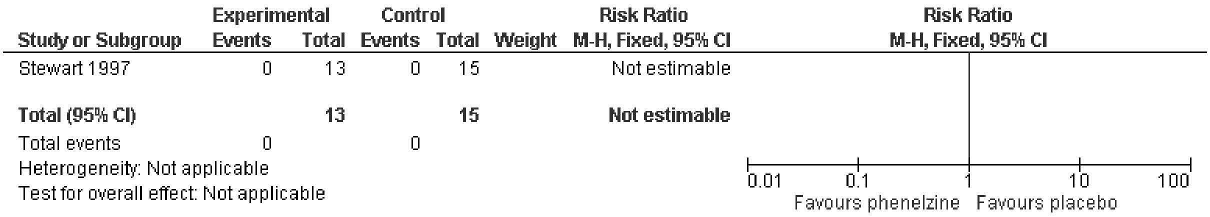
Relapse (≥3 on CGI-I on 2 consecutive weeks)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stewart 1997	3	13	13	15	100.0%	0.27 [0.10, 0.73]
Total (95% CI)		**13**		**15**	**100.0%**	**0.27 [0.10, 0.73]**
Total events	3		13			

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

Discontinuation for any reason

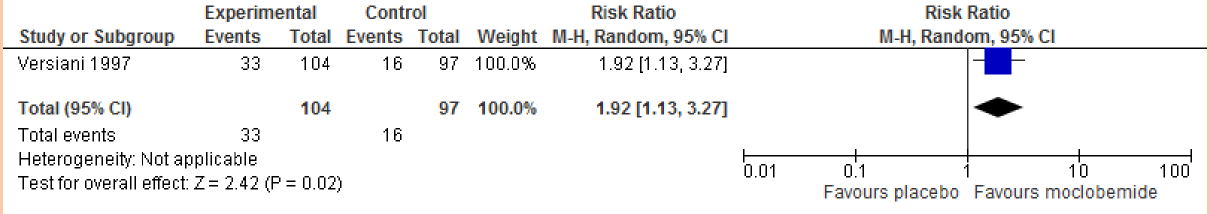


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stewart 1997	0	13	0	15		Not estimable
Total (95% CI)		**13**		**15**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Moclobemide versus placebo for chronic depressive symptoms

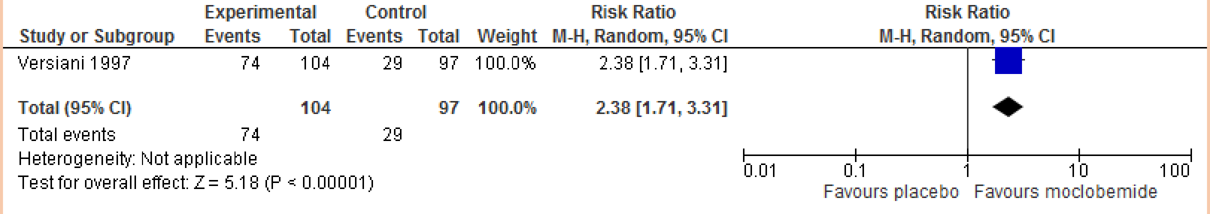
Remission (≤4 on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	33	104	16	97	100.0%	1.92 [1.13, 3.27]
Total (95% CI)		**104**		**97**	**100.0%**	**1.92 [1.13, 3.27]**
Total events	33		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)

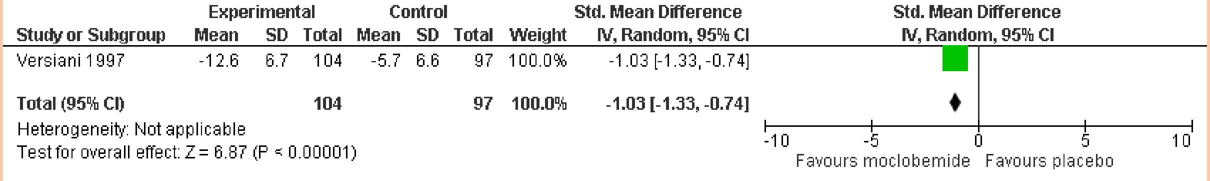
Response (≥50% improvement on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	74	104	29	97	100.0%	2.38 [1.71, 3.31]
Total (95% CI)		**104**		**97**	**100.0%**	**2.38 [1.71, 3.31]**
Total events	74		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.18 (P < 0.00001)

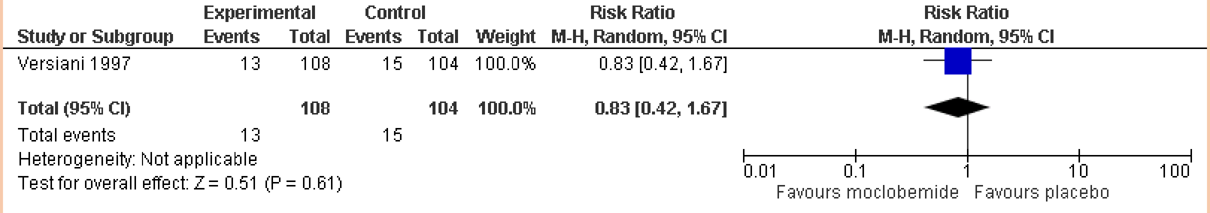
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Versiani 1997	-12.6	6.7	104	-5.7	6.6	97	100.0%	-1.03 [-1.33, -0.74]
Total (95% CI)			**104**			**97**	**100.0%**	**-1.03 [-1.33, -0.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.87 (P < 0.00001)

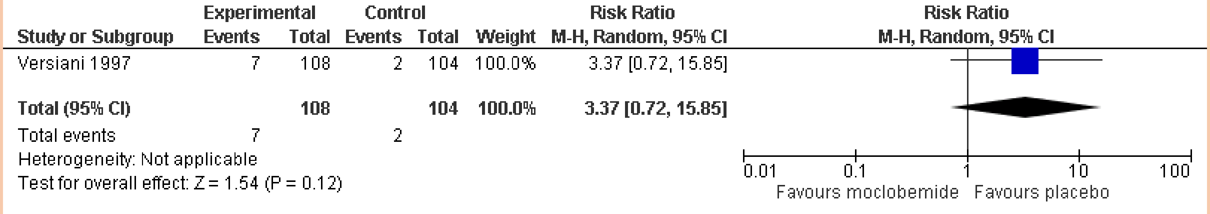
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	13	108	15	104	100.0%	0.83 [0.42, 1.67]
Total (95% CI)		**108**		**104**	**100.0%**	**0.83 [0.42, 1.67]**
Total events	13		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)

Discontinuation due to adverse events

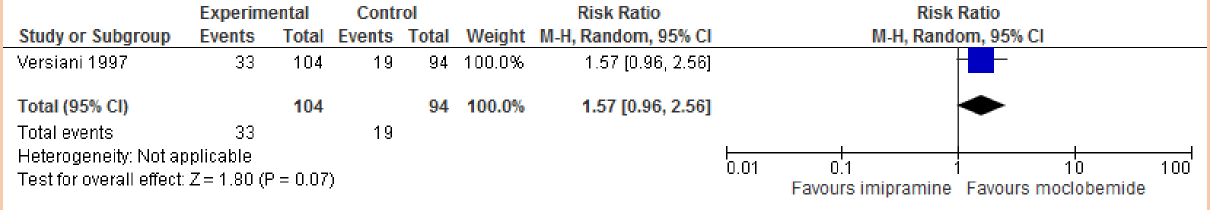


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	7	108	2	104	100.0%	3.37 [0.72, 15.85]
Total (95% CI)		**108**		**104**	**100.0%**	**3.37 [0.72, 15.85]**
Total events	7		2			

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

Moclobemide versus imipramine for chronic depressive symptoms

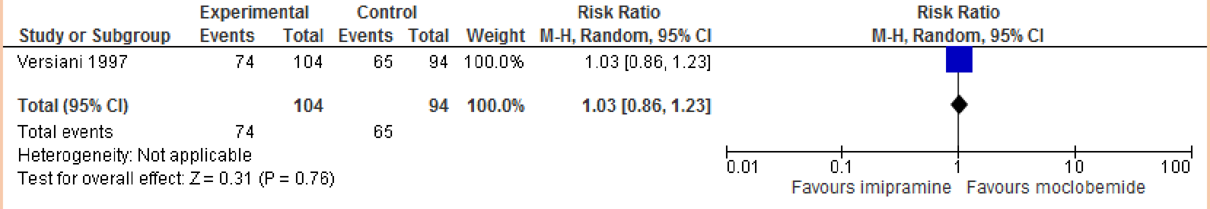
Remission (≤4 on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	33	104	19	94	100.0%	1.57 [0.96, 2.56]
Total (95% CI)		**104**		**94**	**100.0%**	**1.57 [0.96, 2.56]**
Total events	33		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)

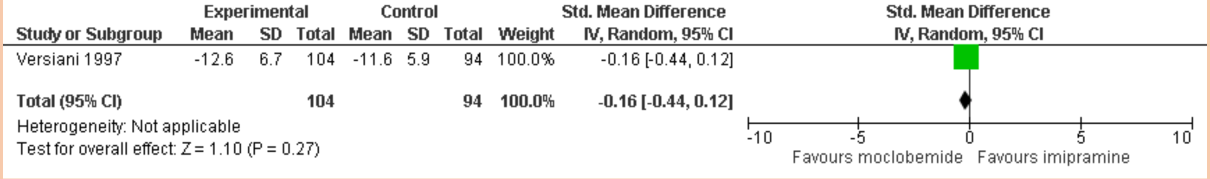
Response (≥50% improvement on HAM-D)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	74	104	65	94	100.0%	1.03 [0.86, 1.23]
Total (95% CI)		**104**		**94**	**100.0%**	**1.03 [0.86, 1.23]**
Total events	74		65			

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

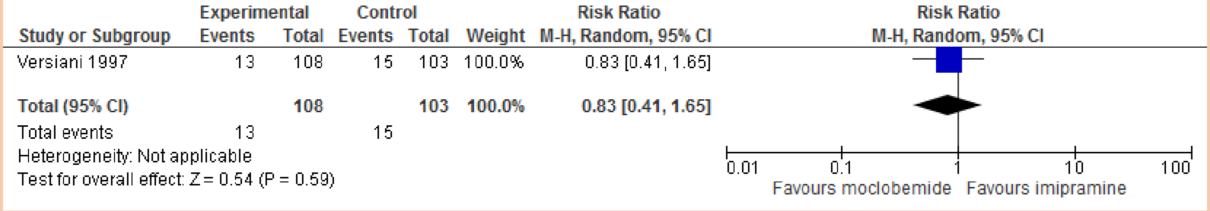
Depression symptomatology (HAMD change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Versiani 1997	-12.6	6.7	104	-11.6	5.9	94	100.0%	-0.16 [-0.44, 0.12]
Total (95% CI)			**104**			**94**	**100.0%**	**-0.16 [-0.44, 0.12]**

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

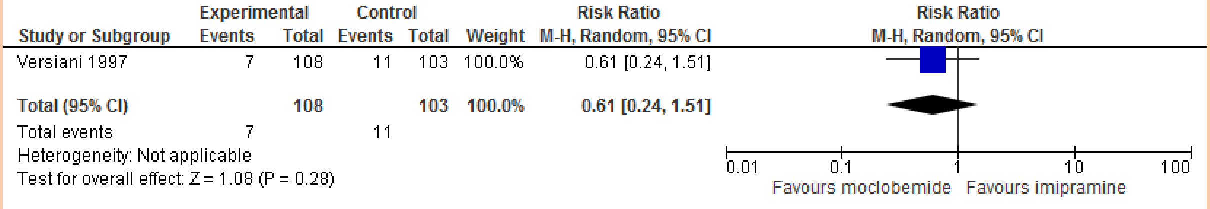
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	13	108	15	103	100.0%	0.83 [0.41, 1.65]
Total (95% CI)		**108**		**103**	**100.0%**	**0.83 [0.41, 1.65]**
Total events	13		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

Discontinuation due to adverse events

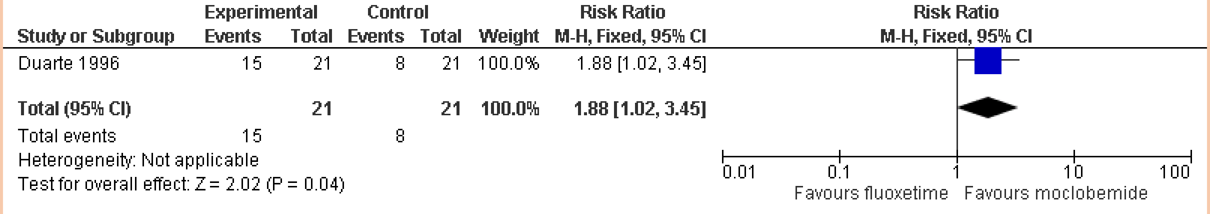


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Versiani 1997	7	108	11	103	100.0%	0.61 [0.24, 1.51]
Total (95% CI)		**108**		**103**	**100.0%**	**0.61 [0.24, 1.51]**
Total events	7		11			

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

Moclobemide versus fluoxetine for double depression

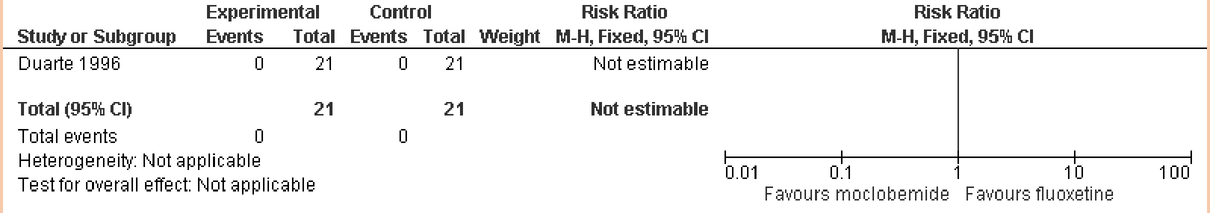
Response (≥50% improvement on HAMD score)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Duarte 1996	15	21	8	21	100.0%	1.88 [1.02, 3.45]
Total (95% CI)		**21**		**21**	**100.0%**	**1.88 [1.02, 3.45]**
Total events	15		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)

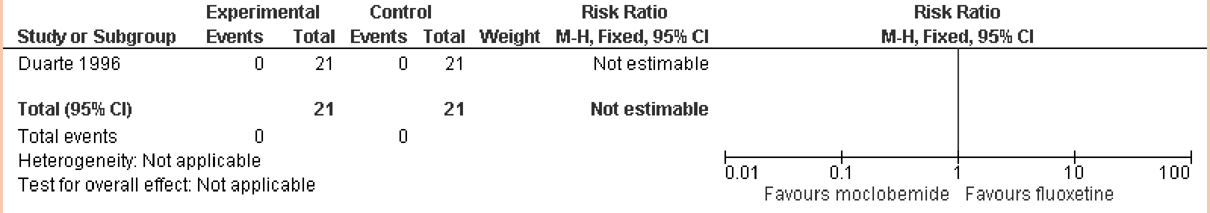
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Duarte 1996	0	21	0	21		Not estimable
Total (95% CI)		**21**		**21**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Discontinuation due to adverse events

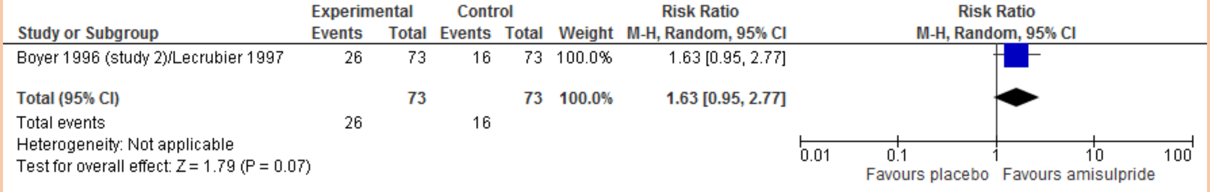


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Duarte 1996	0	21	0	21		Not estimable
Total (95% CI)		**21**		**21**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Amisulpride versus placebo for chronic depressive symptoms

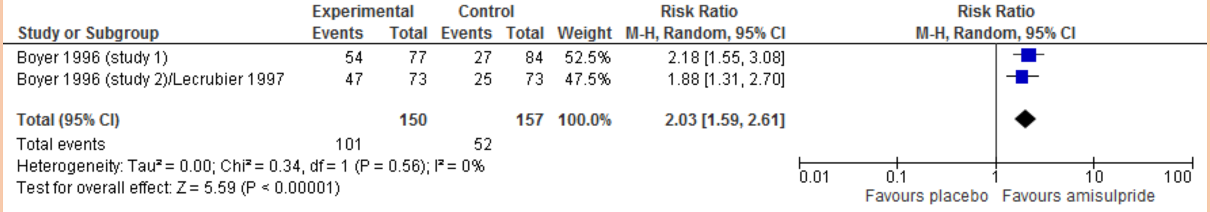
Remission (<8 on MADRS)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Boyer 1996 (study 2)/Lecrubier 1997	26	73	16	73	100.0%	1.63 [0.95, 2.77]
Total (95% CI)		**73**		**73**	**100.0%**	**1.63 [0.95, 2.77]**
Total events	26		16			

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

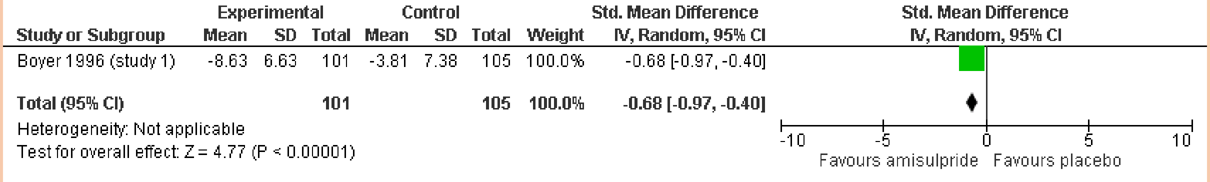
Response (CGI-I score 1-2 [much/very much improved])



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Boyer 1996 (study 1)	54	77	27	84	52.5%	2.18 [1.55, 3.08]
Boyer 1996 (study 2)/Lecrubier 1997	47	73	25	73	47.5%	1.88 [1.31, 2.70]
Total (95% CI)		**150**		**157**	**100.0%**	**2.03 [1.59, 2.61]**
Total events	101		52			

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 5.59 (P < 0.00001)

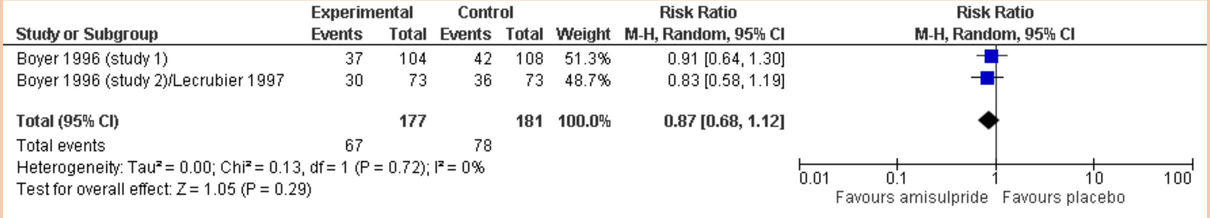
Depression symptomatology (MADRS change score)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Boyer 1996 (study 1)	-8.63	6.63	101	-3.81	7.38	105	100.0%	-0.68 [-0.97, -0.40]
Total (95% CI)			**101**			**105**	**100.0%**	**-0.68 [-0.97, -0.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.77 (P < 0.00001)

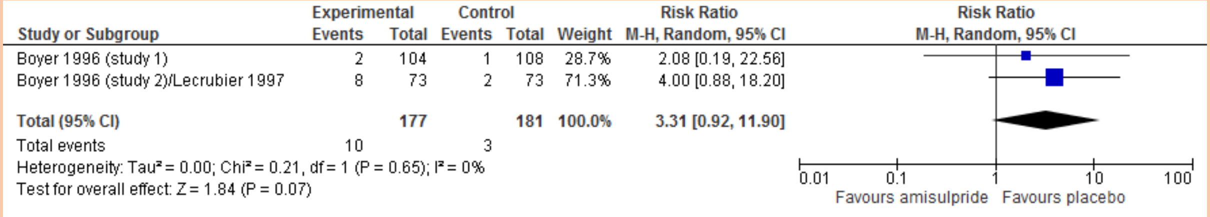
Discontinuation for any reason



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Boyer 1996 (study 1)	37	104	42	108	51.3%	0.91 [0.64, 1.30]
Boyer 1996 (study 2)/Lecrubier 1997	30	73	36	73	48.7%	0.83 [0.58, 1.19]
Total (95% CI)		**177**		**181**	**100.0%**	**0.87 [0.68, 1.12]**
Total events	67		78			

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)

Discontinuation due to adverse events



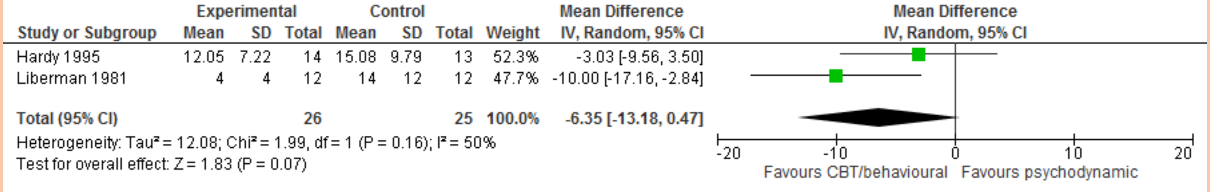
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Boyer 1996 (study 1)	2	104	1	108	28.7%	2.08 [0.19, 22.56]
Boyer 1996 (study 2)/Lecrubier 1997	8	73	2	73	71.3%	4.00 [0.88, 18.20]
Total (95% CI)		**177**		**181**	**100.0%**	**3.31 [0.92, 11.90]**
Total events	10		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)

Complex depression (chapter 10)

CBT/behavioural therapies versus psychodynamic therapies for complex depression

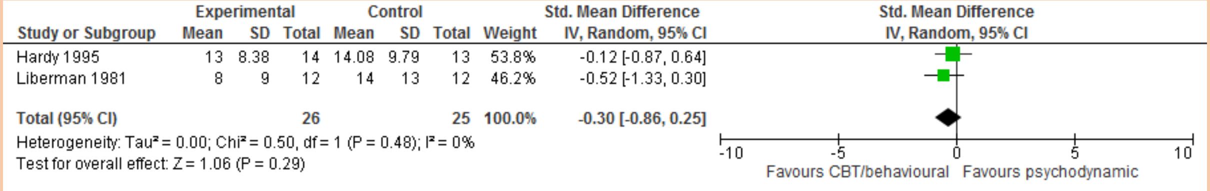
Depression symptomatology at endpoint (BDI)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hardy 1995	12.05	7.22	14	15.08	9.79	13	52.3%	-3.03 [-9.56, 3.50]
Liberman 1981	4	4	12	14	12	12	47.7%	-10.00 [-17.16, -2.84]
Total (95% CI)			**26**			**25**	**100.0%**	**-6.35 [-13.18, 0.47]**

Heterogeneity: Tau² = 12.08; Chi² = 1.99, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 1.83 (P = 0.07)

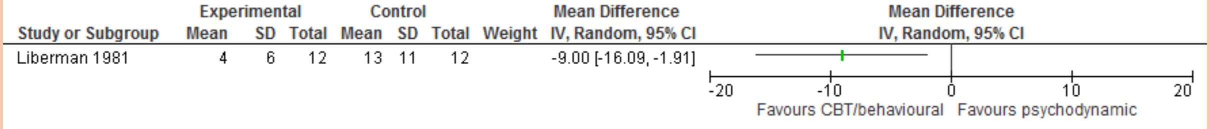
Depression symptomatology at 12 week follow-up (BDI)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hardy 1995	13	8.38	14	14.08	9.79	13	53.8%	-0.12 [-0.87, 0.64]
Liberman 1981	8	9	12	14	13	12	46.2%	-0.52 [-1.33, 0.30]
Total (95% CI)			**26**			**25**	**100.0%**	**-0.30 [-0.86, 0.25]**

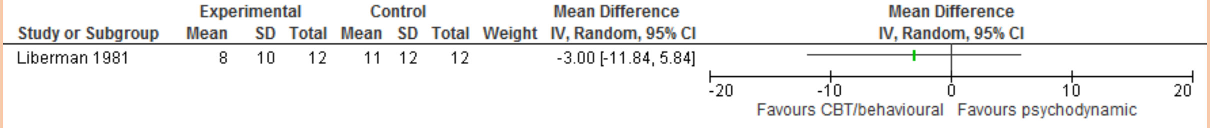
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

Depression symptomatology at 24 week follow-up (BDI)



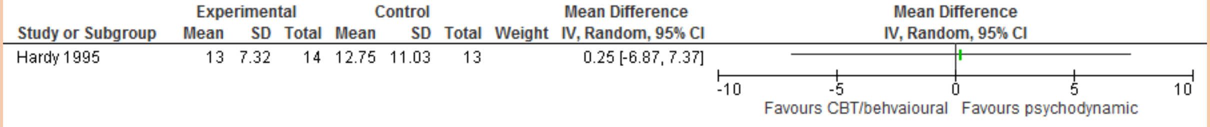
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Liberman 1981	4	6	12	13	11	12		-9.00 [-16.09, -1.91]

Depression symptomatology at 36 week follow-up (BDI)



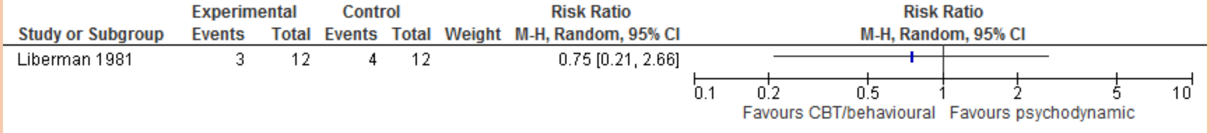
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Liberman 1981	8	10	12	11	12	12		-3.00 [-11.84, 5.84]

Depression symptomatology at 1 year follow-up (BDI)



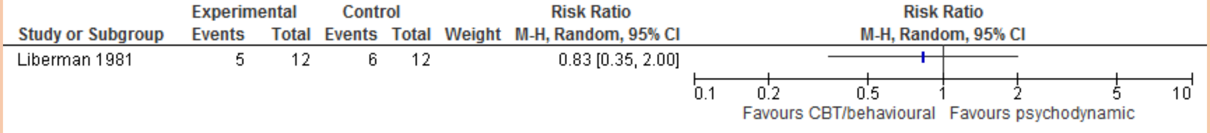
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hardy 1995	13	7.32	14	12.75	11.03	13		0.25 [-6.87, 7.37]

Suicide attempts at 24 week follow-up



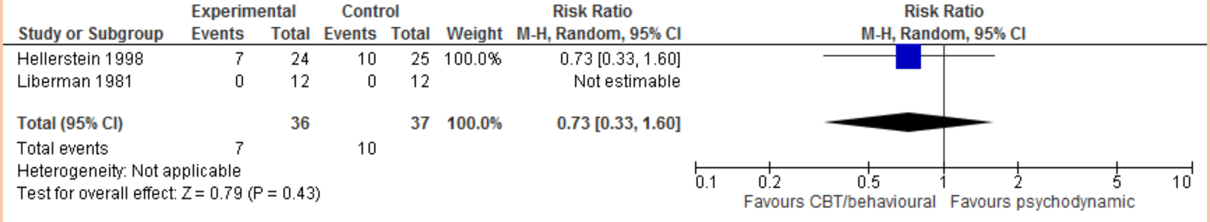
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Liberman 1981	3	12	4	12		0.75 [0.21, 2.66]

Suicide attempts at 2 year follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Liberman 1981	5	12	6	12		0.83 [0.35, 2.00]

Discontinuations for any reason

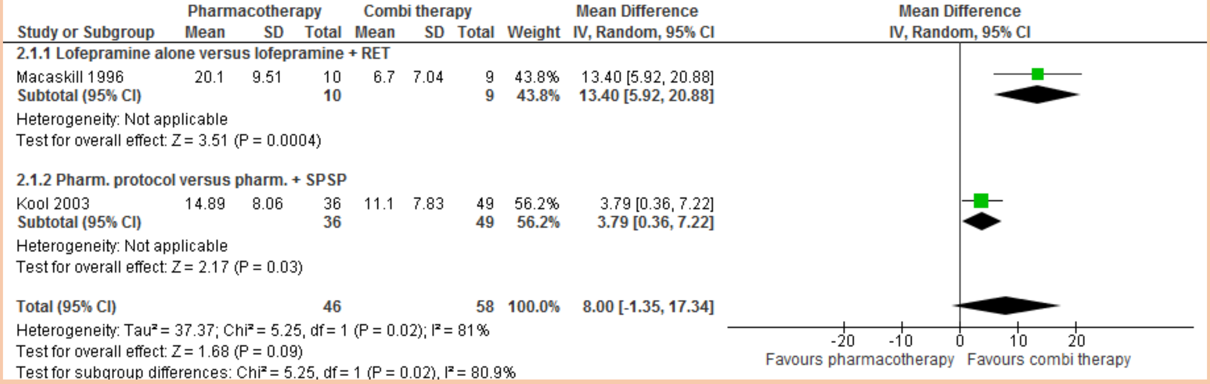


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hellerstein 1998	7	24	10	25	100.0%	0.73 [0.33, 1.60]
Liberman 1981	0	12	0	12		Not estimable
Total (95% CI)		**36**		**37**	**100.0%**	**0.73 [0.33, 1.60]**
Total events	7		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

Pharmacotherapy versus combination therapy for complex depression

Depression symptomatology at endpoint (HAM-D 17)

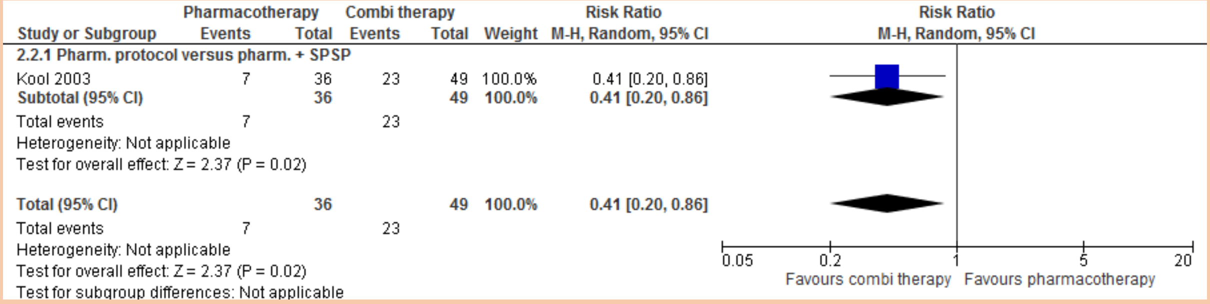


Study or Subgroup	Pharmacotherapy Mean	Pharmacotherapy SD	Pharmacotherapy Total	Combi therapy Mean	Combi therapy SD	Combi therapy Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Lofepramine alone versus lofepramine + RET								
Macaskill 1996	20.1	9.51	10	6.7	7.04	9	43.8%	13.40 [5.92, 20.88]
Subtotal (95% CI)			**10**			**9**	**43.8%**	**13.40 [5.92, 20.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.51 (P = 0.0004)								
2.1.2 Pharm. protocol versus pharm. + SPSP								
Kool 2003	14.89	8.06	36	11.1	7.83	49	56.2%	3.79 [0.36, 7.22]
Subtotal (95% CI)			**36**			**49**	**56.2%**	**3.79 [0.36, 7.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.17 (P = 0.03)								
Total (95% CI)			**46**			**58**	**100.0%**	**8.00 [-1.35, 17.34]**

Heterogeneity: Tau² = 37.37; Chi² = 5.25, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Chi² = 5.25, df = 1 (P = 0.02), I² = 80.9%

Mean Difference
IV, Random, 95% CI
-20
-10
0
10
20
Favours pharmacotherapy
Favours combi therapy

Remission at endpoint (HAM-D 17)

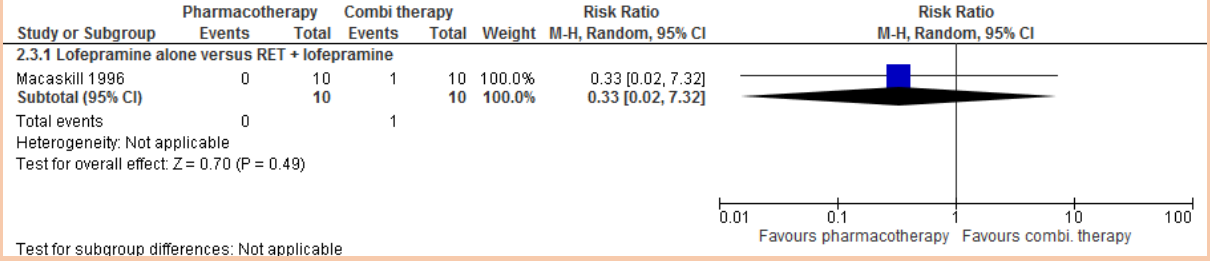


Study or Subgroup	Pharmacotherapy Events	Pharmacotherapy Total	Combi therapy Events	Combi therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Pharm. protocol versus pharm. + SPSP						
Kool 2003	7	36	23	49	100.0%	0.41 [0.20, 0.86]
Subtotal (95% CI)		**36**		**49**	**100.0%**	**0.41 [0.20, 0.86]**
Total events	7		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**36**		**49**	**100.0%**	**0.41 [0.20, 0.86]**
Total events	7		23			

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

Risk Ratio
M-H, Random, 95% CI
0.05
0.2
1
5
20
Favours combi therapy
Favours pharmacotherapy

Discontinuations for any reason



Study or Subgroup	Pharmacotherapy Events	Pharmacotherapy Total	Combi therapy Events	Combi therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Lofepramine alone versus RET + lofepramine						
Macaskill 1996	0	10	1	10	100.0%	0.33 [0.02, 7.32]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.33 [0.02, 7.32]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						

Test for subgroup differences: Not applicable

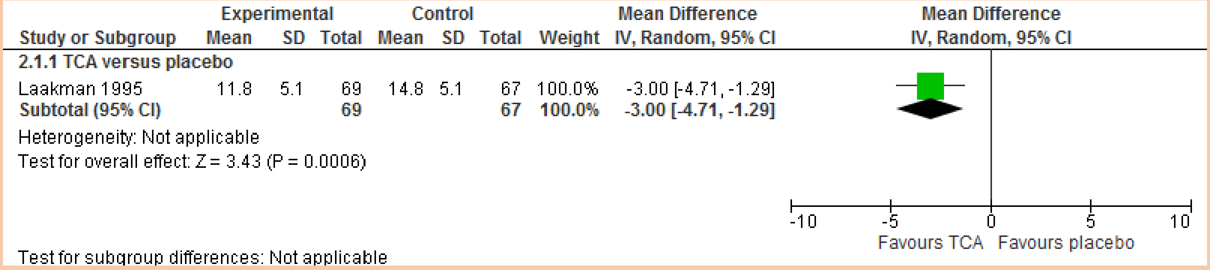
Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours pharmacotherapy
Favours combi. therapy

Psychotic depression (chapter 10)

Antidepressants versus other pharmacological interventions

Antidepressant versus placebo

Depressive symptoms at endpoint (HAMD 17)

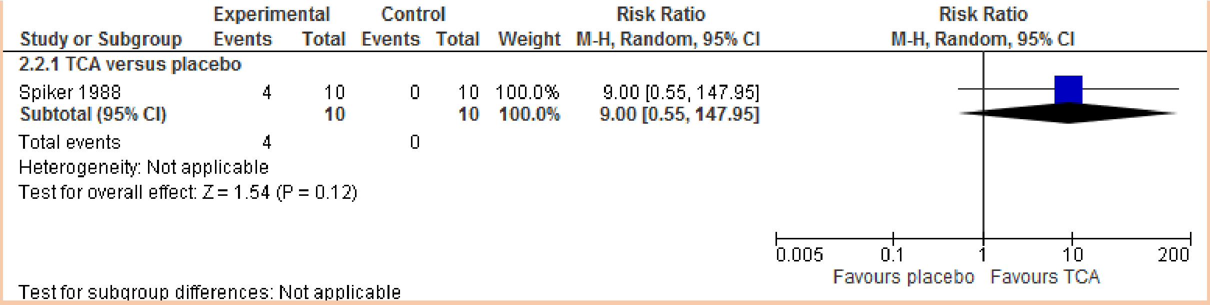


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 TCA versus placebo								
Laakman 1995	11.8	5.1	69	14.8	5.1	67	100.0%	-3.00 [-4.71, -1.29]
Subtotal (95% CI)			**69**			**67**	**100.0%**	**-3.00 [-4.71, -1.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								

Test for subgroup differences: Not applicable

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours TCA
Favours placebo

Remission

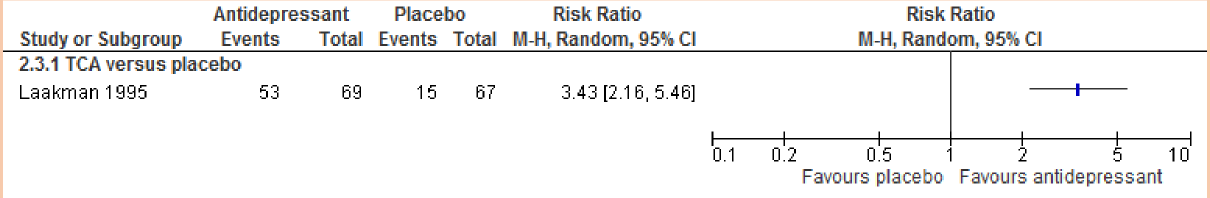


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 TCA versus placebo						
Spiker 1988	4	10	0	10	100.0%	9.00 [0.55, 147.95]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**9.00 [0.55, 147.95]**
Total events	4		0			

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

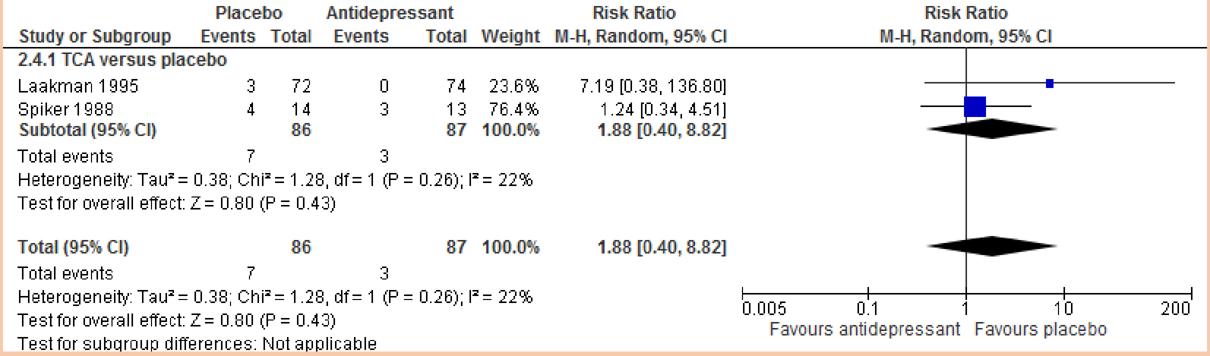
Test for subgroup differences: Not applicable

Response



Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
2.3.1 TCA versus placebo					
Laakman 1995	53	69	15	67	3.43 [2.16, 5.46]

Discontinuation



Study or Subgroup	Placebo Events	Placebo Total	Antidepressant Events	Antidepressant Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 TCA versus placebo						
Laakman 1995	3	72	0	74	23.6%	7.19 [0.38, 136.80]
Spiker 1988	4	14	3	13	76.4%	1.24 [0.34, 4.51]
Subtotal (95% CI)		**86**		**87**	**100.0%**	**1.88 [0.40, 8.82]**
Total events	7		3			

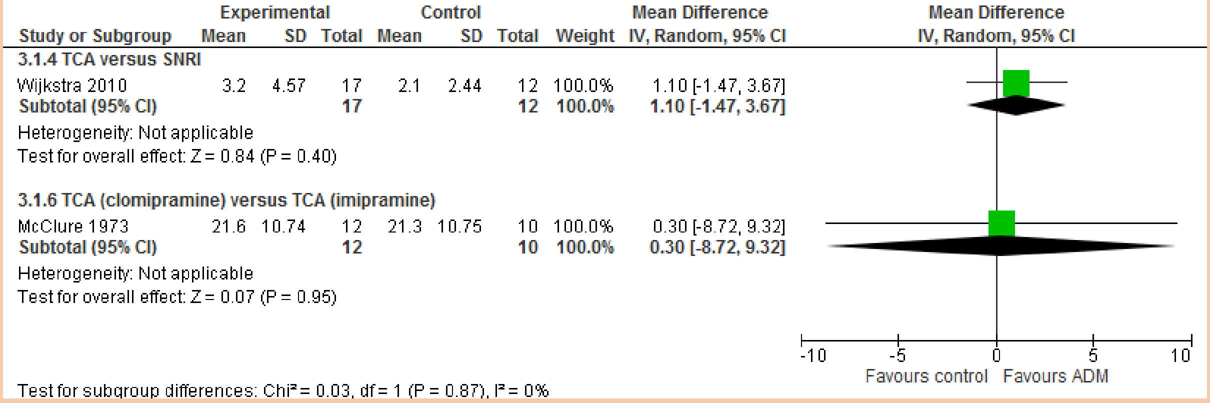
Heterogeneity: Tau² = 0.38; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 0.80 (P = 0.43)

Total (95% CI)		**86**		**87**	**100.0%**	**1.88 [0.40, 8.82]**
Total events	7		3			

Heterogeneity: Tau² = 0.38; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 0.80 (P = 0.43)
Test for subgroup differences: Not applicable

Antidepressant versus antidepressant

Depressive symptoms at endpoint



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.1.4 TCA versus SNRI								
Wijkstra 2010	3.2	4.57	17	2.1	2.44	12	100.0%	1.10 [-1.47, 3.67]
Subtotal (95% CI)			**17**			**12**	**100.0%**	**1.10 [-1.47, 3.67]**

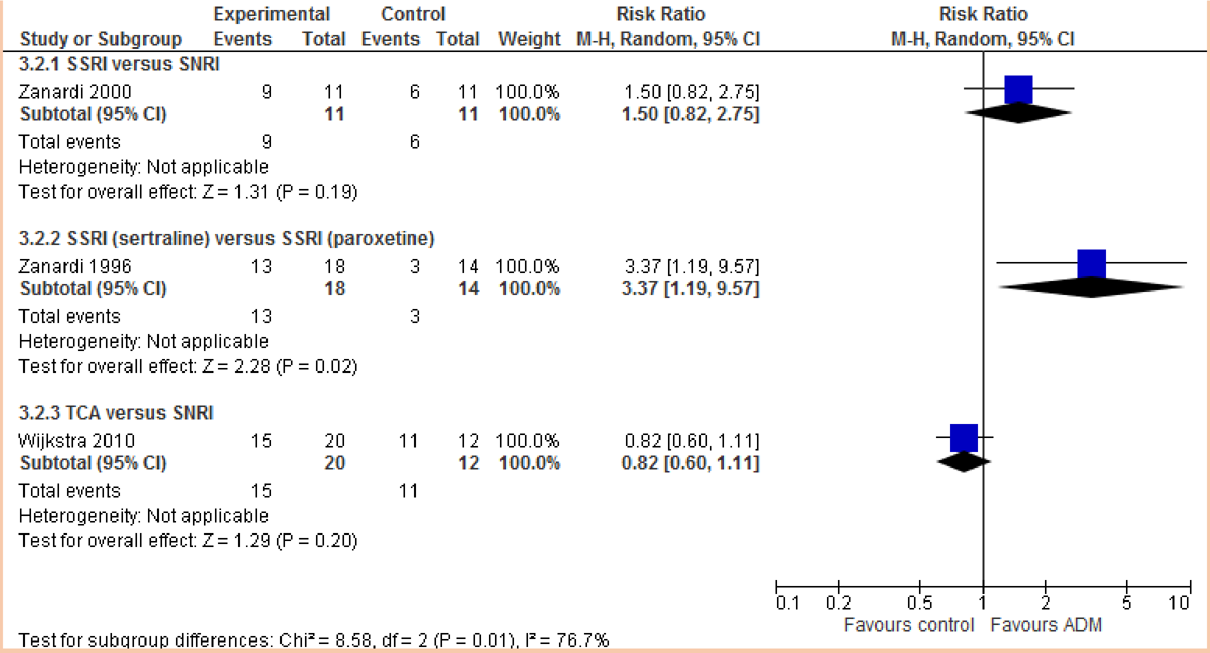
Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

3.1.6 TCA (clomipramine) versus TCA (imipramine)								
McClure 1973	21.6	10.74	12	21.3	10.75	10	100.0%	0.30 [-8.72, 9.32]
Subtotal (95% CI)			**12**			**10**	**100.0%**	**0.30 [-8.72, 9.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.95)

Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%

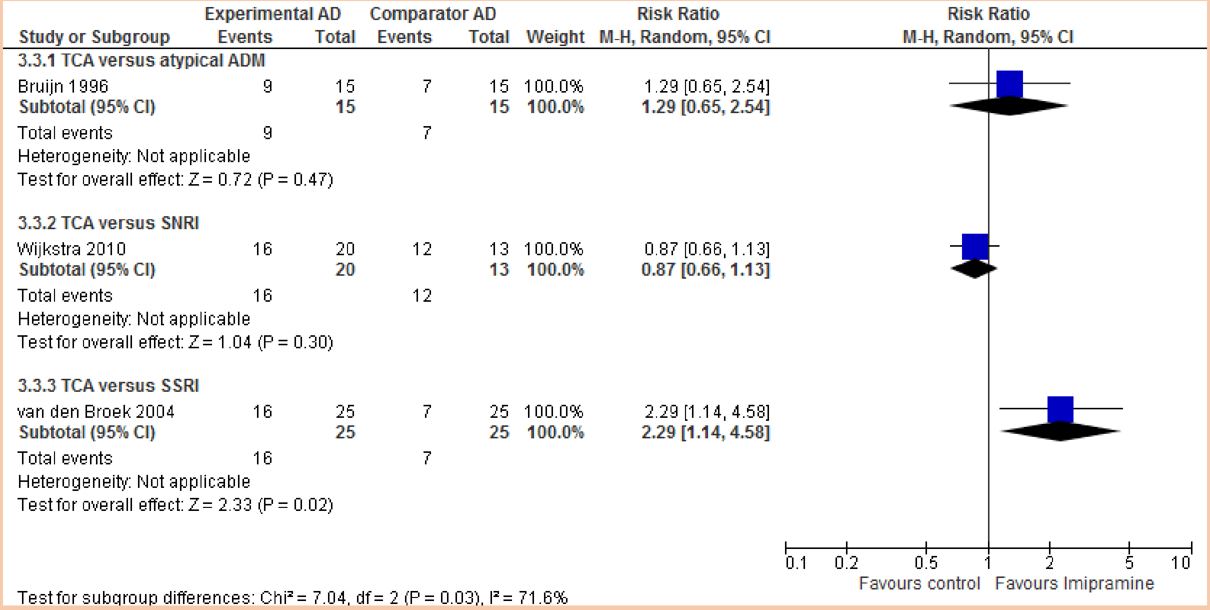
Remission



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 SSRI versus SNRI						
Zanardi 2000	9	11	6	11	100.0%	1.50 [0.82, 2.75]
Subtotal (95% CI)		**11**		**11**	**100.0%**	**1.50 [0.82, 2.75]**
Total events	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
3.2.2 SSRI (sertraline) versus SSRI (paroxetine)						
Zanardi 1996	13	18	3	14	100.0%	3.37 [1.19, 9.57]
Subtotal (95% CI)		**18**		**14**	**100.0%**	**3.37 [1.19, 9.57]**
Total events	13		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						
3.2.3 TCA versus SNRI						
Wijkstra 2010	15	20	11	12	100.0%	0.82 [0.60, 1.11]
Subtotal (95% CI)		**20**		**12**	**100.0%**	**0.82 [0.60, 1.11]**
Total events	15		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						

Test for subgroup differences: Chi² = 8.58, df = 2 (P = 0.01), I² = 76.7%

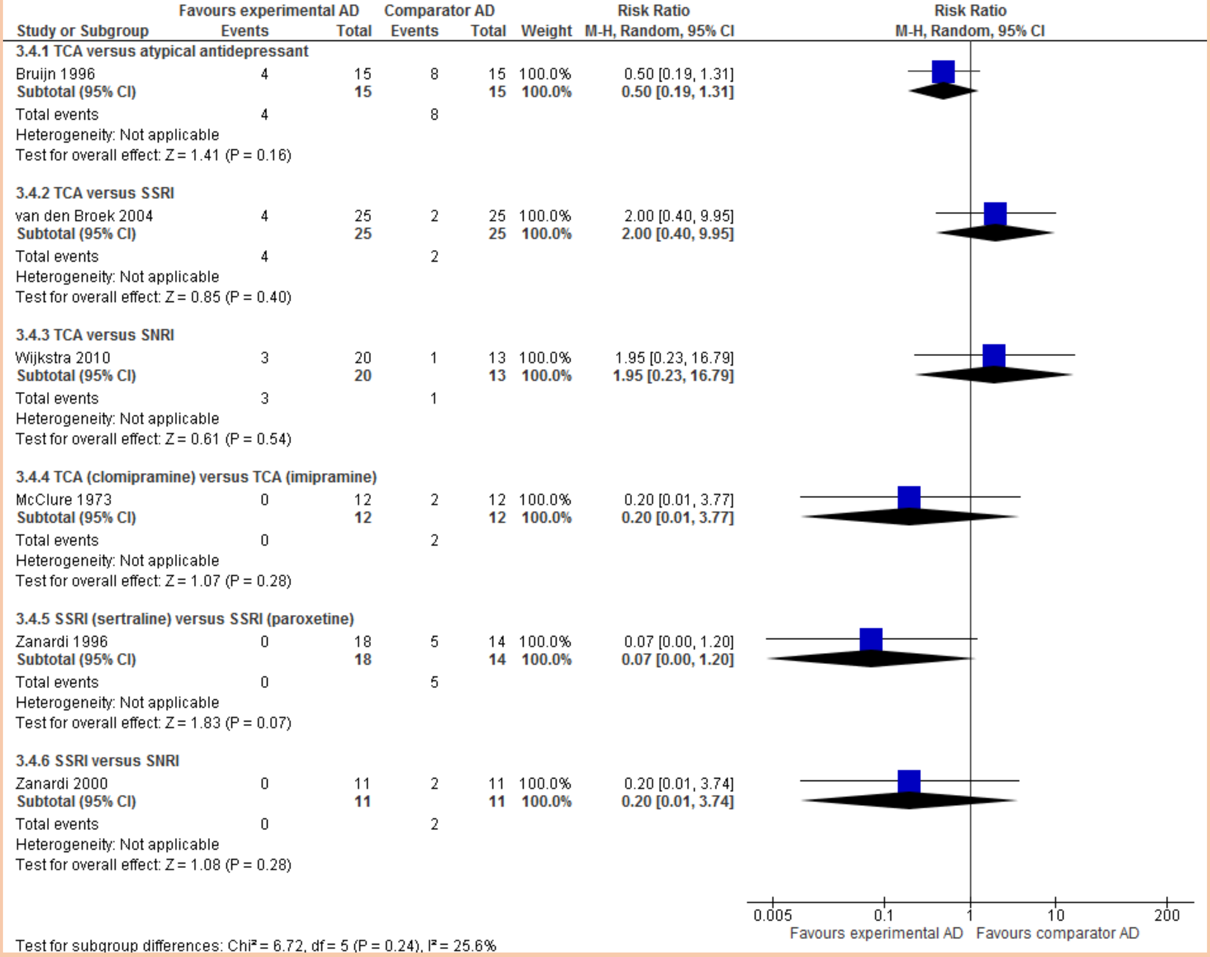
Response



Study or Subgroup	Experimental AD Events	Experimental AD Total	Comparator AD Events	Comparator AD Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 TCA versus atypical ADM						
Bruijn 1996	9	15	7	15	100.0%	1.29 [0.65, 2.54]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**1.29 [0.65, 2.54]**
Total events	9		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
3.3.2 TCA versus SNRI						
Wijkstra 2010	16	20	12	13	100.0%	0.87 [0.66, 1.13]
Subtotal (95% CI)		**20**		**13**	**100.0%**	**0.87 [0.66, 1.13]**
Total events	16		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
3.3.3 TCA versus SSRI						
van den Broek 2004	16	25	7	25	100.0%	2.29 [1.14, 4.58]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**2.29 [1.14, 4.58]**
Total events	16		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.33 (P = 0.02)						

Test for subgroup differences: Chi² = 7.04, df = 2 (P = 0.03), I² = 71.6%

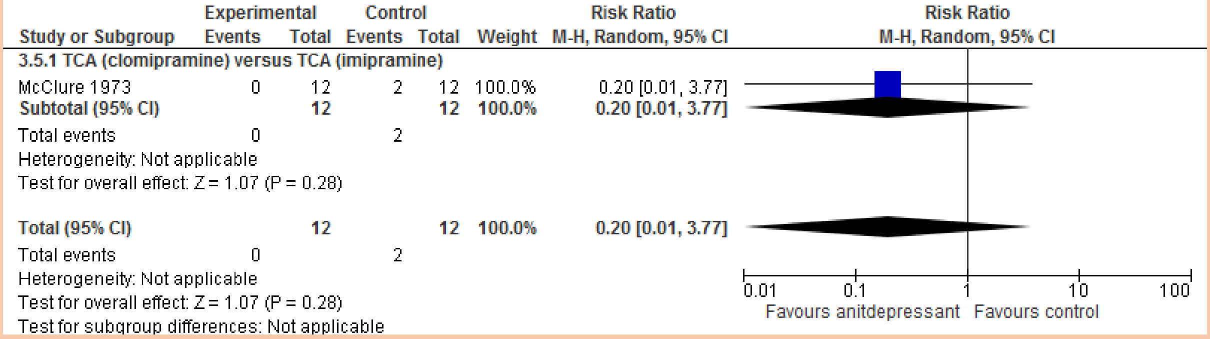
Discontinuation



Study or Subgroup	Favours experimental AD Events	Total	Comparator AD Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 TCA versus atypical antidepressant						
Bruijn 1996	4	15	8	15	100.0%	0.50 [0.19, 1.31]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.50 [0.19, 1.31]**
Total events	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
3.4.2 TCA versus SSRI						
van den Broek 2004	4	25	2	25	100.0%	2.00 [0.40, 9.95]
Subtotal (95% CI)		**25**		**25**	**100.0%**	**2.00 [0.40, 9.95]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
3.4.3 TCA versus SNRI						
Wijkstra 2010	3	20	1	13	100.0%	1.95 [0.23, 16.79]
Subtotal (95% CI)		**20**		**13**	**100.0%**	**1.95 [0.23, 16.79]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
3.4.4 TCA (clomipramine) versus TCA (imipramine)						
McClure 1973	0	12	2	12	100.0%	0.20 [0.01, 3.77]
Subtotal (95% CI)		**12**		**12**	**100.0%**	**0.20 [0.01, 3.77]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
3.4.5 SSRI (sertraline) versus SSRI (paroxetine)						
Zanardi 1996	0	18	5	14	100.0%	0.07 [0.00, 1.20]
Subtotal (95% CI)		**18**		**14**	**100.0%**	**0.07 [0.00, 1.20]**
Total events	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
3.4.6 SSRI versus SNRI						
Zanardi 2000	0	11	2	11	100.0%	0.20 [0.01, 3.74]
Subtotal (95% CI)		**11**		**11**	**100.0%**	**0.20 [0.01, 3.74]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						

Test for subgroup differences: Chi² = 6.72, df = 5 (P = 0.24), I² = 25.6%

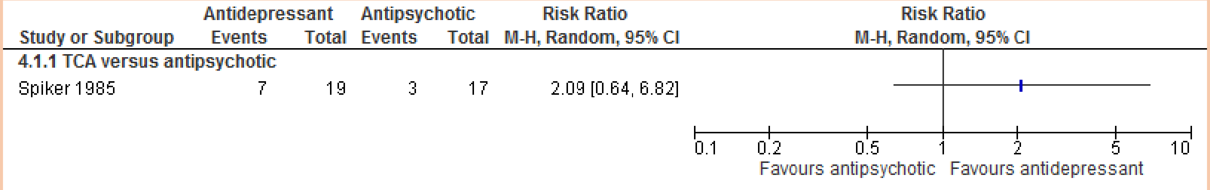
Discontinuation due to side effects



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 TCA (clomipramine) versus TCA (imipramine)						
McClure 1973	0	12	2	12	100.0%	0.20 [0.01, 3.77]
Subtotal (95% CI)		**12**		**12**	**100.0%**	**0.20 [0.01, 3.77]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**12**		**12**	**100.0%**	**0.20 [0.01, 3.77]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Not applicable						

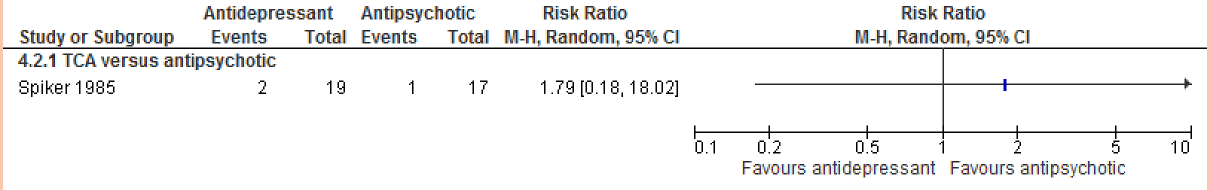
Antidepressant versus antipsychotic

Remission



Study or Subgroup	Antidepressant Events	Antidepressant Total	Antipsychotic Events	Antipsychotic Total	Risk Ratio M-H, Random, 95% CI
4.1.1 TCA versus antipsychotic					
Spiker 1985	7	19	3	17	2.09 [0.64, 6.82]

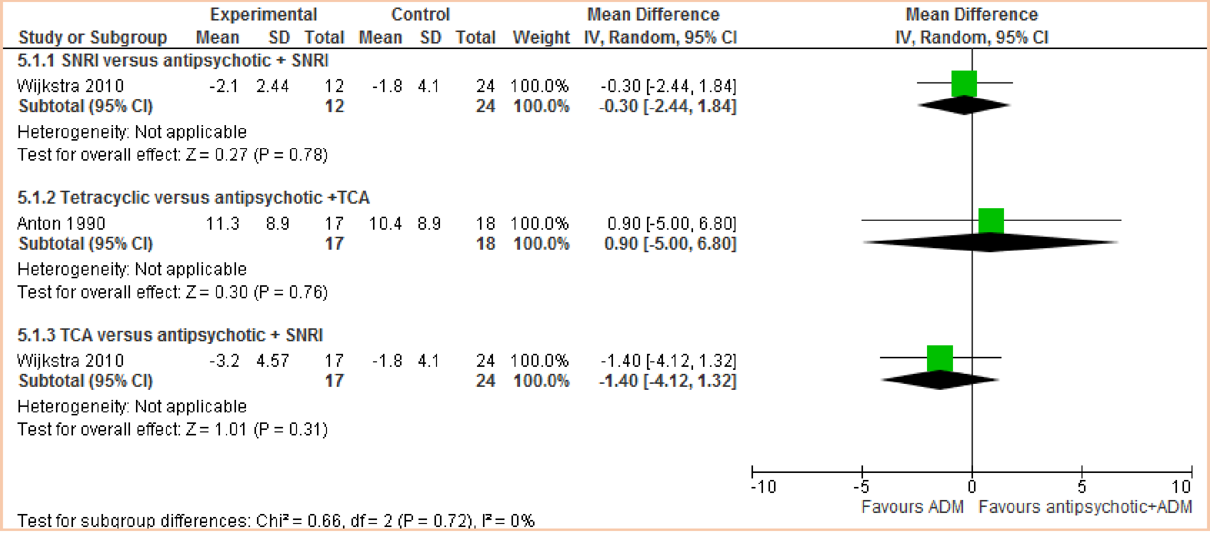
Discontinuation



Study or Subgroup	Antidepressant Events	Antidepressant Total	Antipsychotic Events	Antipsychotic Total	Risk Ratio M-H, Random, 95% CI
4.2.1 TCA versus antipsychotic					
Spiker 1985	2	19	1	17	1.79 [0.18, 18.02]

Antidepressant versus antipsychotic plus antidepressant

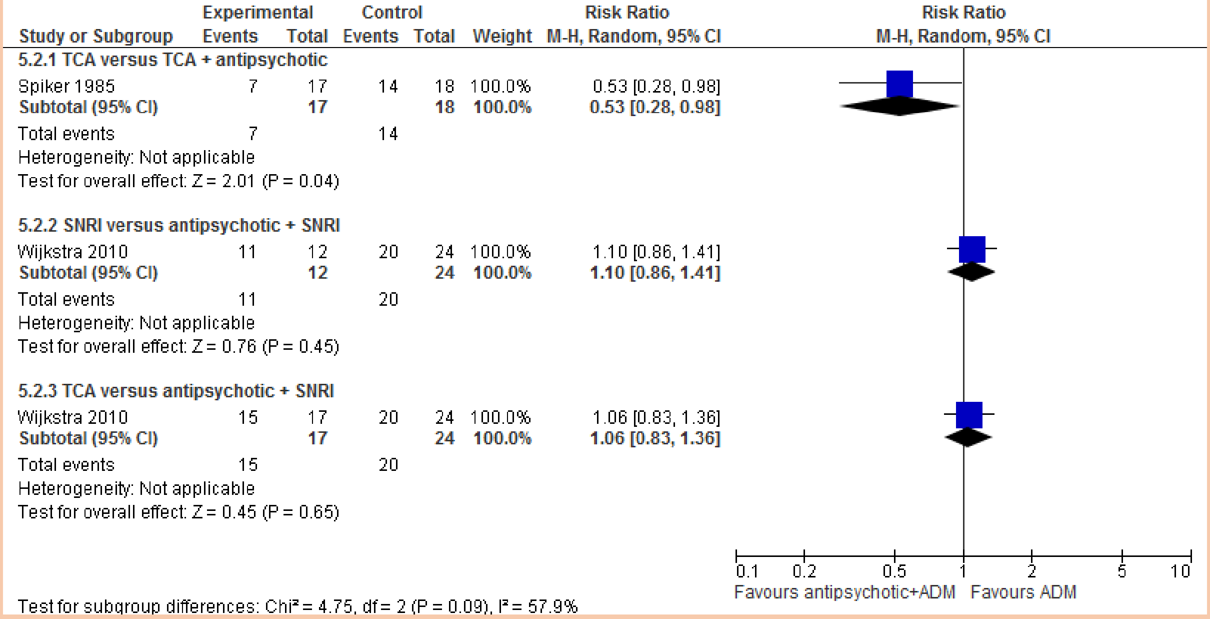
Depression symptomatology at endpoint (HAMD 17)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 SNRI versus antipsychotic + SNRI								
Wijkstra 2010	-2.1	2.44	12	-1.8	4.1	24	100.0%	-0.30 [-2.44, 1.84]
Subtotal (95% CI)			**12**			**24**	**100.0%**	**-0.30 [-2.44, 1.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.27 (P = 0.78)								
5.1.2 Tetracyclic versus antipsychotic +TCA								
Anton 1990	11.3	8.9	17	10.4	8.9	18	100.0%	0.90 [-5.00, 6.80]
Subtotal (95% CI)			**17**			**18**	**100.0%**	**0.90 [-5.00, 6.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								
5.1.3 TCA versus antipsychotic + SNRI								
Wijkstra 2010	-3.2	4.57	17	-1.8	4.1	24	100.0%	-1.40 [-4.12, 1.32]
Subtotal (95% CI)			**17**			**24**	**100.0%**	**-1.40 [-4.12, 1.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								

Test for subgroup differences: Chi² = 0.66, df = 2 (P = 0.72), I² = 0%

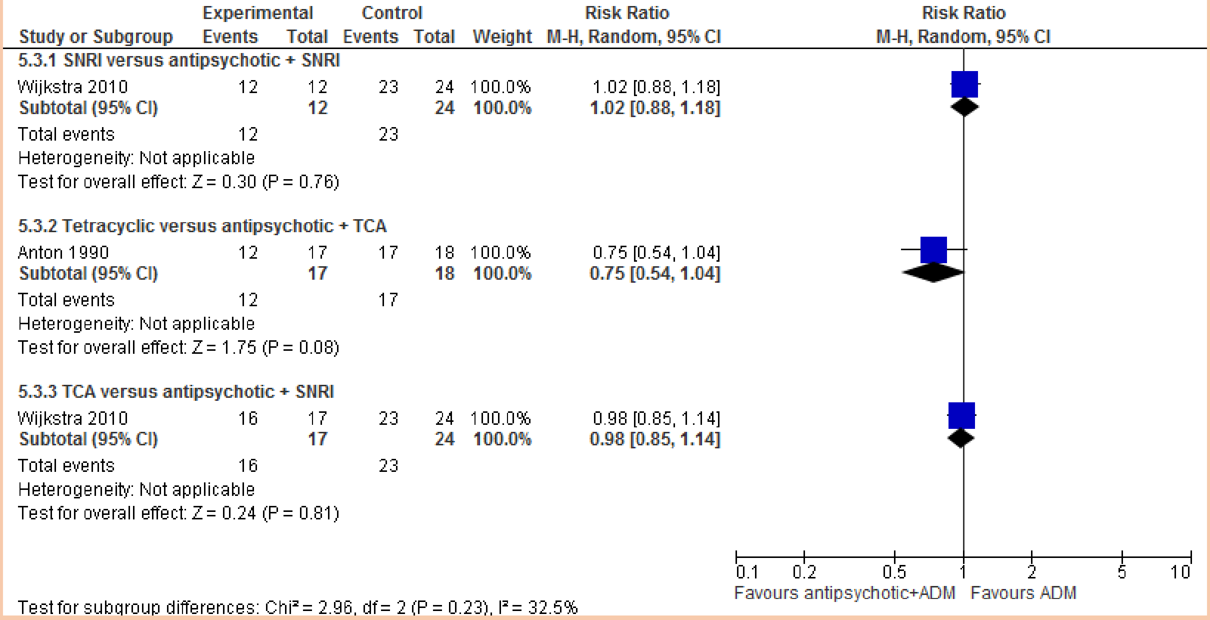
Remission



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 TCA versus TCA + antipsychotic						
Spiker 1985	7	17	14	18	100.0%	0.53 [0.28, 0.98]
Subtotal (95% CI)		**17**		**18**	**100.0%**	**0.53 [0.28, 0.98]**
Total events	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
5.2.2 SNRI versus antipsychotic + SNRI						
Wijkstra 2010	11	12	20	24	100.0%	1.10 [0.86, 1.41]
Subtotal (95% CI)		**12**		**24**	**100.0%**	**1.10 [0.86, 1.41]**
Total events	11		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
5.2.3 TCA versus antipsychotic + SNRI						
Wijkstra 2010	15	17	20	24	100.0%	1.06 [0.83, 1.36]
Subtotal (95% CI)		**17**		**24**	**100.0%**	**1.06 [0.83, 1.36]**
Total events	15		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						

Test for subgroup differences: Chi² = 4.75, df = 2 (P = 0.09), I² = 57.9%

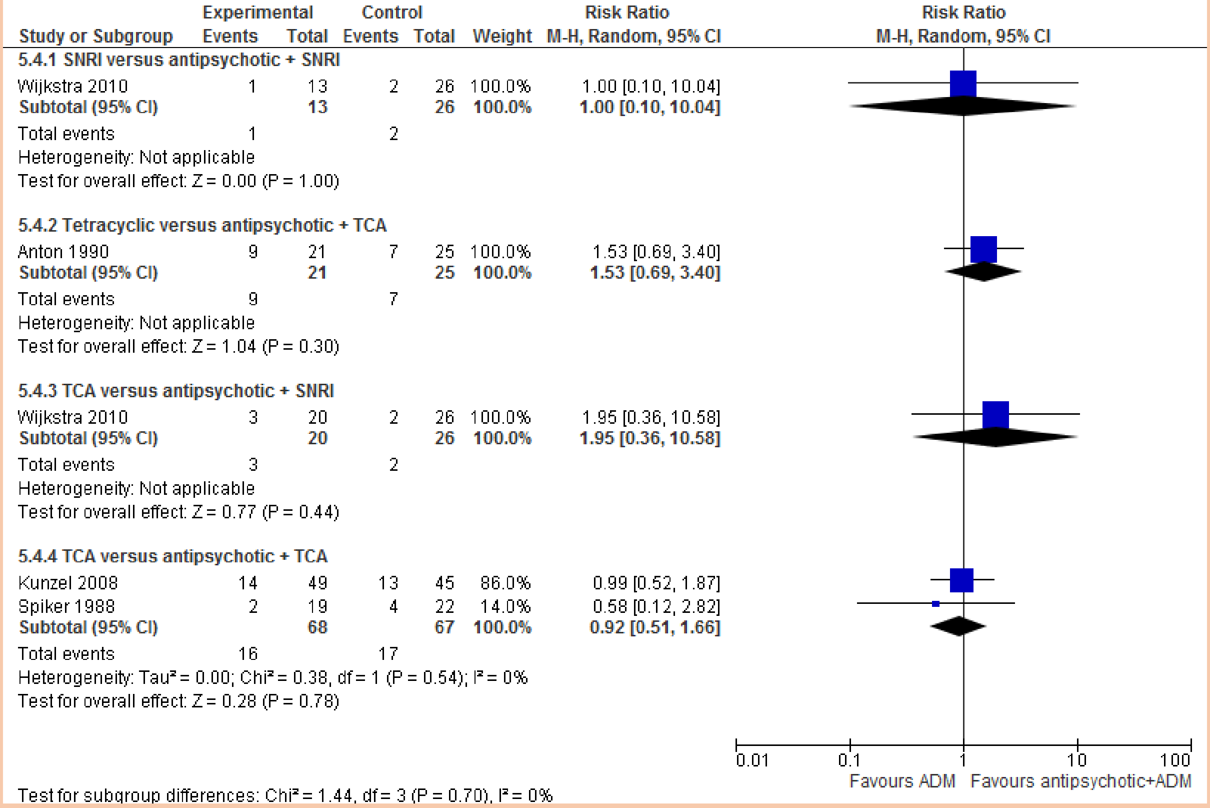
Response



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 SNRI versus antipsychotic + SNRI						
Wijkstra 2010	12	12	23	24	100.0%	1.02 [0.88, 1.18]
Subtotal (95% CI)		**12**		**24**	**100.0%**	**1.02 [0.88, 1.18]**
Total events	12		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
5.3.2 Tetracyclic versus antipsychotic + TCA						
Anton 1990	12	17	17	18	100.0%	0.75 [0.54, 1.04]
Subtotal (95% CI)		**17**		**18**	**100.0%**	**0.75 [0.54, 1.04]**
Total events	12		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
5.3.3 TCA versus antipsychotic + SNRI						
Wijkstra 2010	16	17	23	24	100.0%	0.98 [0.85, 1.14]
Subtotal (95% CI)		**17**		**24**	**100.0%**	**0.98 [0.85, 1.14]**
Total events	16		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						

Test for subgroup differences: Chi² = 2.96, df = 2 (P = 0.23), I² = 32.5%

Discontinuation

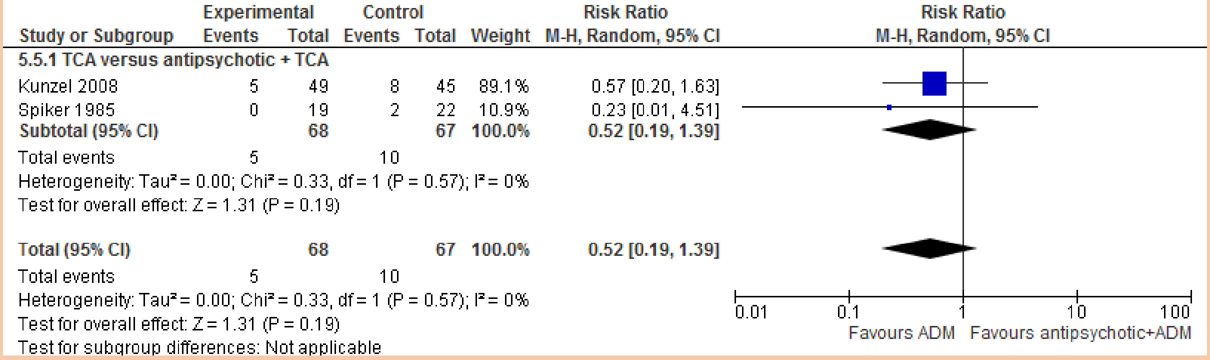


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 SNRI versus antipsychotic + SNRI						
Wijkstra 2010	1	13	2	26	100.0%	1.00 [0.10, 10.04]
Subtotal (95% CI)		**13**		**26**	**100.0%**	**1.00 [0.10, 10.04]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
5.4.2 Tetracyclic versus antipsychotic + TCA						
Anton 1990	9	21	7	25	100.0%	1.53 [0.69, 3.40]
Subtotal (95% CI)		**21**		**25**	**100.0%**	**1.53 [0.69, 3.40]**
Total events	9		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
5.4.3 TCA versus antipsychotic + SNRI						
Wijkstra 2010	3	20	2	26	100.0%	1.95 [0.36, 10.58]
Subtotal (95% CI)		**20**		**26**	**100.0%**	**1.95 [0.36, 10.58]**
Total events	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
5.4.4 TCA versus antipsychotic + TCA						
Kunzel 2008	14	49	13	45	86.0%	0.99 [0.52, 1.87]
Spiker 1988	2	19	4	22	14.0%	0.58 [0.12, 2.82]
Subtotal (95% CI)		**68**		**67**	**100.0%**	**0.92 [0.51, 1.66]**
Total events	16		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						

Test for subgroup differences: Chi² = 1.44, df = 3 (P = 0.70), I² = 0%

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours ADM
Favours antipsychotic+ADM

Discontinuation due to side effects



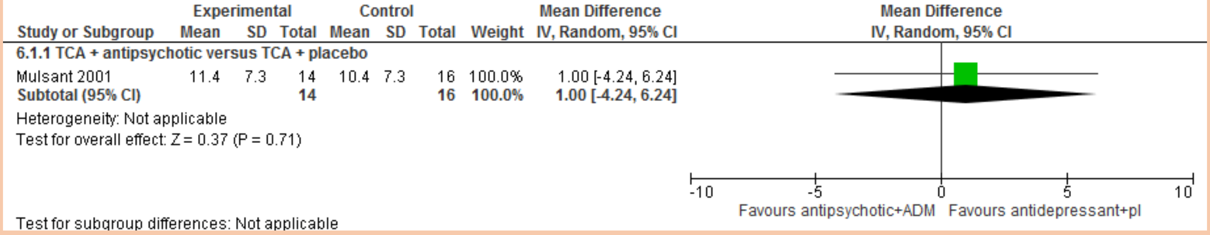
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 TCA versus antipsychotic + TCA						
Kunzel 2008	5	49	8	45	89.1%	0.57 [0.20, 1.63]
Spiker 1985	0	19	2	22	10.9%	0.23 [0.01, 4.51]
Subtotal (95% CI)		**68**		**67**	**100.0%**	**0.52 [0.19, 1.39]**
Total events	5		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**68**		**67**	**100.0%**	**0.52 [0.19, 1.39]**
Total events	5		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours ADM
Favours antipsychotic+ADM

Combined antidepressant and antipsychotic versus other pharmacological interventions

Antidepressant plus antipsychotic versus antidepressant plus placebo

Depression symptomatology at endpoint (HAMD 17)

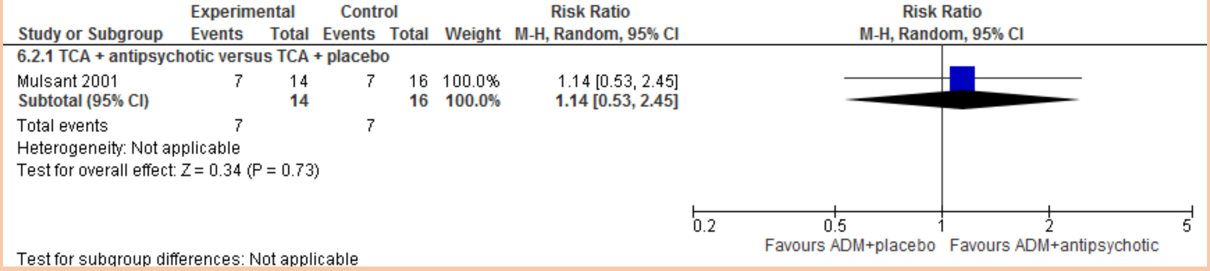


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
6.1.1 TCA + antipsychotic versus TCA + placebo								
Mulsant 2001	11.4	7.3	14	10.4	7.3	16	100.0%	1.00 [-4.24, 6.24]
Subtotal (95% CI)			**14**			**16**	**100.0%**	**1.00 [-4.24, 6.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								

Test for subgroup differences: Not applicable

Mean Difference
IV, Random, 95% CI
-10
-5
0
5
10
Favours antipsychotic+ADM
Favours antidepressant+pl

Remission



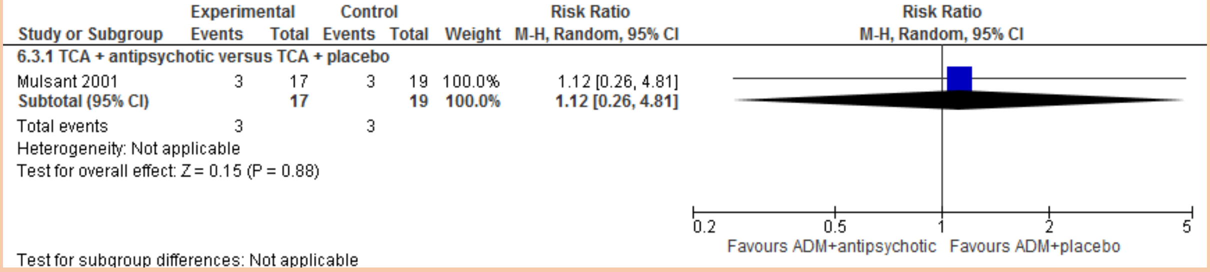
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 TCA + antipsychotic versus TCA + placebo						
Mulsant 2001	7	14	7	16	100.0%	1.14 [0.53, 2.45]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**1.14 [0.53, 2.45]**
Total events	7		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.2
0.5
1
2
5
Favours ADM+placebo
Favours ADM+antipsychotic

Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 TCA + antipsychotic versus TCA + placebo						
Mulsant 2001	3	17	3	19	100.0%	1.12 [0.26, 4.81]
Subtotal (95% CI)		**17**		**19**	**100.0%**	**1.12 [0.26, 4.81]**
Total events	3		3			

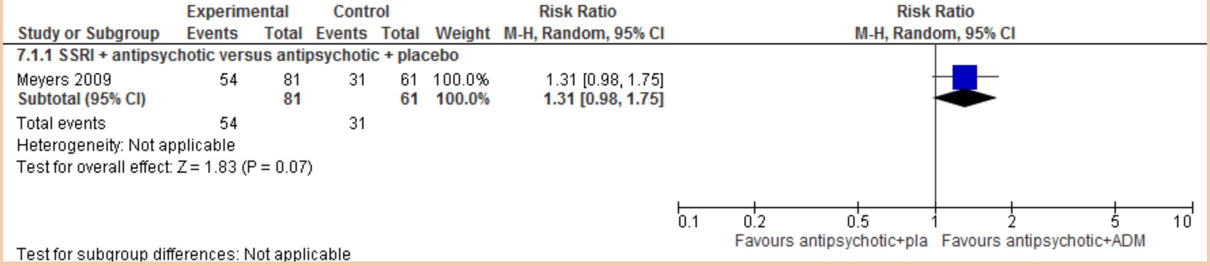
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.2
0.5
1
2
5
Favours ADM+antipsychotic
Favours ADM+placebo

Antidepressant plus antipsychotic versus antipsychotic plus placebo

Remission



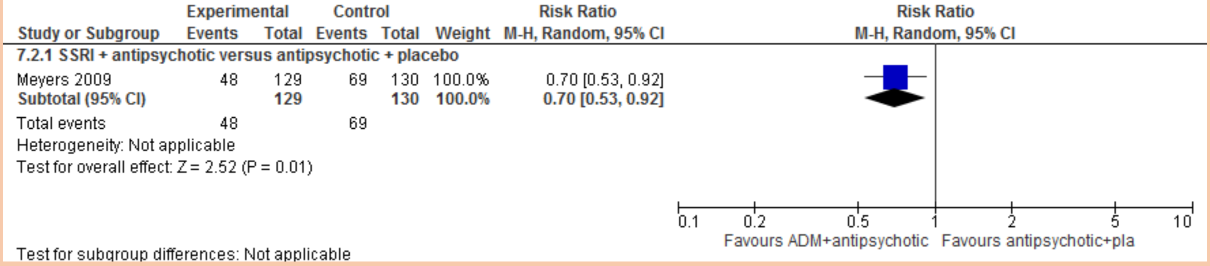
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 SSRI + antipsychotic versus antipsychotic + placebo						
Meyers 2009	54	81	31	61	100.0%	1.31 [0.98, 1.75]
Subtotal (95% CI)		**81**		**61**	**100.0%**	**1.31 [0.98, 1.75]**
Total events	54		31			

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

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours antipsychotic+pla
Favours antipsychotic+ADM

Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 SSRI + antipsychotic versus antipsychotic + placebo						
Meyers 2009	48	129	69	130	100.0%	0.70 [0.53, 0.92]
Subtotal (95% CI)		**129**		**130**	**100.0%**	**0.70 [0.53, 0.92]**
Total events	48		69			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)

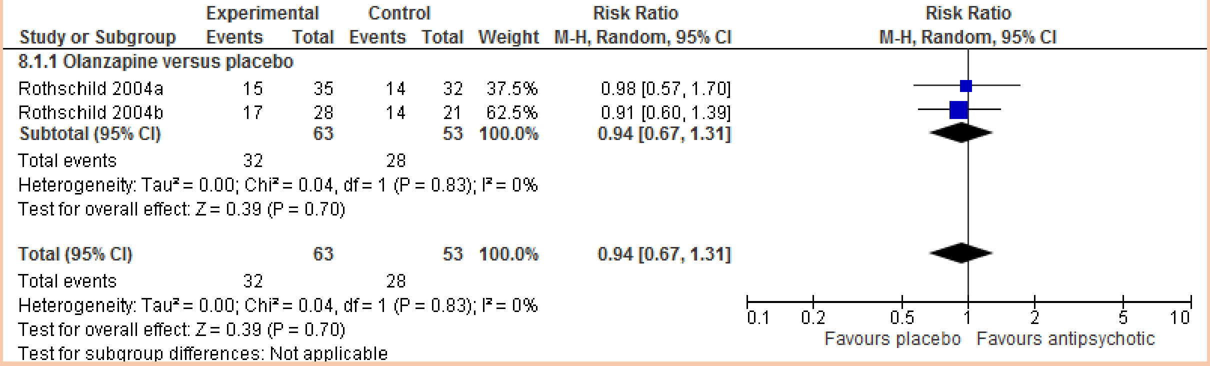
Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours ADM+antipsychotic
Favours antipsychotic+pla

Antipsychotics versus other pharmacological interventions

Antipsychotics versus placebo

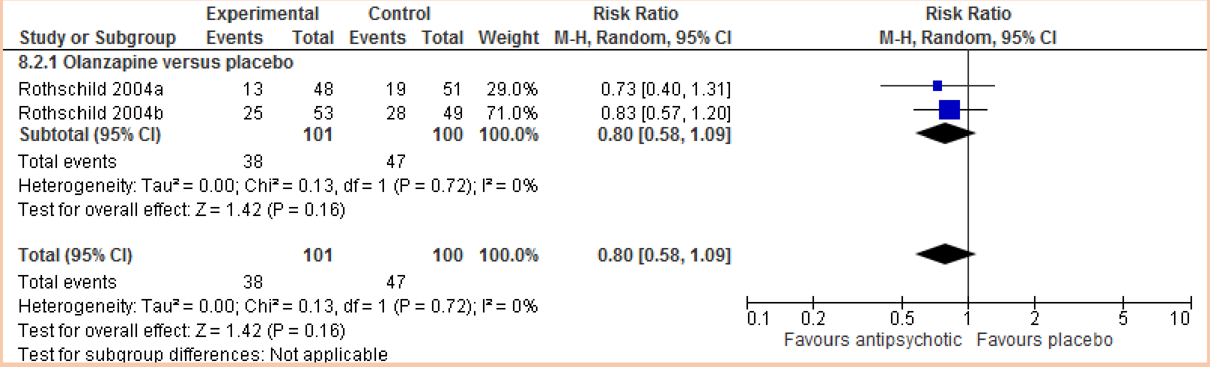
Response



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Olanzapine versus placebo						
Rothschild 2004a	15	35	14	32	37.5%	0.98 [0.57, 1.70]
Rothschild 2004b	17	28	14	21	62.5%	0.91 [0.60, 1.39]
Subtotal (95% CI)		**63**		**53**	**100.0%**	**0.94 [0.67, 1.31]**
Total events	32		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**63**		**53**	**100.0%**	**0.94 [0.67, 1.31]**
Total events	32		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours placebo
Favours antipsychotic

Discontinuation

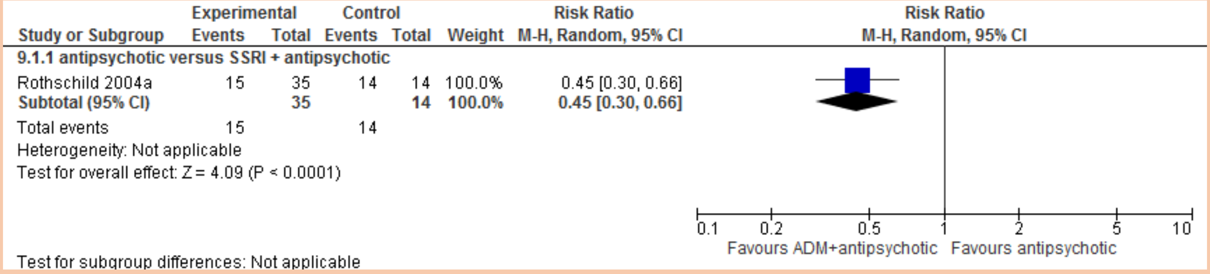


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Olanzapine versus placebo						
Rothschild 2004a	13	48	19	51	29.0%	0.73 [0.40, 1.31]
Rothschild 2004b	25	53	28	49	71.0%	0.83 [0.57, 1.20]
Subtotal (95% CI)		**101**		**100**	**100.0%**	**0.80 [0.58, 1.09]**
Total events	38		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Total (95% CI)		**101**		**100**	**100.0%**	**0.80 [0.58, 1.09]**
Total events	38		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours antipsychotic
Favours placebo

Antipsychotics versus antipsychotics plus antidepressants

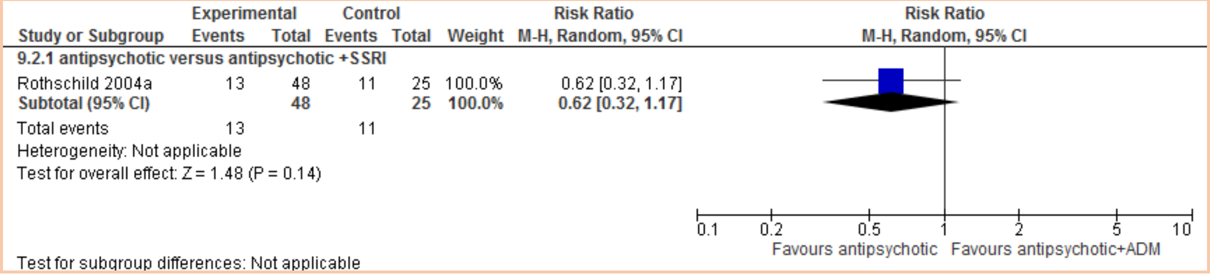
Response



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 antipsychotic versus SSRI + antipsychotic						
Rothschild 2004a	15	35	14	14	100.0%	0.45 [0.30, 0.66]
Subtotal (95% CI)		**35**		**14**	**100.0%**	**0.45 [0.30, 0.66]**
Total events	15		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.09 (P < 0.0001)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours ADM+antipsychotic
Favours antipsychotic

Discontinuation



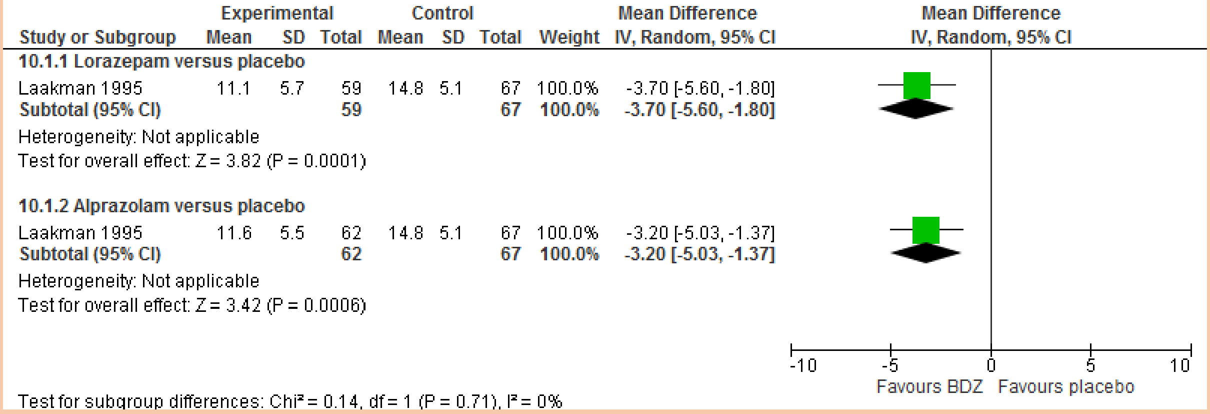
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.2.1 antipsychotic versus antipsychotic +SSRI						
Rothschild 2004a	13	48	11	25	100.0%	0.62 [0.32, 1.17]
Subtotal (95% CI)		**48**		**25**	**100.0%**	**0.62 [0.32, 1.17]**
Total events	13		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.1
0.2
0.5
1
2
5
10
Favours antipsychotic
Favours antipsychotic+ADM

Benzodiazepines versus other pharmacological interventions

Benzodiazepines versus placebo

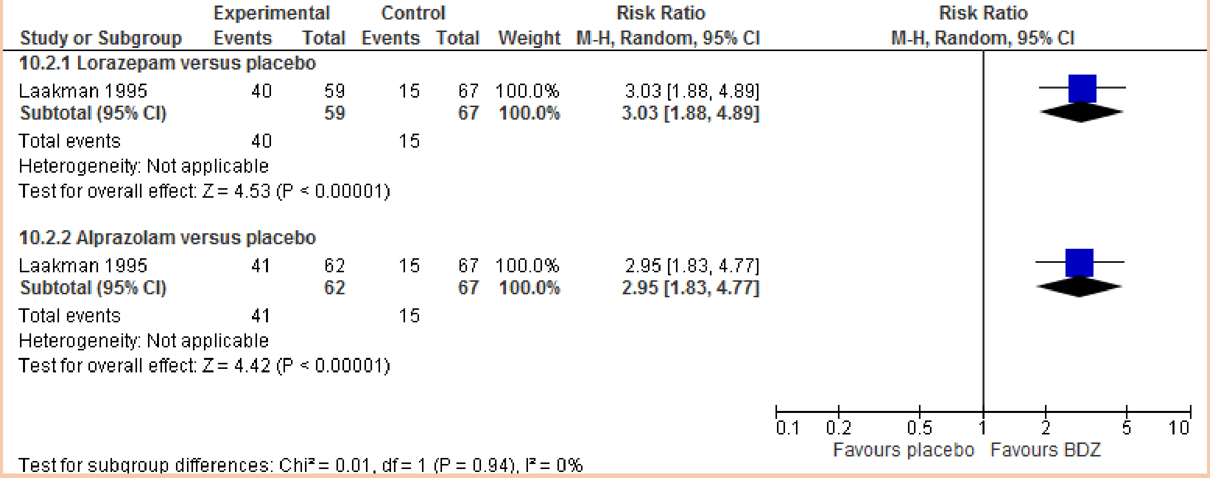
Depression symptomatology at endpoint (HAMD-17)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
10.1.1 Lorazepam versus placebo								
Laakman 1995	11.1	5.7	59	14.8	5.1	67	100.0%	-3.70 [-5.60, -1.80]
Subtotal (95% CI)			**59**			**67**	**100.0%**	**-3.70 [-5.60, -1.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.82 (P = 0.0001)								
10.1.2 Alprazolam versus placebo								
Laakman 1995	11.6	5.5	62	14.8	5.1	67	100.0%	-3.20 [-5.03, -1.37]
Subtotal (95% CI)			**62**			**67**	**100.0%**	**-3.20 [-5.03, -1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.42 (P = 0.0006)								

Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%

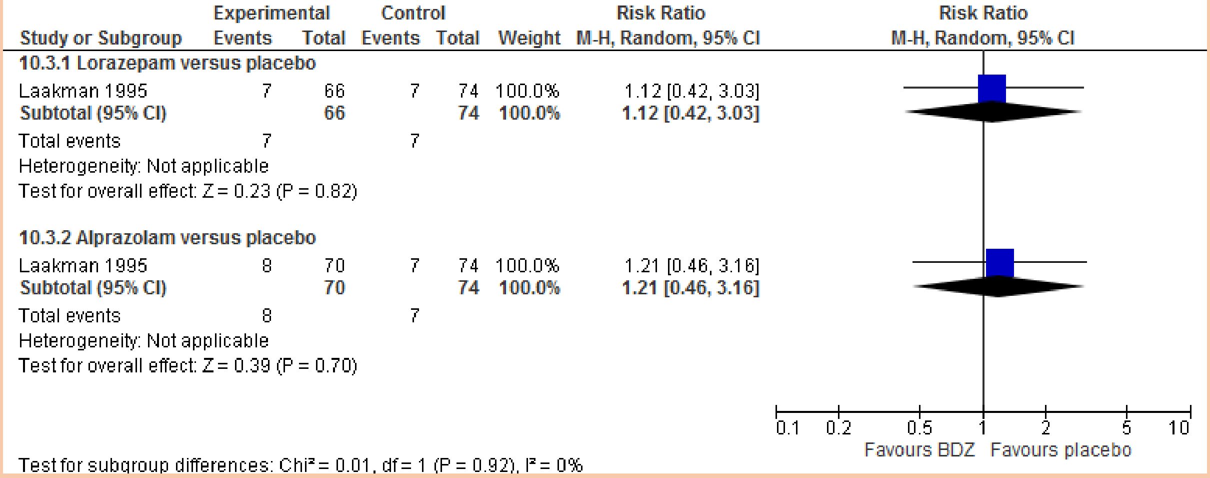
Response



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.2.1 Lorazepam versus placebo						
Laakman 1995	40	59	15	67	100.0%	3.03 [1.88, 4.89]
Subtotal (95% CI)		**59**		**67**	**100.0%**	**3.03 [1.88, 4.89]**
Total events	40		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.53 (P < 0.00001)						
10.2.2 Alprazolam versus placebo						
Laakman 1995	41	62	15	67	100.0%	2.95 [1.83, 4.77]
Subtotal (95% CI)		**62**		**67**	**100.0%**	**2.95 [1.83, 4.77]**
Total events	41		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.42 (P < 0.00001)						

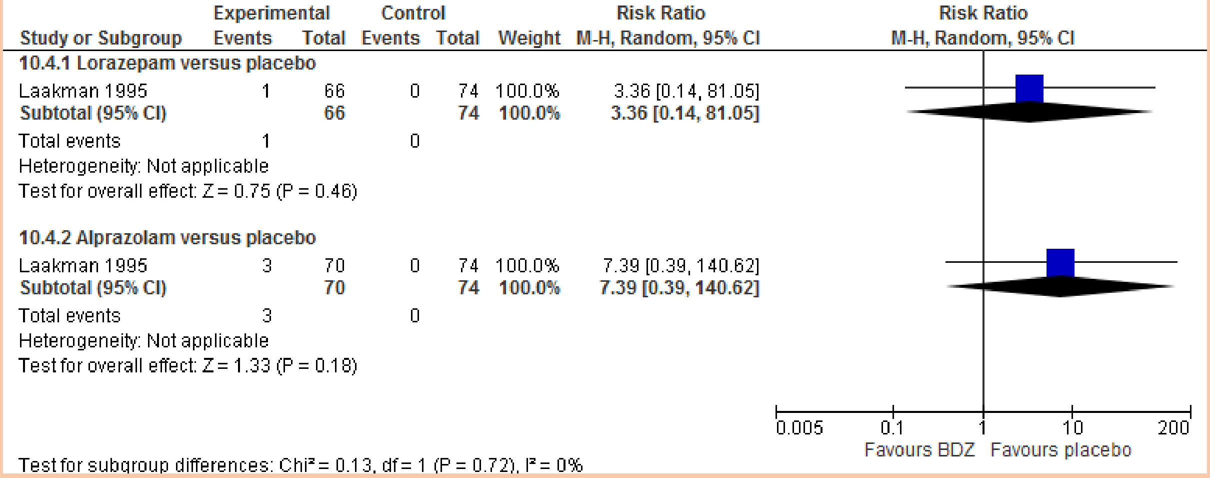
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%

Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 Lorazepam versus placebo						
Laakman 1995	7	66	7	74	100.0%	1.12 [0.42, 3.03]
Subtotal (95% CI)		**66**		**74**	**100.0%**	**1.12 [0.42, 3.03]**
Total events	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
10.3.2 Alprazolam versus placebo						
Laakman 1995	8	70	7	74	100.0%	1.21 [0.46, 3.16]
Subtotal (95% CI)		**70**		**74**	**100.0%**	**1.21 [0.46, 3.16]**
Total events	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 = 0%						

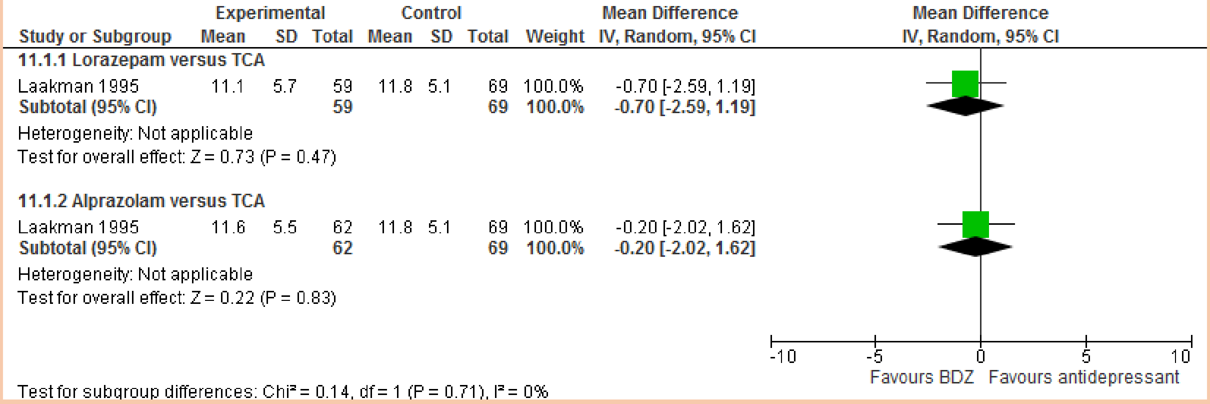
Discontinuation due to side effects



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
10.4.1 Lorazepam versus placebo						
Laakman 1995	1	66	0	74	100.0%	3.36 [0.14, 81.05]
Subtotal (95% CI)		**66**		**74**	**100.0%**	**3.36 [0.14, 81.05]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.46)						
10.4.2 Alprazolam versus placebo						
Laakman 1995	3	70	0	74	100.0%	7.39 [0.39, 140.62]
Subtotal (95% CI)		**70**		**74**	**100.0%**	**7.39 [0.39, 140.62]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Chi^2 = 0.13, df = 1 (P = 0.72), I^2 = 0%						

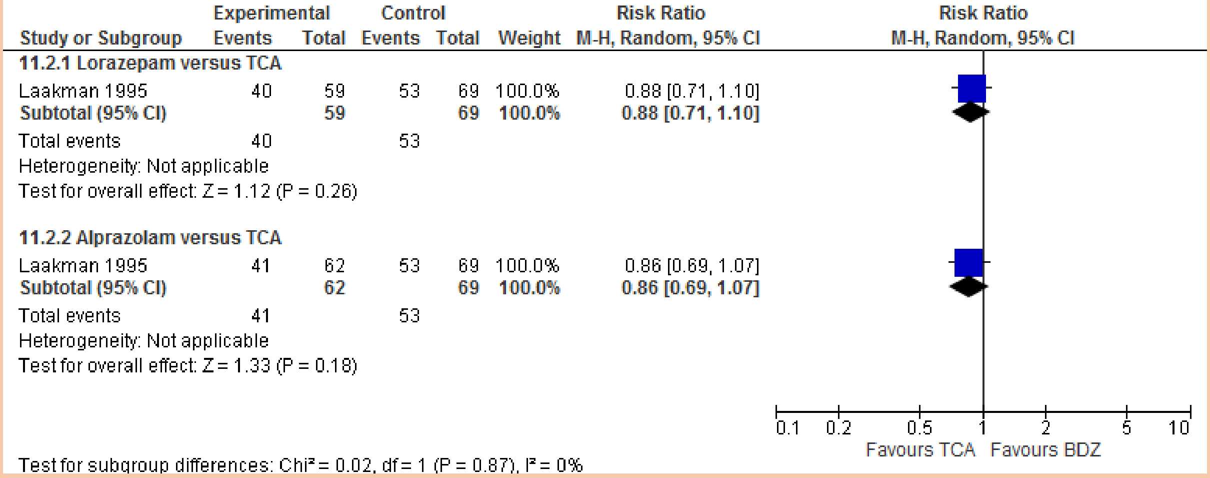
Benzodiazepines versus antidepressants

Depression symptomatology at endpoint (HAMD 17)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
11.1.1 Lorazepam versus TCA								
Laakman 1995	11.1	5.7	59	11.8	5.1	69	100.0%	-0.70 [-2.59, 1.19]
Subtotal (95% CI)			**59**			**69**	**100.0%**	**-0.70 [-2.59, 1.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								
11.1.2 Alprazolam versus TCA								
Laakman 1995	11.6	5.5	62	11.8	5.1	69	100.0%	-0.20 [-2.02, 1.62]
Subtotal (95% CI)			**62**			**69**	**100.0%**	**-0.20 [-2.02, 1.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.83)								
Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.71), I^2 = 0%								

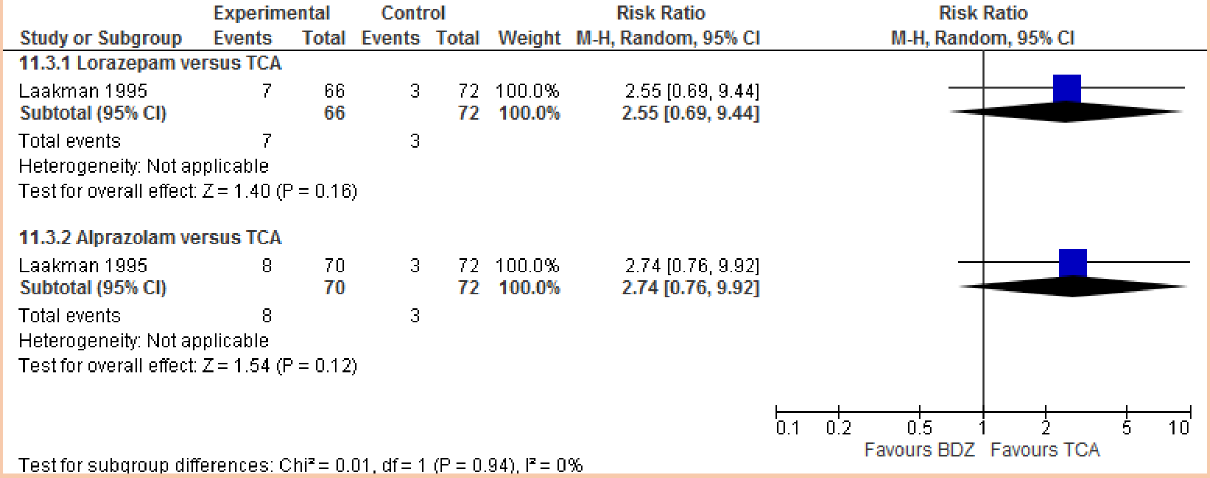
Response



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.2.1 Lorazepam versus TCA						
Laakman 1995	40	59	53	69	100.0%	0.88 [0.71, 1.10]
Subtotal (95% CI)		**59**		**69**	**100.0%**	**0.88 [0.71, 1.10]**
Total events	40		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
11.2.2 Alprazolam versus TCA						
Laakman 1995	41	62	53	69	100.0%	0.86 [0.69, 1.07]
Subtotal (95% CI)		**62**		**69**	**100.0%**	**0.86 [0.69, 1.07]**
Total events	41		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						

Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.87), I² = 0%

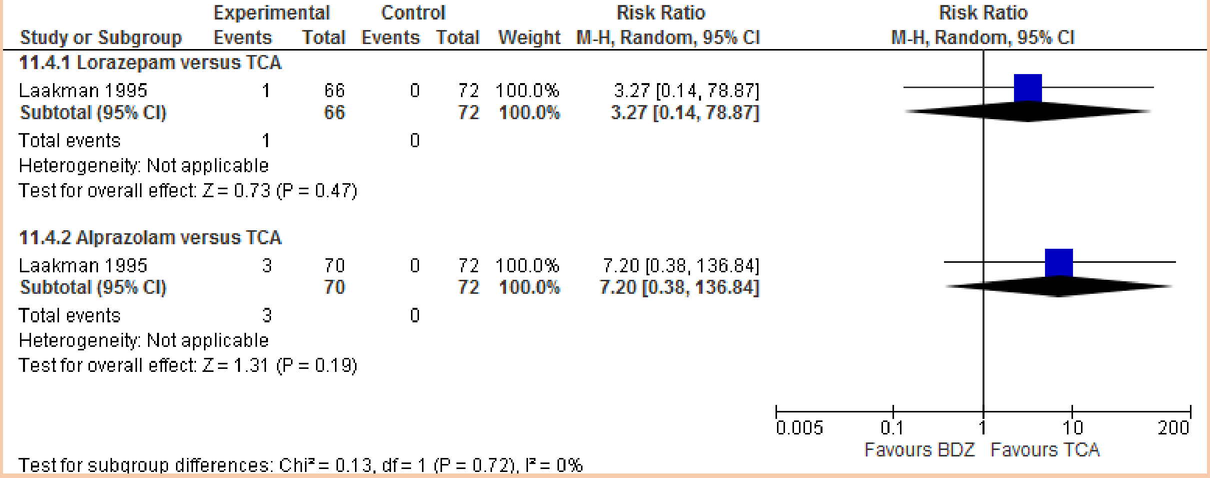
Discontinuation



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.3.1 Lorazepam versus TCA						
Laakman 1995	7	66	3	72	100.0%	2.55 [0.69, 9.44]
Subtotal (95% CI)		**66**		**72**	**100.0%**	**2.55 [0.69, 9.44]**
Total events	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
11.3.2 Alprazolam versus TCA						
Laakman 1995	8	70	3	72	100.0%	2.74 [0.76, 9.92]
Subtotal (95% CI)		**70**		**72**	**100.0%**	**2.74 [0.76, 9.92]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						

Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%

Discontinuation due to side effects

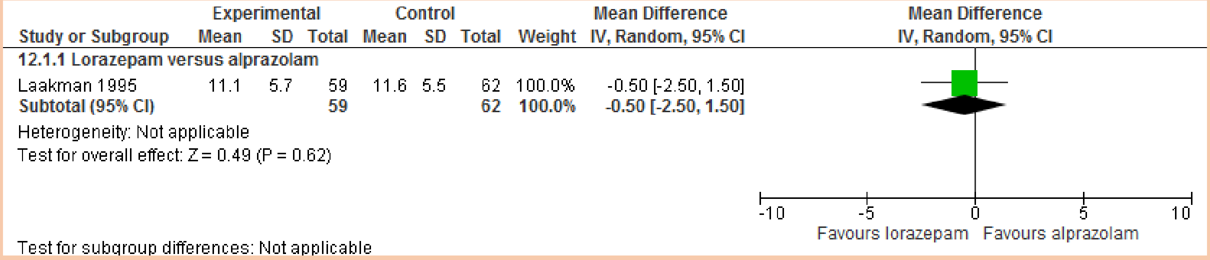


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.4.1 Lorazepam versus TCA						
Laakman 1995	1	66	0	72	100.0%	3.27 [0.14, 78.87]
Subtotal (95% CI)		**66**		**72**	**100.0%**	**3.27 [0.14, 78.87]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
11.4.2 Alprazolam versus TCA						
Laakman 1995	3	70	0	72	100.0%	7.20 [0.38, 136.84]
Subtotal (95% CI)		**70**		**72**	**100.0%**	**7.20 [0.38, 136.84]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						

Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

Benzodiazepines versus benzodiazepines

Depression symptomatology at endpoint (HAMD 17)

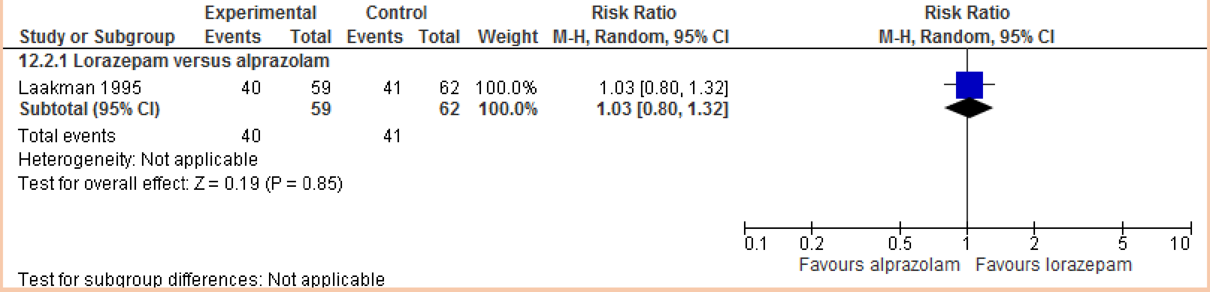


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
12.1.1 Lorazepam versus alprazolam								
Laakman 1995	11.1	5.7	59	11.6	5.5	62	100.0%	-0.50 [-2.50, 1.50]
Subtotal (95% CI)			**59**			**62**	**100.0%**	**-0.50 [-2.50, 1.50]**

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

Test for subgroup differences: Not applicable

Response

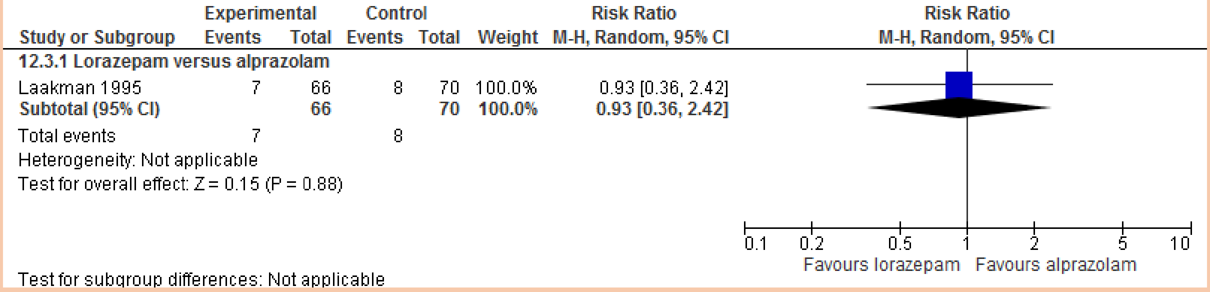


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.2.1 Lorazepam versus alprazolam						
Laakman 1995	40	59	41	62	100.0%	1.03 [0.80, 1.32]
Subtotal (95% CI)		**59**		**62**	**100.0%**	**1.03 [0.80, 1.32]**
Total events	40		41			

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

Test for subgroup differences: Not applicable

Discontinuation

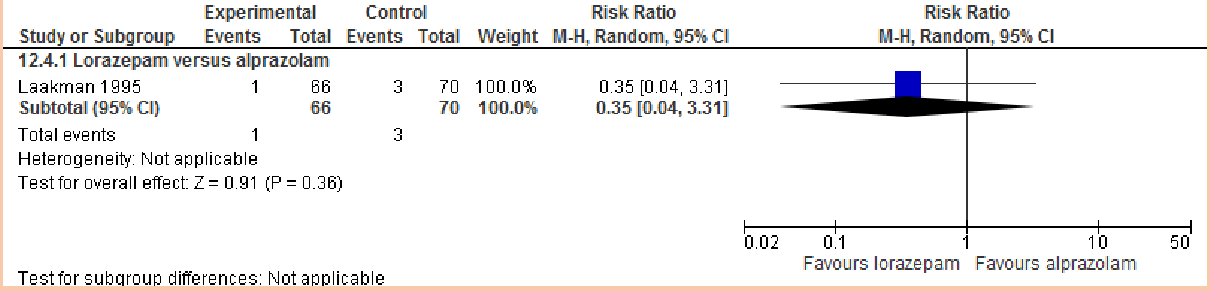


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 Lorazepam versus alprazolam						
Laakman 1995	7	66	8	70	100.0%	0.93 [0.36, 2.42]
Subtotal (95% CI)		**66**		**70**	**100.0%**	**0.93 [0.36, 2.42]**
Total events	7		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable

Discontinuation due to side effects



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
12.4.1 Lorazepam versus alprazolam						
Laakman 1995	1	66	3	70	100.0%	0.35 [0.04, 3.31]
Subtotal (95% CI)		**66**		**70**	**100.0%**	**0.35 [0.04, 3.31]**
Total events	1		3			

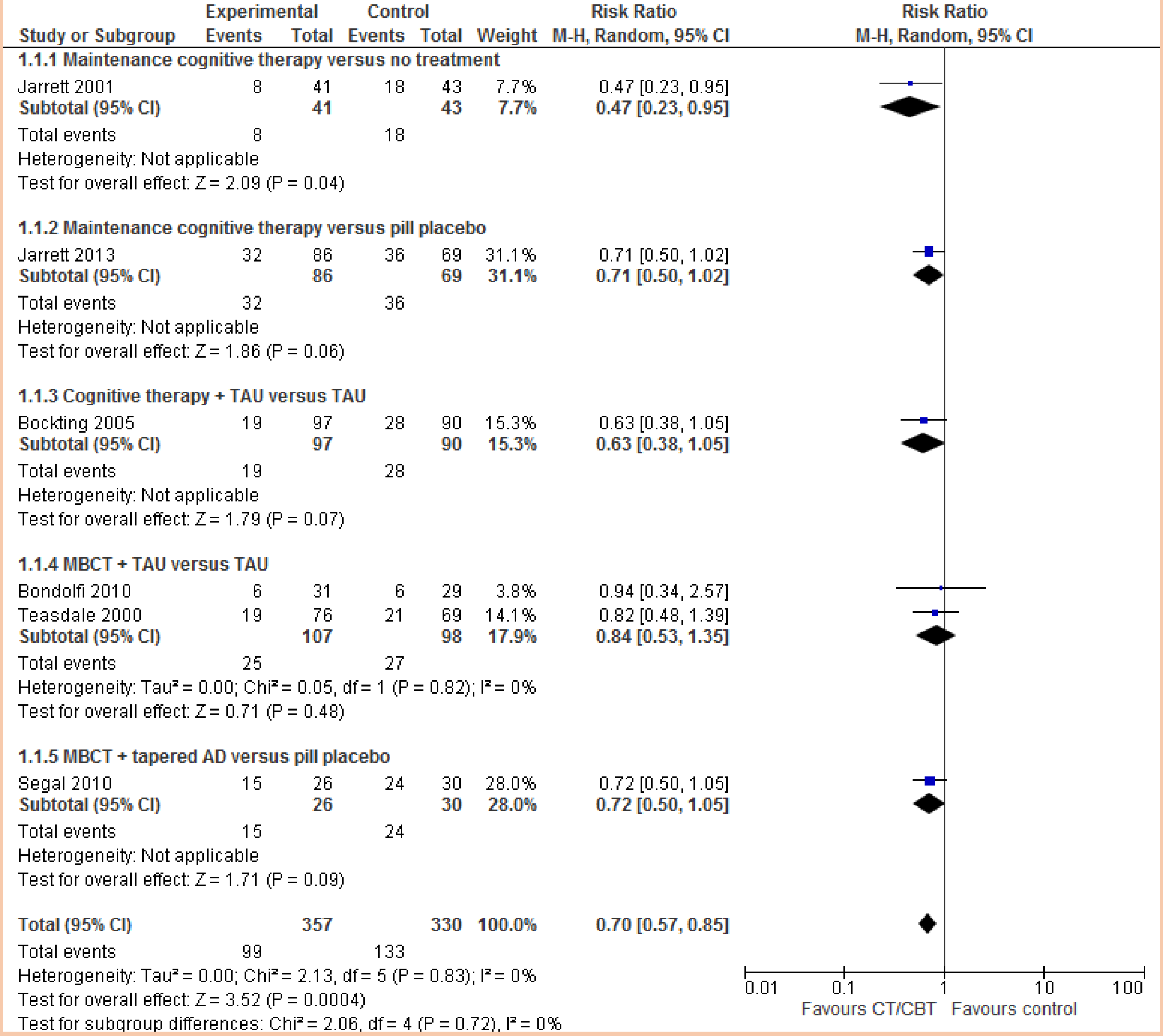
Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable

Relapse prevention (chapter 11)

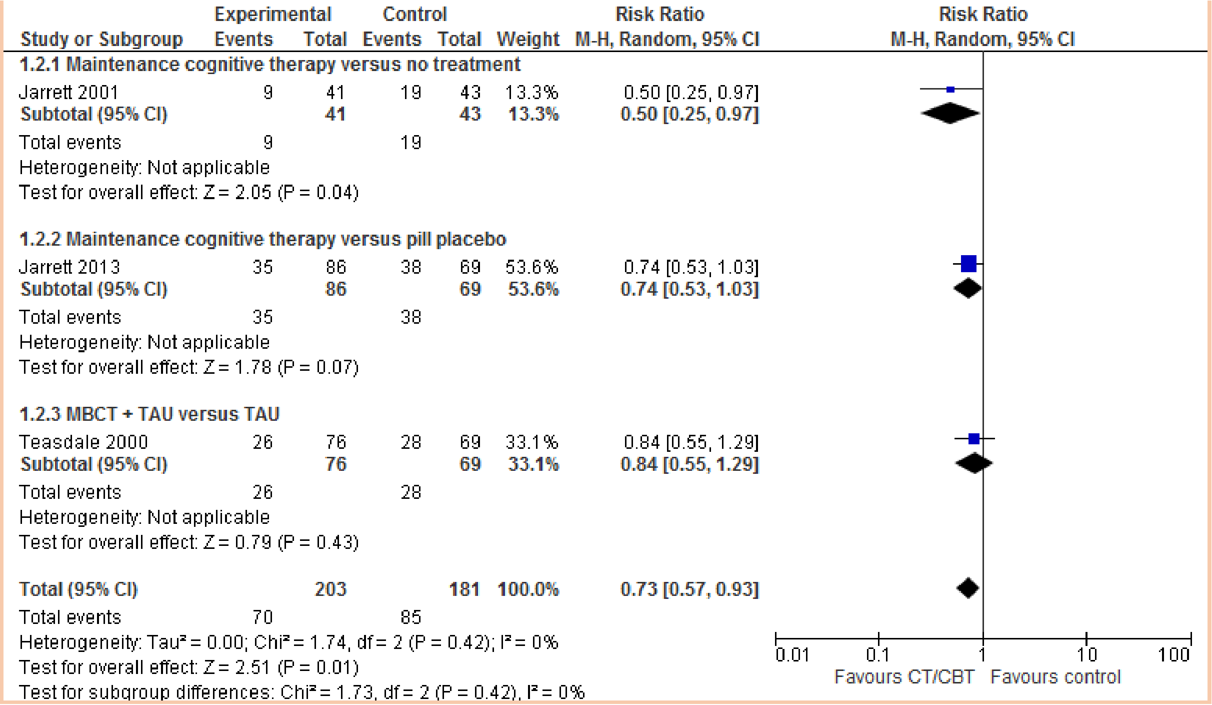
Cognitive or cognitive behavioural therapies versus control

Relapse at endpoint



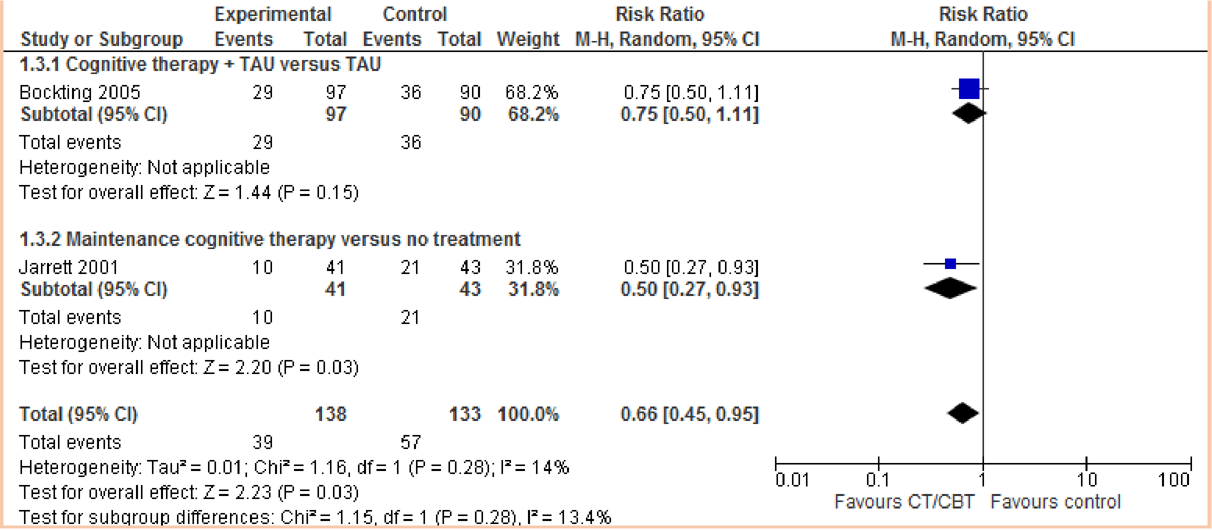
	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
1.1.1 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	8	41	18	43	7.7%	0.47 [0.23, 0.95]
Subtotal (95% CI)		**41**		**43**	**7.7%**	**0.47 [0.23, 0.95]**
Total events	8		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.09 (P = 0.04)						
1.1.2 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	32	86	36	69	31.1%	0.71 [0.50, 1.02]
Subtotal (95% CI)		**86**		**69**	**31.1%**	**0.71 [0.50, 1.02]**
Total events	32		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
1.1.3 Cognitive therapy + TAU versus TAU						
Bockting 2005	19	97	28	90	15.3%	0.63 [0.38, 1.05]
Subtotal (95% CI)		**97**		**90**	**15.3%**	**0.63 [0.38, 1.05]**
Total events	19		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
1.1.4 MBCT + TAU versus TAU						
Bondolfi 2010	6	31	6	29	3.8%	0.94 [0.34, 2.57]
Teasdale 2000	19	76	21	69	14.1%	0.82 [0.48, 1.39]
Subtotal (95% CI)		**107**		**98**	**17.9%**	**0.84 [0.53, 1.35]**
Total events	25		27			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.1.5 MBCT + tapered AD versus pill placebo						
Segal 2010	15	26	24	30	28.0%	0.72 [0.50, 1.05]
Subtotal (95% CI)		**26**		**30**	**28.0%**	**0.72 [0.50, 1.05]**
Total events	15		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
Total (95% CI)		**357**		**330**	**100.0%**	**0.70 [0.57, 0.85]**
Total events	99		133			
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 5 (P = 0.83); I² = 0%						
Test for overall effect: Z = 3.52 (P = 0.0004)						
Test for subgroup differences: Chi² = 2.06, df = 4 (P = 0.72), I² = 0%						

Relapse at 1-2 month follow-up



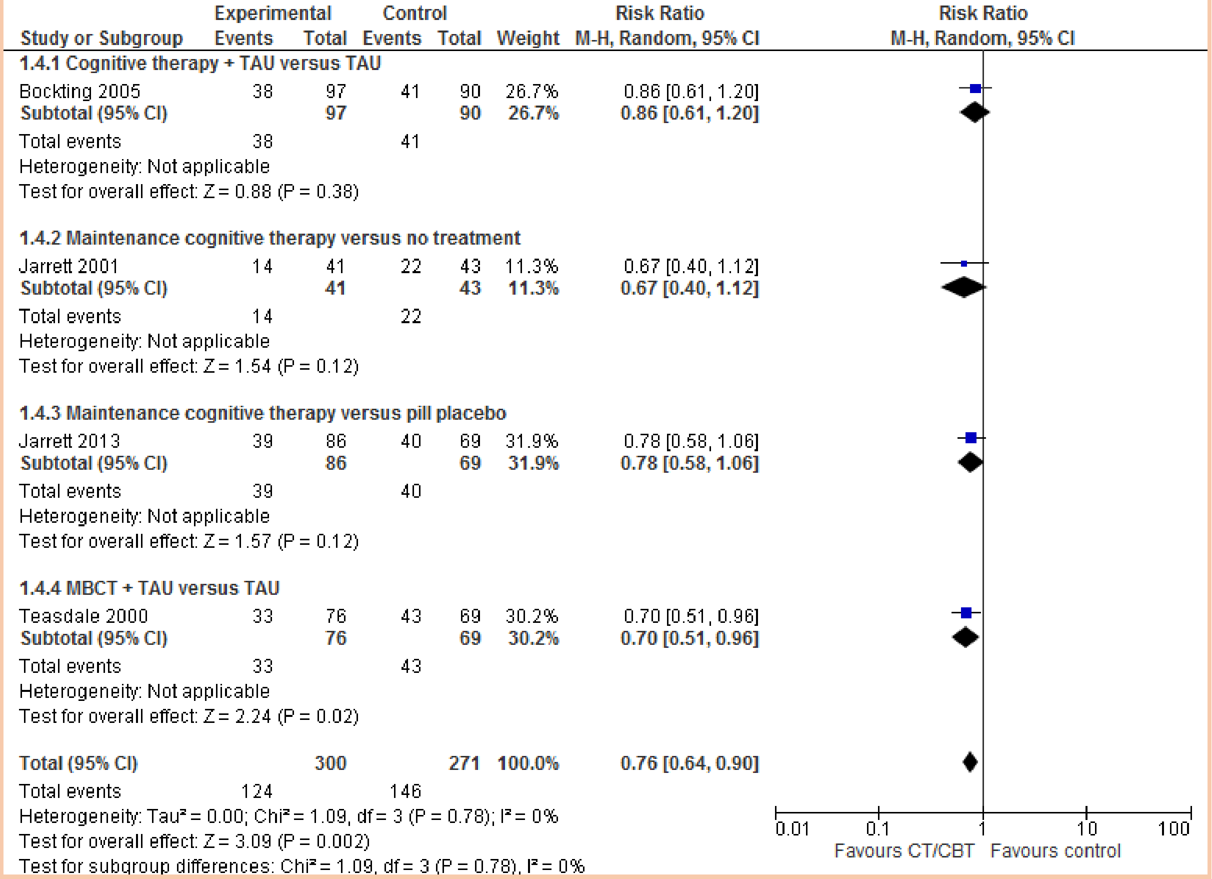
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	9	41	19	43	13.3%	0.50 [0.25, 0.97]
Subtotal (95% CI)		**41**		**43**	**13.3%**	**0.50 [0.25, 0.97]**
Total events	9		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.2.2 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	35	86	38	69	53.6%	0.74 [0.53, 1.03]
Subtotal (95% CI)		**86**		**69**	**53.6%**	**0.74 [0.53, 1.03]**
Total events	35		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.07)						
1.2.3 MBCT + TAU versus TAU						
Teasdale 2000	26	76	28	69	33.1%	0.84 [0.55, 1.29]
Subtotal (95% CI)		**76**		**69**	**33.1%**	**0.84 [0.55, 1.29]**
Total events	26		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**203**		**181**	**100.0%**	**0.73 [0.57, 0.93]**
Total events	70		85			
Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: Chi² = 1.73, df = 2 (P = 0.42), I² = 0%						

Relapse at 3-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	29	97	36	90	68.2%	0.75 [0.50, 1.11]
Subtotal (95% CI)		**97**		**90**	**68.2%**	**0.75 [0.50, 1.11]**
Total events	29		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.3.2 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	10	41	21	43	31.8%	0.50 [0.27, 0.93]
Subtotal (95% CI)		**41**		**43**	**31.8%**	**0.50 [0.27, 0.93]**
Total events	10		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)		**138**		**133**	**100.0%**	**0.66 [0.45, 0.95]**
Total events	39		57			
Heterogeneity: Tau² = 0.01; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Test for subgroup differences: Chi² = 1.15, df = 1 (P = 0.28), I² = 13.4%						

Relapse at 5-7 month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	38	97	41	90	26.7%	0.86 [0.61, 1.20]
Subtotal (95% CI)		**97**		**90**	**26.7%**	**0.86 [0.61, 1.20]**
Total events	38		41			
1.4.2 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	14	41	22	43	11.3%	0.67 [0.40, 1.12]
Subtotal (95% CI)		**41**		**43**	**11.3%**	**0.67 [0.40, 1.12]**
Total events	14		22			
1.4.3 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	39	86	40	69	31.9%	0.78 [0.58, 1.06]
Subtotal (95% CI)		**86**		**69**	**31.9%**	**0.78 [0.58, 1.06]**
Total events	39		40			
1.4.4 MBCT + TAU versus TAU						
Teasdale 2000	33	76	43	69	30.2%	0.70 [0.51, 0.96]
Subtotal (95% CI)		**76**		**69**	**30.2%**	**0.70 [0.51, 0.96]**
Total events	33		43			
Total (95% CI)		**300**		**271**	**100.0%**	**0.76 [0.64, 0.90]**
Total events	124		146			

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

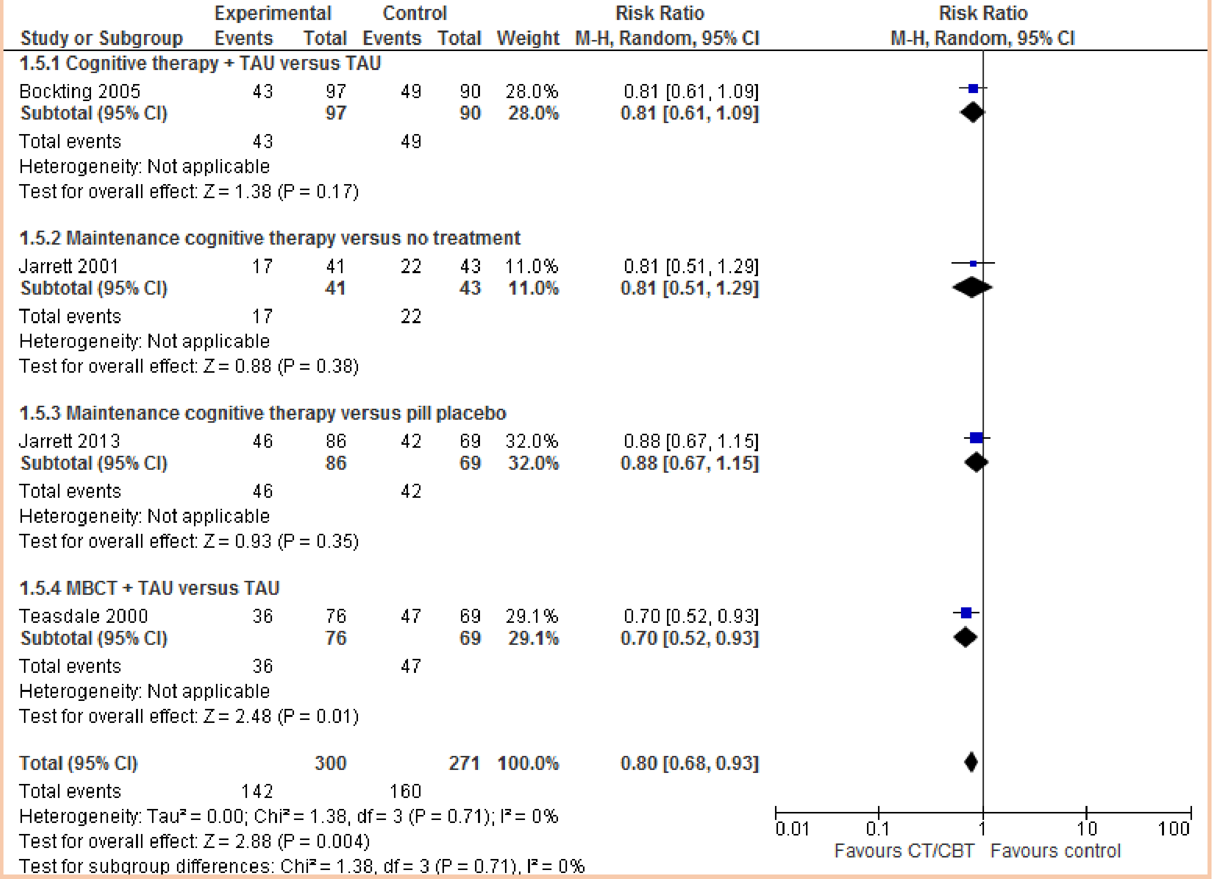
1.4.2: Heterogeneity: Not applicable; Test for overall effect: Z = 1.54 (P = 0.12)

1.4.3: Heterogeneity: Not applicable; Test for overall effect: Z = 1.57 (P = 0.12)

1.4.4: Heterogeneity: Not applicable; Test for overall effect: Z = 2.24 (P = 0.02)

Total: Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.09, df = 3 (P = 0.78); I^2 = 0%
Test for overall effect: Z = 3.09 (P = 0.002)
Test for subgroup differences: Chi^2 = 1.09, df = 3 (P = 0.78), I^2 = 0%

Relapse at 8-9 month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	43	97	49	90	28.0%	0.81 [0.61, 1.09]
Subtotal (95% CI)		**97**		**90**	**28.0%**	**0.81 [0.61, 1.09]**
Total events	43		49			
1.5.2 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	17	41	22	43	11.0%	0.81 [0.51, 1.29]
Subtotal (95% CI)		**41**		**43**	**11.0%**	**0.81 [0.51, 1.29]**
Total events	17		22			
1.5.3 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	46	86	42	69	32.0%	0.88 [0.67, 1.15]
Subtotal (95% CI)		**86**		**69**	**32.0%**	**0.88 [0.67, 1.15]**
Total events	46		42			
1.5.4 MBCT + TAU versus TAU						
Teasdale 2000	36	76	47	69	29.1%	0.70 [0.52, 0.93]
Subtotal (95% CI)		**76**		**69**	**29.1%**	**0.70 [0.52, 0.93]**
Total events	36		47			
Total (95% CI)		**300**		**271**	**100.0%**	**0.80 [0.68, 0.93]**
Total events	142		160			

1.5.1: Heterogeneity: Not applicable; Test for overall effect: Z = 1.38 (P = 0.17)

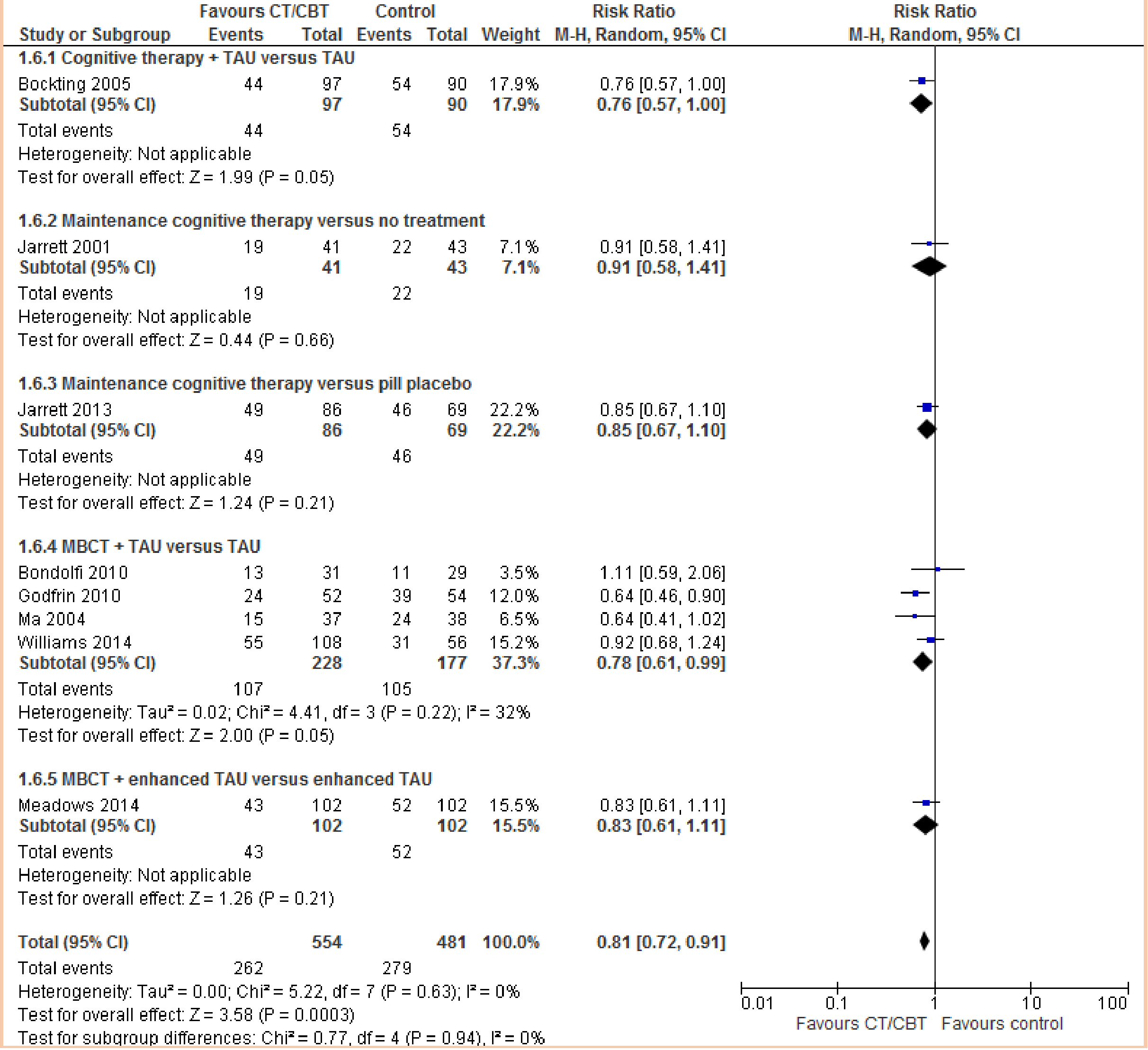
1.5.2: Heterogeneity: Not applicable; Test for overall effect: Z = 0.88 (P = 0.38)

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

1.5.4: Heterogeneity: Not applicable; Test for overall effect: Z = 2.48 (P = 0.01)

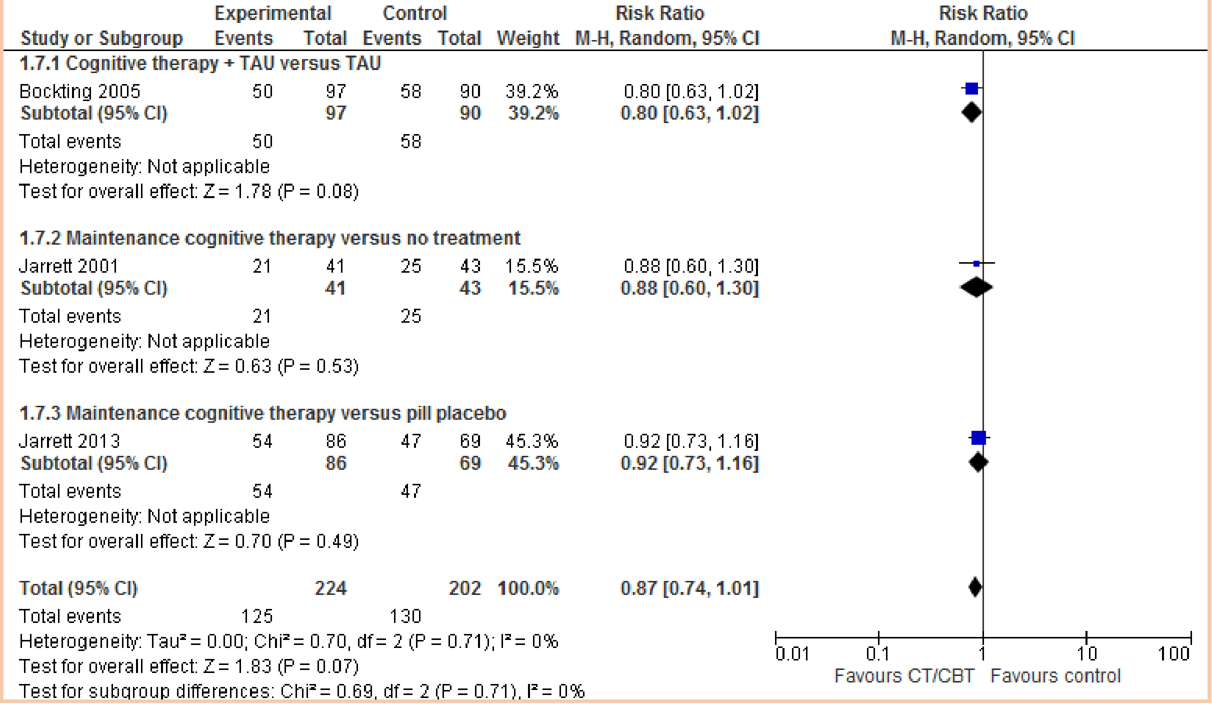
Total: Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.38, df = 3 (P = 0.71); I^2 = 0%
Test for overall effect: Z = 2.88 (P = 0.004)
Test for subgroup differences: Chi^2 = 1.38, df = 3 (P = 0.71), I^2 = 0%

Relapse at 11-12 month follow-up



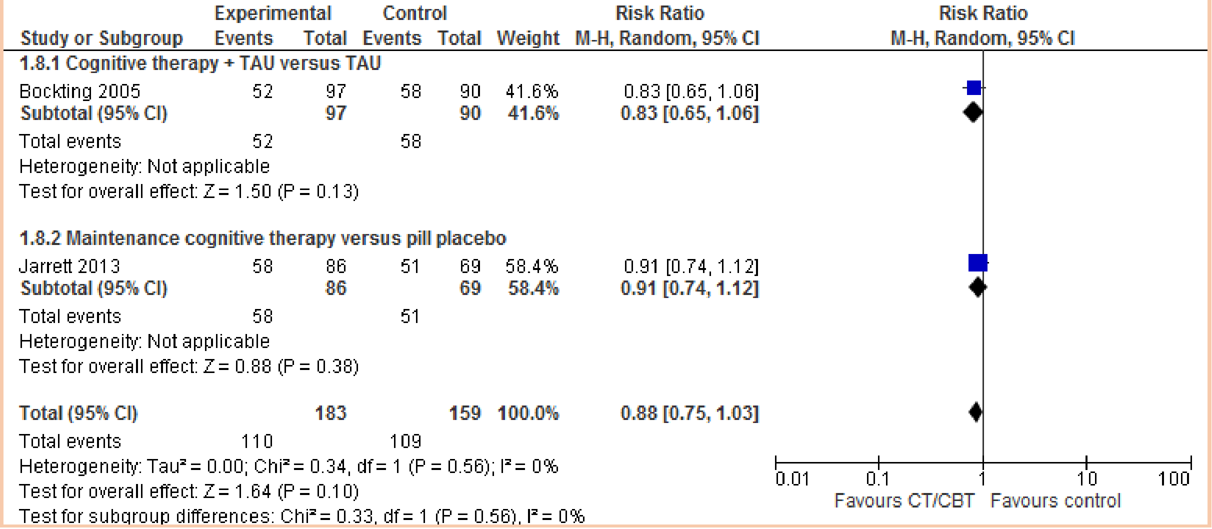
	Favours CT/CBT		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
1.6.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	44	97	54	90	17.9%	0.76 [0.57, 1.00]
Subtotal (95% CI)		**97**		**90**	**17.9%**	**0.76 [0.57, 1.00]**
Total events	44		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.6.2 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	19	41	22	43	7.1%	0.91 [0.58, 1.41]
Subtotal (95% CI)		**41**		**43**	**7.1%**	**0.91 [0.58, 1.41]**
Total events	19		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.6.3 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	49	86	46	69	22.2%	0.85 [0.67, 1.10]
Subtotal (95% CI)		**86**		**69**	**22.2%**	**0.85 [0.67, 1.10]**
Total events	49		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
1.6.4 MBCT + TAU versus TAU						
Bondolfi 2010	13	31	11	29	3.5%	1.11 [0.59, 2.06]
Godfrin 2010	24	52	39	54	12.0%	0.64 [0.46, 0.90]
Ma 2004	15	37	24	38	6.5%	0.64 [0.41, 1.02]
Williams 2014	55	108	31	56	15.2%	0.92 [0.68, 1.24]
Subtotal (95% CI)		**228**		**177**	**37.3%**	**0.78 [0.61, 0.99]**
Total events	107		105			
Heterogeneity: Tau² = 0.02; Chi² = 4.41, df = 3 (P = 0.22); I² = 32%						
Test for overall effect: Z = 2.00 (P = 0.05)						
1.6.5 MBCT + enhanced TAU versus enhanced TAU						
Meadows 2014	43	102	52	102	15.5%	0.83 [0.61, 1.11]
Subtotal (95% CI)		**102**		**102**	**15.5%**	**0.83 [0.61, 1.11]**
Total events	43		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)		**554**		**481**	**100.0%**	**0.81 [0.72, 0.91]**
Total events	262		279			
Heterogeneity: Tau² = 0.00; Chi² = 5.22, df = 7 (P = 0.63); I² = 0%						
Test for overall effect: Z = 3.58 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.77, df = 4 (P = 0.94), I² = 0%						

Relapse at 15-16 month follow-up



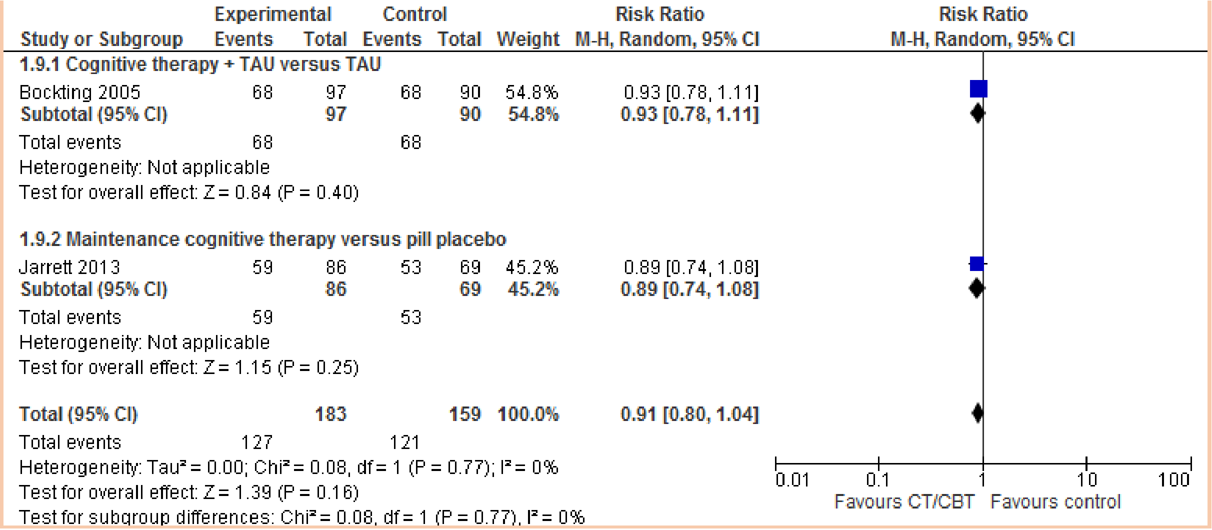
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	50	97	58	90	39.2%	0.80 [0.63, 1.02]
Subtotal (95% CI)		**97**		**90**	**39.2%**	**0.80 [0.63, 1.02]**
Total events	50		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.08)						
1.7.2 Maintenance cognitive therapy versus no treatment						
Jarrett 2001	21	41	25	43	15.5%	0.88 [0.60, 1.30]
Subtotal (95% CI)		**41**		**43**	**15.5%**	**0.88 [0.60, 1.30]**
Total events	21		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.7.3 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	54	86	47	69	45.3%	0.92 [0.73, 1.16]
Subtotal (95% CI)		**86**		**69**	**45.3%**	**0.92 [0.73, 1.16]**
Total events	54		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
Total (95% CI)		**224**		**202**	**100.0%**	**0.87 [0.74, 1.01]**
Total events	125		130			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Chi² = 0.69, df = 2 (P = 0.71), I² = 0%						

Relapse at 18-month follow-up



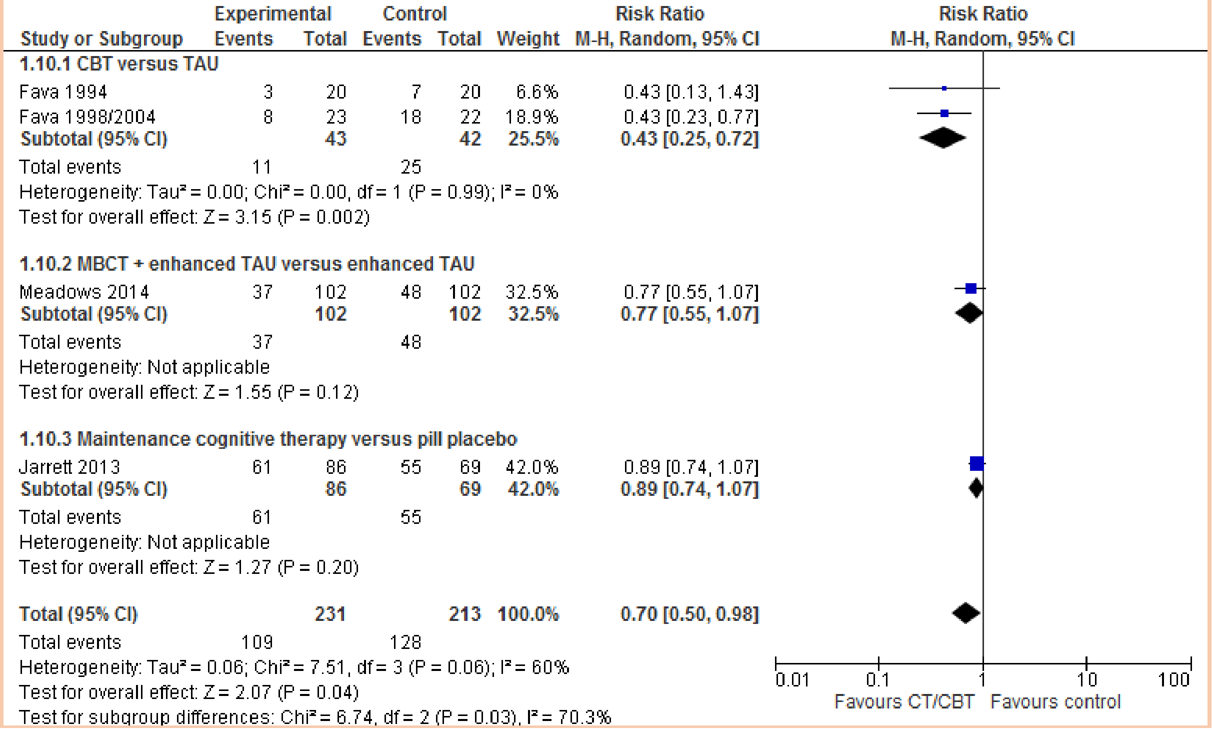
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	52	97	58	90	41.6%	0.83 [0.65, 1.06]
Subtotal (95% CI)		**97**		**90**	**41.6%**	**0.83 [0.65, 1.06]**
Total events	52		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.8.2 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	58	86	51	69	58.4%	0.91 [0.74, 1.12]
Subtotal (95% CI)		**86**		**69**	**58.4%**	**0.91 [0.74, 1.12]**
Total events	58		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**183**		**159**	**100.0%**	**0.88 [0.75, 1.03]**
Total events	110		109			
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%						

Relapse at 21-month follow-up



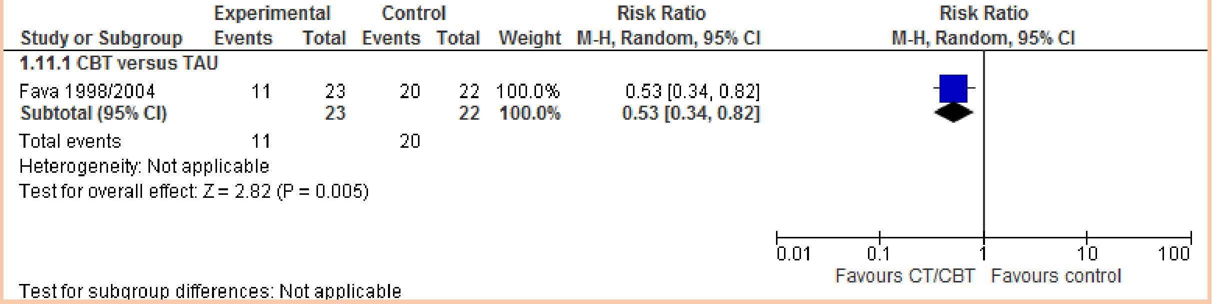
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Cognitive therapy + TAU versus TAU						
Bockting 2005	68	97	68	90	54.8%	0.93 [0.78, 1.11]
Subtotal (95% CI)		**97**		**90**	**54.8%**	**0.93 [0.78, 1.11]**
Total events	68		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.9.2 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	59	86	53	69	45.2%	0.89 [0.74, 1.08]
Subtotal (95% CI)		**86**		**69**	**45.2%**	**0.89 [0.74, 1.08]**
Total events	59		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**183**		**159**	**100.0%**	**0.91 [0.80, 1.04]**
Total events	127		121			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						

Relapse at 2-year follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 CBT versus TAU						
Fava 1994	3	20	7	20	6.6%	0.43 [0.13, 1.43]
Fava 1998/2004	8	23	18	22	18.9%	0.43 [0.23, 0.77]
Subtotal (95% CI)		**43**		**42**	**25.5%**	**0.43 [0.25, 0.72]**
Total events	11		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 3.15 (P = 0.002)						
1.10.2 MBCT + enhanced TAU versus enhanced TAU						
Meadows 2014	37	102	48	102	32.5%	0.77 [0.55, 1.07]
Subtotal (95% CI)		**102**		**102**	**32.5%**	**0.77 [0.55, 1.07]**
Total events	37		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.10.3 Maintenance cognitive therapy versus pill placebo						
Jarrett 2013	61	86	55	69	42.0%	0.89 [0.74, 1.07]
Subtotal (95% CI)		**86**		**69**	**42.0%**	**0.89 [0.74, 1.07]**
Total events	61		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
Total (95% CI)		**231**		**213**	**100.0%**	**0.70 [0.50, 0.98]**
Total events	109		128			
Heterogeneity: Tau² = 0.06; Chi² = 7.51, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 2.07 (P = 0.04)						
Test for subgroup differences: Chi² = 6.74, df = 2 (P = 0.03), I² = 70.3%						

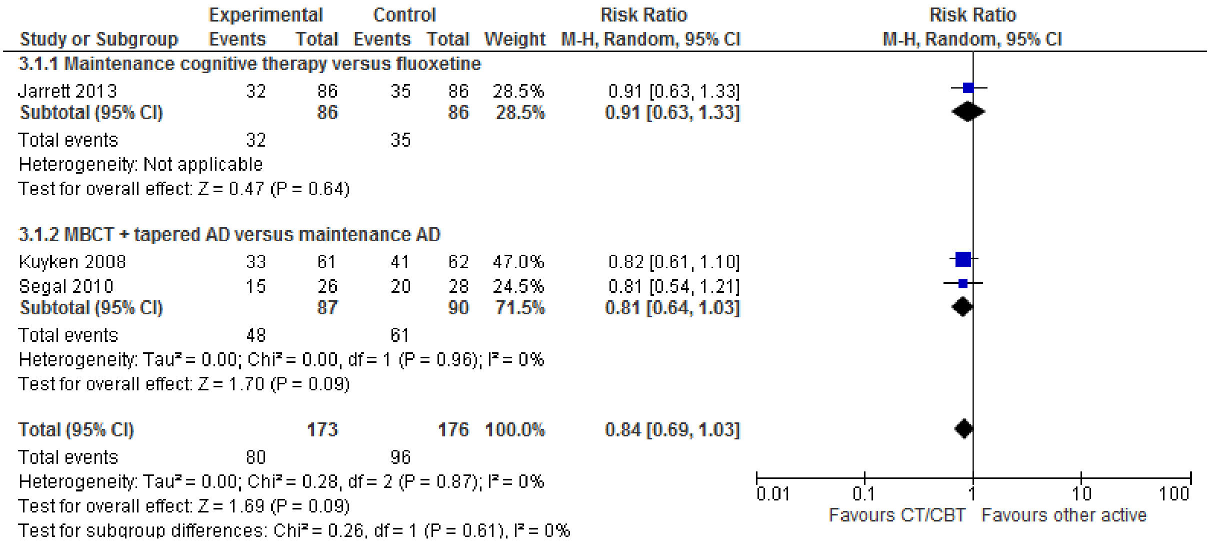
Relapse at 6-year follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 CBT versus TAU						
Fava 1998/2004	11	23	20	22	100.0%	0.53 [0.34, 0.82]
Subtotal (95% CI)		**23**		**22**	**100.0%**	**0.53 [0.34, 0.82]**
Total events	11		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.82 (P = 0.005)						
Test for subgroup differences: Not applicable						

Cognitive or cognitive behavioural therapies versus active intervention

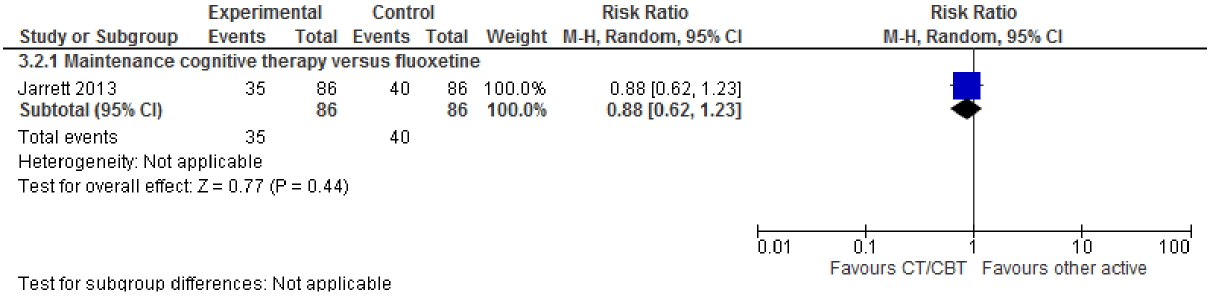
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	32	86	35	86	28.5%	0.91 [0.63, 1.33]
Subtotal (95% CI)		**86**		**86**	**28.5%**	**0.91 [0.63, 1.33]**
Total events	32		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
3.1.2 MBCT + tapered AD versus maintenance AD						
Kuyken 2008	33	61	41	62	47.0%	0.82 [0.61, 1.10]
Segal 2010	15	26	20	28	24.5%	0.81 [0.54, 1.21]
Subtotal (95% CI)		**87**		**90**	**71.5%**	**0.81 [0.64, 1.03]**
Total events	48		61			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
Total (95% CI)		**173**		**176**	**100.0%**	**0.84 [0.69, 1.03]**
Total events	80		96			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

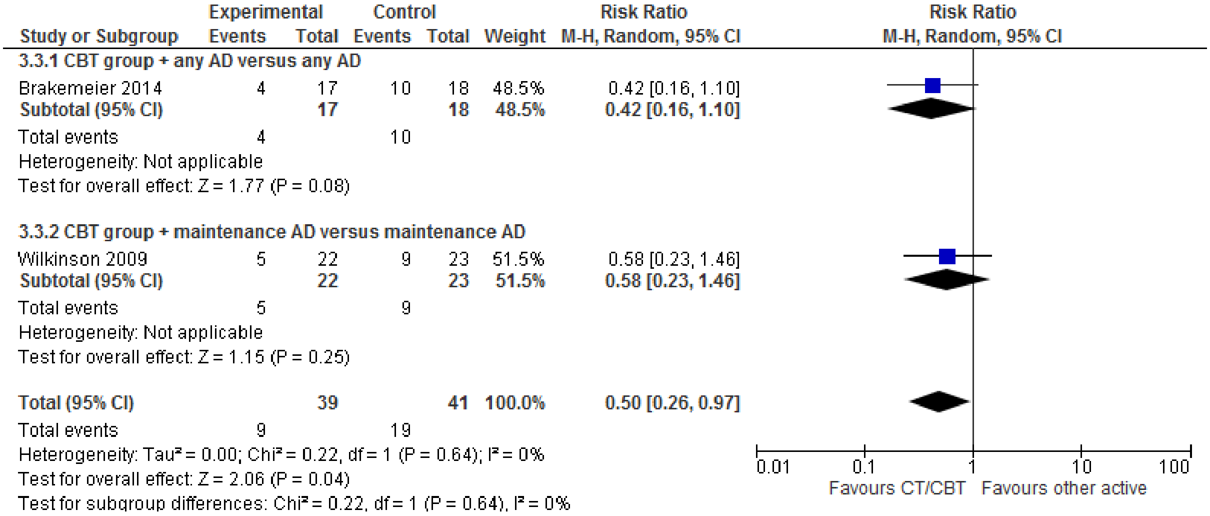
Relapse at 2-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	35	86	40	86	100.0%	0.88 [0.62, 1.23]
Subtotal (95% CI)		**86**		**86**	**100.0%**	**0.88 [0.62, 1.23]**
Total events	35		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

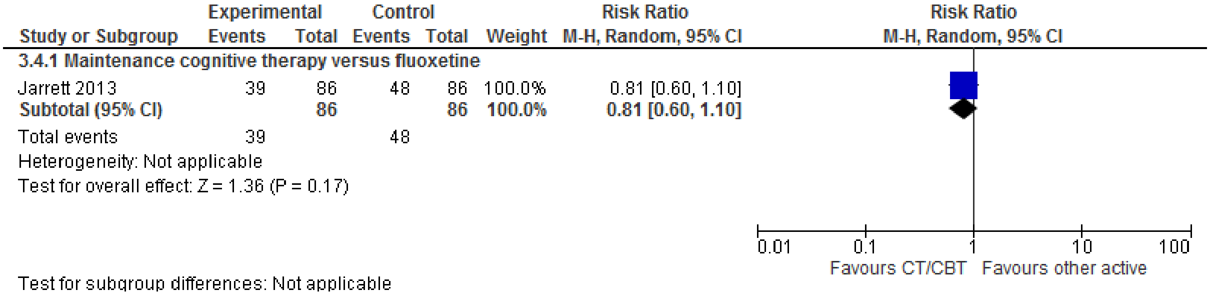
Relapse at 3-4 month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 CBT group + any AD versus any AD						
Brakemeier 2014	4	17	10	18	48.5%	0.42 [0.16, 1.10]
Subtotal (95% CI)		**17**		**18**	**48.5%**	**0.42 [0.16, 1.10]**
Total events	4		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
3.3.2 CBT group + maintenance AD versus maintenance AD						
Wilkinson 2009	5	22	9	23	51.5%	0.58 [0.23, 1.46]
Subtotal (95% CI)		**22**		**23**	**51.5%**	**0.58 [0.23, 1.46]**
Total events	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**39**		**41**	**100.0%**	**0.50 [0.26, 0.97]**
Total events	9		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

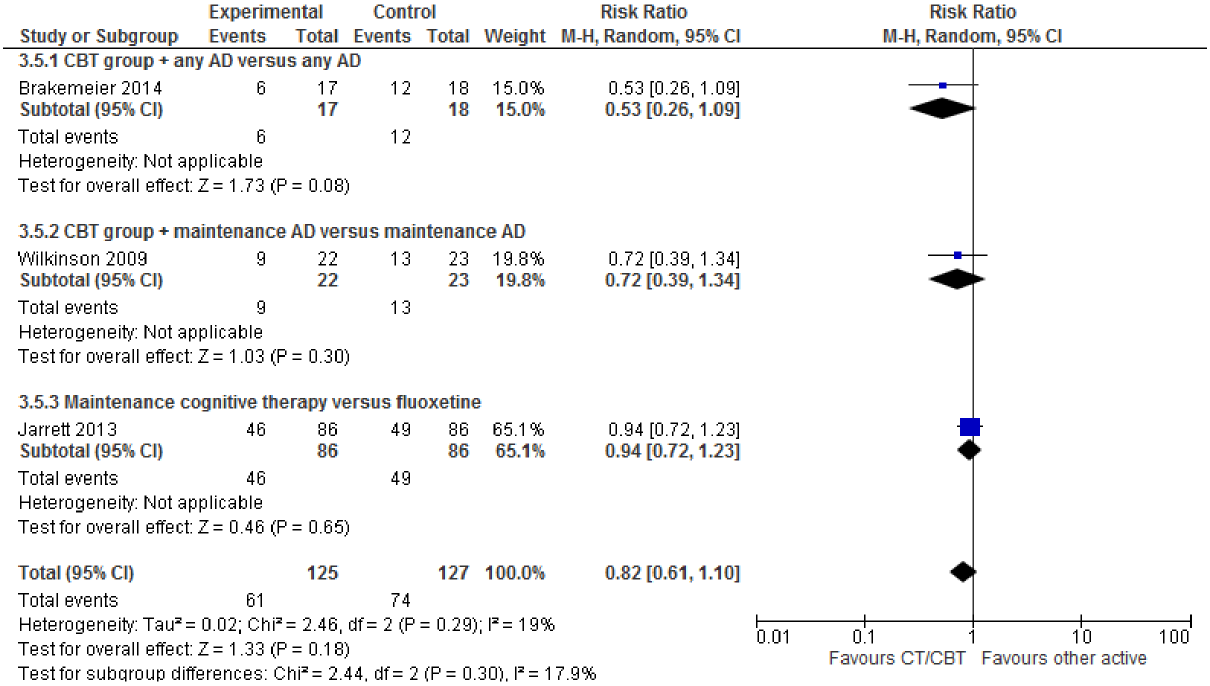
Relapse at 5-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	39	86	48	86	100.0%	0.81 [0.60, 1.10]
Subtotal (95% CI)		**86**		**86**	**100.0%**	**0.81 [0.60, 1.10]**
Total events	39		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
Test for subgroup differences: Not applicable						

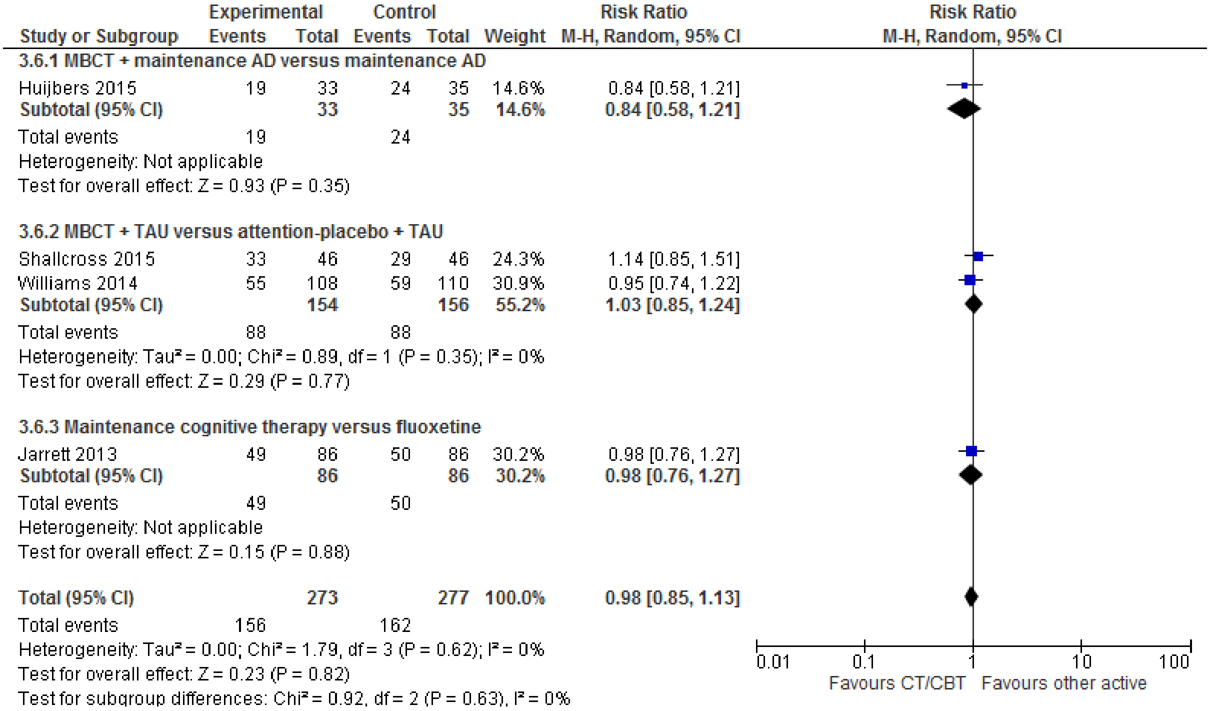
Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

Relapse at 8-10 month follow-up



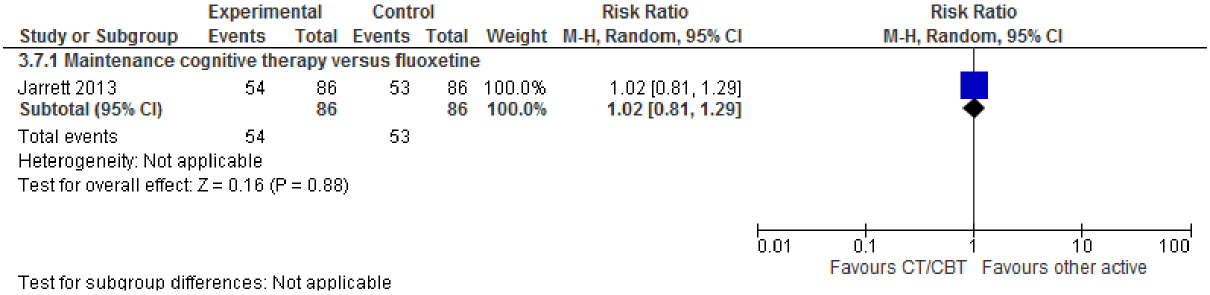
	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
3.5.1 CBT group + any AD versus any AD						
Brakemeier 2014	6	17	12	18	15.0%	0.53 [0.26, 1.09]
Subtotal (95% CI)		**17**		**18**	**15.0%**	**0.53 [0.26, 1.09]**
Total events	6		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
3.5.2 CBT group + maintenance AD versus maintenance AD						
Wilkinson 2009	9	22	13	23	19.8%	0.72 [0.39, 1.34]
Subtotal (95% CI)		**22**		**23**	**19.8%**	**0.72 [0.39, 1.34]**
Total events	9		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
3.5.3 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	46	86	49	86	65.1%	0.94 [0.72, 1.23]
Subtotal (95% CI)		**86**		**86**	**65.1%**	**0.94 [0.72, 1.23]**
Total events	46		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**125**		**127**	**100.0%**	**0.82 [0.61, 1.10]**
Total events	61		74			
Heterogeneity: Tau² = 0.02; Chi² = 2.46, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Chi² = 2.44, df = 2 (P = 0.30), I² = 17.9%						

Relapse at 11-13 month follow-up



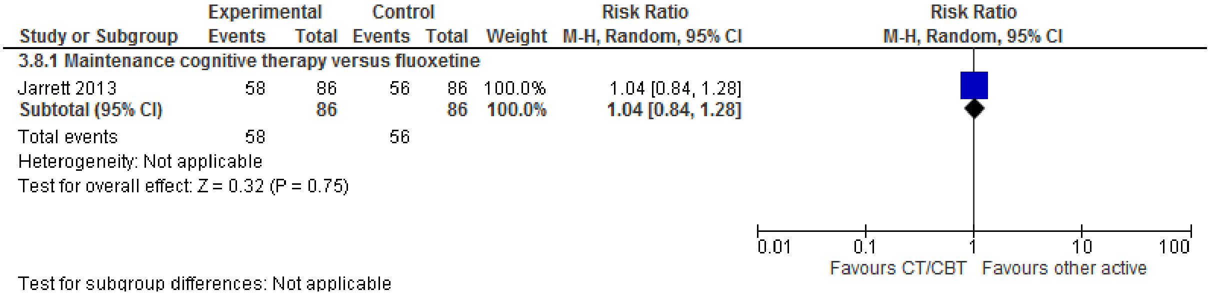
	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
3.6.1 MBCT + maintenance AD versus maintenance AD						
Huijbers 2015	19	33	24	35	14.6%	0.84 [0.58, 1.21]
Subtotal (95% CI)		**33**		**35**	**14.6%**	**0.84 [0.58, 1.21]**
Total events	19		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
3.6.2 MBCT + TAU versus attention-placebo + TAU						
Shallcross 2015	33	46	29	46	24.3%	1.14 [0.85, 1.51]
Williams 2014	55	108	59	110	30.9%	0.95 [0.74, 1.22]
Subtotal (95% CI)		**154**		**156**	**55.2%**	**1.03 [0.85, 1.24]**
Total events	88		88			
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
3.6.3 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	49	86	50	86	30.2%	0.98 [0.76, 1.27]
Subtotal (95% CI)		**86**		**86**	**30.2%**	**0.98 [0.76, 1.27]**
Total events	49		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)		**273**		**277**	**100.0%**	**0.98 [0.85, 1.13]**
Total events	156		162			
Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 3 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Chi² = 0.92, df = 2 (P = 0.63), I² = 0%						

Relapse at 15-month follow-up



	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
3.7.1 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	54	86	53	86	100.0%	1.02 [0.81, 1.29]
Subtotal (95% CI)		**86**		**86**	**100.0%**	**1.02 [0.81, 1.29]**
Total events	54		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Not applicable						

Relapse at 18-month follow-up



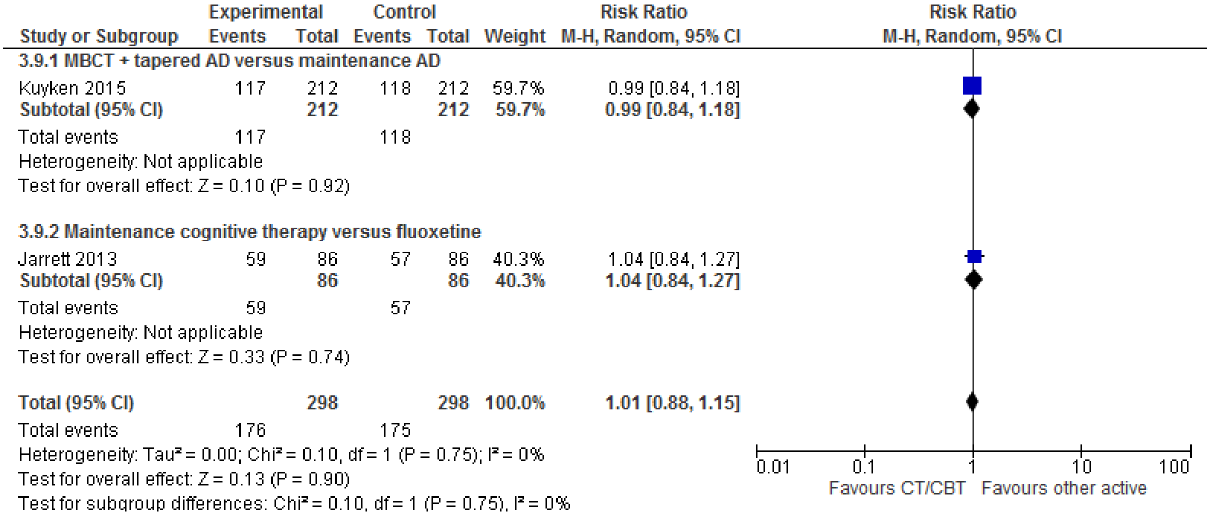
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	58	86	56	86	100.0%	1.04 [0.84, 1.28]
Subtotal (95% CI)		**86**		**86**	**100.0%**	**1.04 [0.84, 1.28]**
Total events	58		56			

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

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

Relapse at 21-22 month follow-up

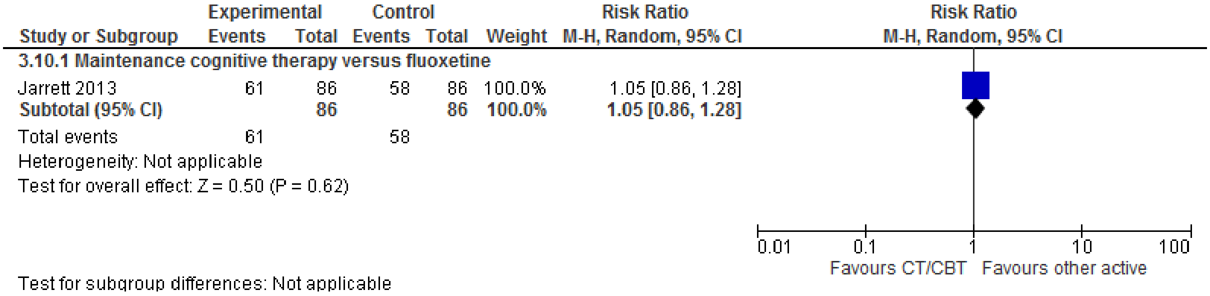


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 MBCT + tapered AD versus maintenance AD						
Kuyken 2015	117	212	118	212	59.7%	0.99 [0.84, 1.18]
Subtotal (95% CI)		**212**		**212**	**59.7%**	**0.99 [0.84, 1.18]**
Total events	117		118			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
3.9.2 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	59	86	57	86	40.3%	1.04 [0.84, 1.27]
Subtotal (95% CI)		**86**		**86**	**40.3%**	**1.04 [0.84, 1.27]**
Total events	59		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**298**		**298**	**100.0%**	**1.01 [0.88, 1.15]**
Total events	176		175			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

Relapse at 2-year follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.10.1 Maintenance cognitive therapy versus fluoxetine						
Jarrett 2013	61	86	58	86	100.0%	1.05 [0.86, 1.28]
Subtotal (95% CI)		**86**		**86**	**100.0%**	**1.05 [0.86, 1.28]**
Total events	61		58			

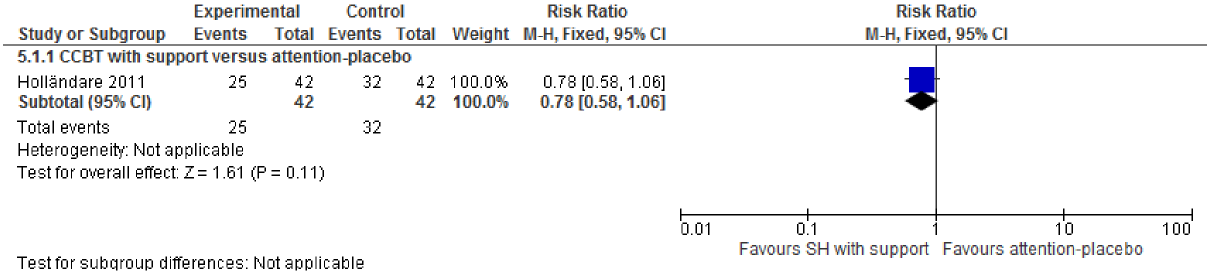
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CT/CBT
Favours other active

Self-help with support versus attention-placebo

Relapse at endpoint



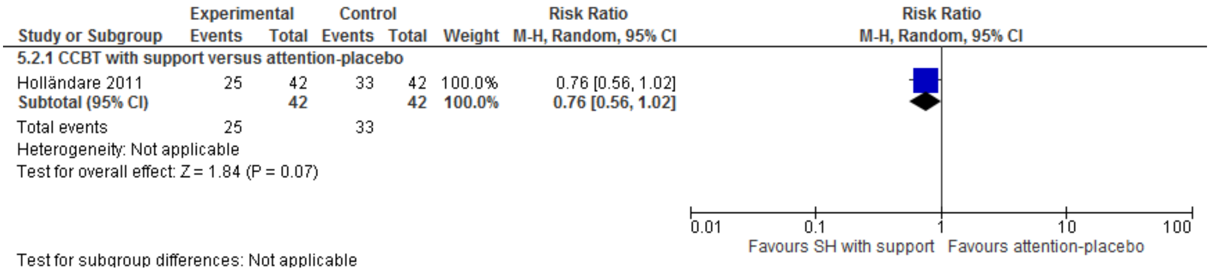
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 CCBT with support versus attention-placebo						
Holländare 2011	25	42	32	42	100.0%	0.78 [0.58, 1.06]
Subtotal (95% CI)		**42**		**42**	**100.0%**	**0.78 [0.58, 1.06]**
Total events	25		32			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Fixed, 95% CI
0.01
0.1
1
10
100
Favours SH with support
Favours attention-placebo

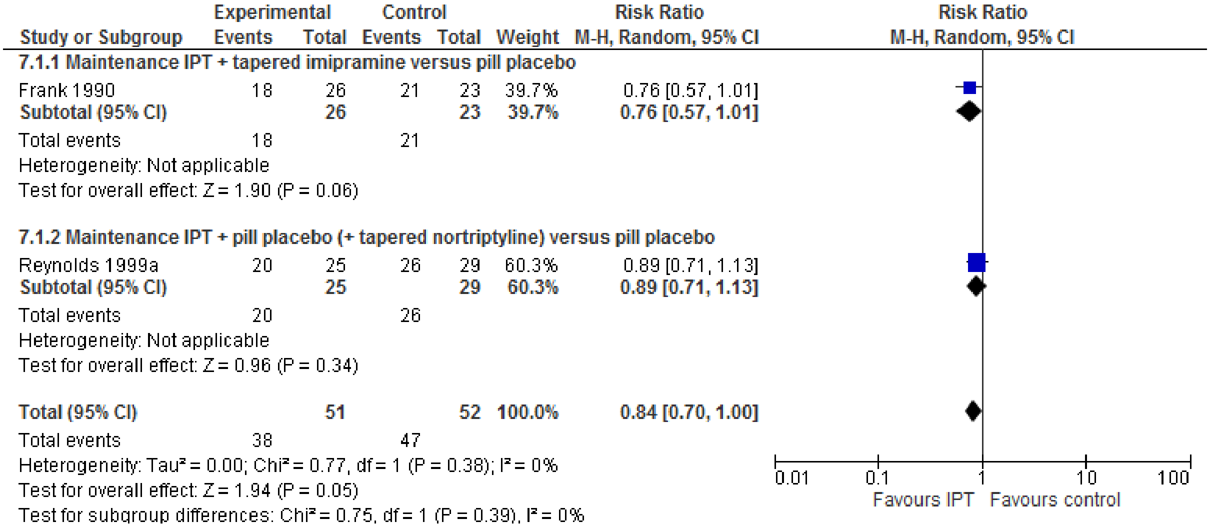
Relapse at 6-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 CCBT with support versus attention-placebo						
Holländare 2011	25	42	33	42	100.0%	0.76 [0.56, 1.02]
Subtotal (95% CI)		**42**		**42**	**100.0%**	**0.76 [0.56, 1.02]**
Total events	25		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Not applicable						

IPT versus control

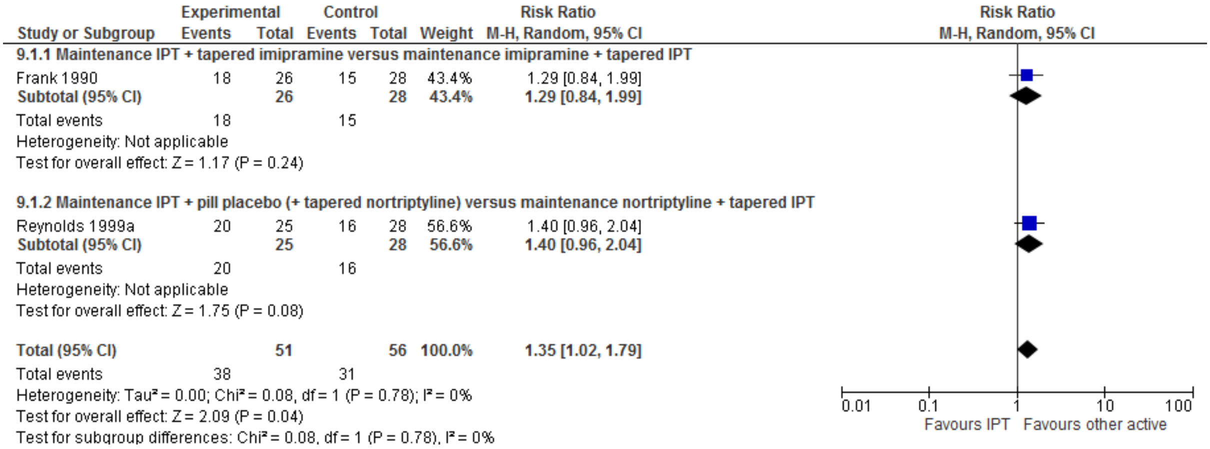
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Maintenance IPT + tapered imipramine versus pill placebo						
Frank 1990	18	26	21	23	39.7%	0.76 [0.57, 1.01]
Subtotal (95% CI)		**26**		**23**	**39.7%**	**0.76 [0.57, 1.01]**
Total events	18		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						
7.1.2 Maintenance IPT + pill placebo (+ tapered nortriptyline) versus pill placebo						
Reynolds 1999a	20	25	26	29	60.3%	0.89 [0.71, 1.13]
Subtotal (95% CI)		**25**		**29**	**60.3%**	**0.89 [0.71, 1.13]**
Total events	20		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Total (95% CI)		**51**		**52**	**100.0%**	**0.84 [0.70, 1.00]**
Total events	38		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
Test for subgroup differences: Chi² = 0.75, df = 1 (P = 0.39), I² = 0%						

IPT versus active intervention

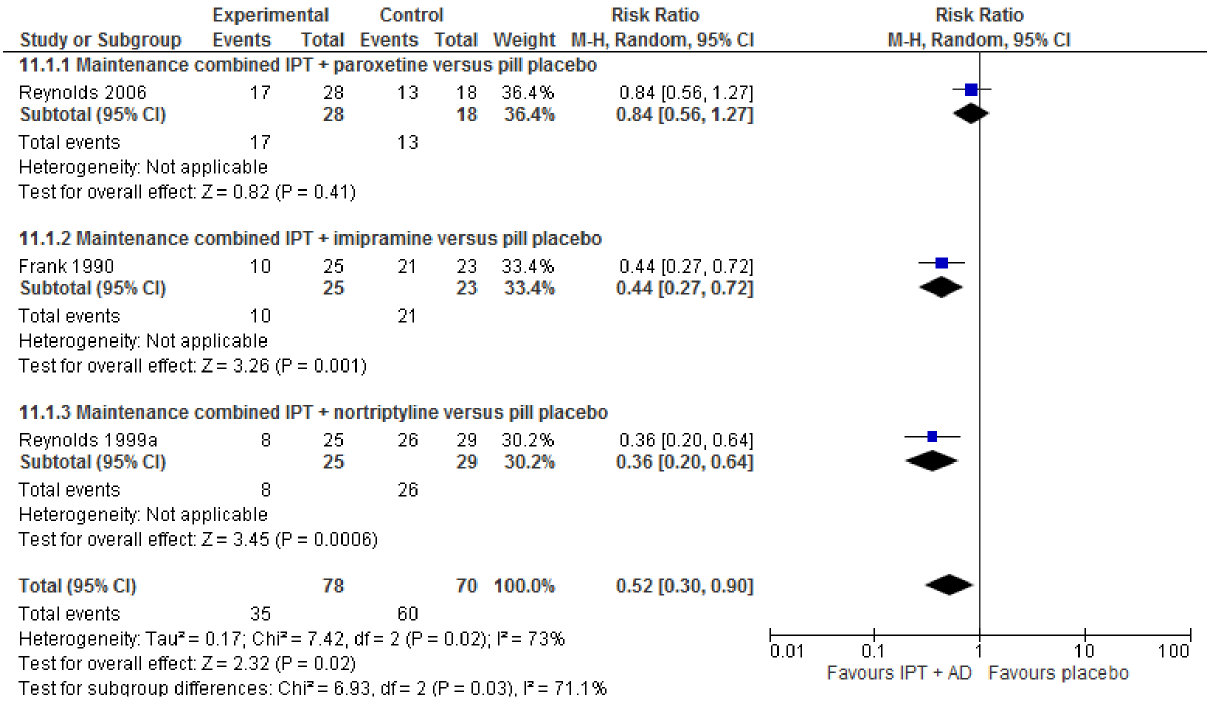
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Maintenance IPT + tapered imipramine versus maintenance imipramine + tapered IPT						
Frank 1990	18	26	15	28	43.4%	1.29 [0.84, 1.99]
Subtotal (95% CI)		**26**		**28**	**43.4%**	**1.29 [0.84, 1.99]**
Total events	18		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
9.1.2 Maintenance IPT + pill placebo (+ tapered nortriptyline) versus maintenance nortriptyline + tapered IPT						
Reynolds 1999a	20	25	16	28	56.6%	1.40 [0.96, 2.04]
Subtotal (95% CI)		**25**		**28**	**56.6%**	**1.40 [0.96, 2.04]**
Total events	20		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**51**		**56**	**100.0%**	**1.35 [1.02, 1.79]**
Total events	38		31			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

Combined IPT + AD versus pill placebo

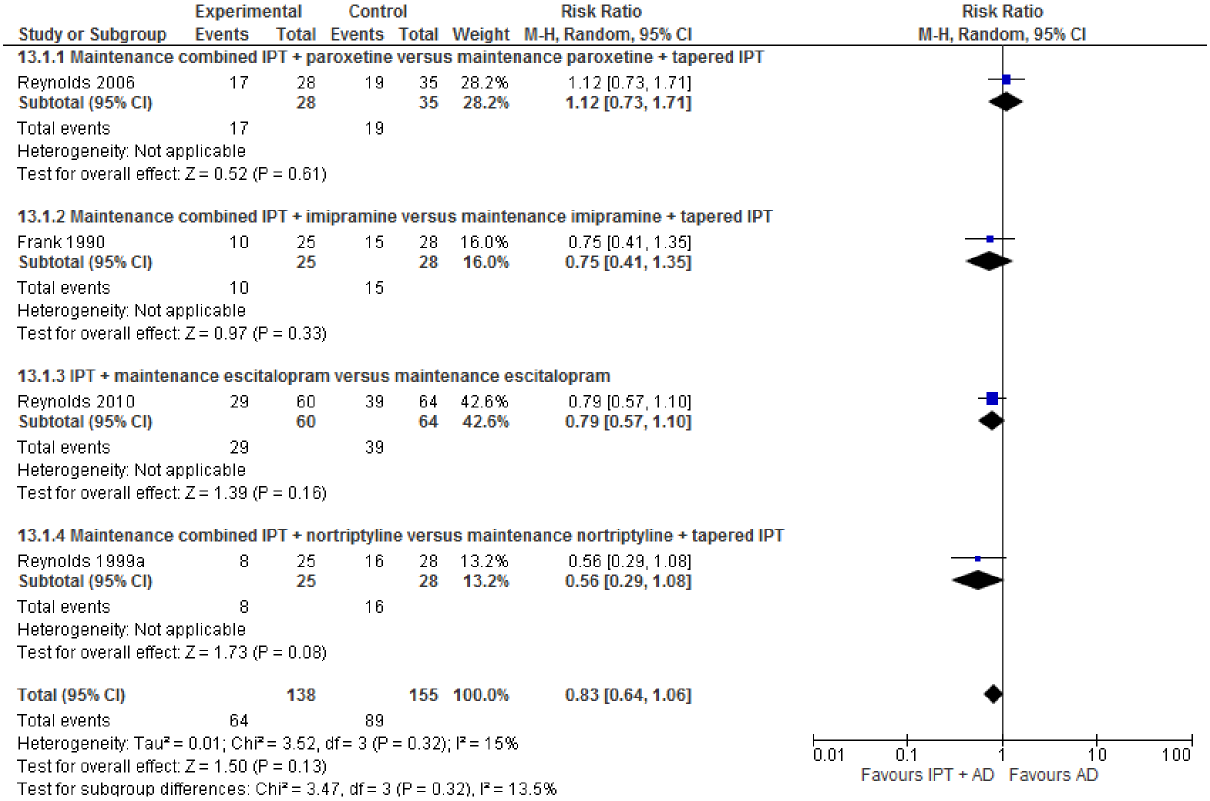
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Maintenance combined IPT + paroxetine versus pill placebo						
Reynolds 2006	17	28	13	18	36.4%	0.84 [0.56, 1.27]
Subtotal (95% CI)		**28**		**18**	**36.4%**	**0.84 [0.56, 1.27]**
Total events	17		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
11.1.2 Maintenance combined IPT + imipramine versus pill placebo						
Frank 1990	10	25	21	23	33.4%	0.44 [0.27, 0.72]
Subtotal (95% CI)		**25**		**23**	**33.4%**	**0.44 [0.27, 0.72]**
Total events	10		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.26 (P = 0.001)						
11.1.3 Maintenance combined IPT + nortriptyline versus pill placebo						
Reynolds 1999a	8	25	26	29	30.2%	0.36 [0.20, 0.64]
Subtotal (95% CI)		**25**		**29**	**30.2%**	**0.36 [0.20, 0.64]**
Total events	8		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Total (95% CI)		**78**		**70**	**100.0%**	**0.52 [0.30, 0.90]**
Total events	35		60			
Heterogeneity: Tau² = 0.17; Chi² = 7.42, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Chi² = 6.93, df = 2 (P = 0.03), I² = 71.1%						

Combined IPT + AD versus AD

Relapse at endpoint

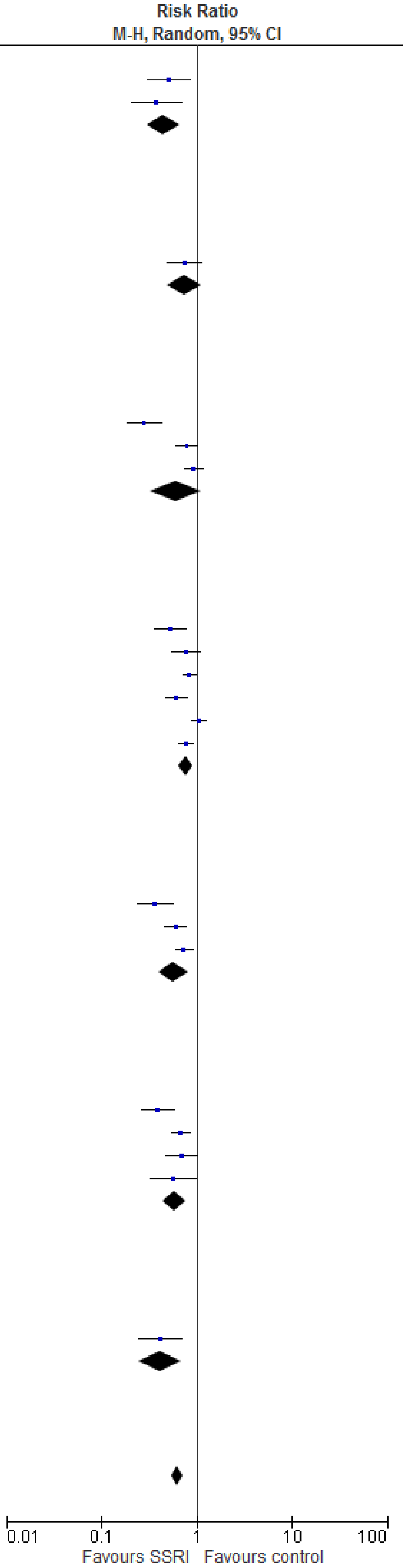


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 Maintenance combined IPT + paroxetine versus maintenance paroxetine + tapered IPT						
Reynolds 2006	17	28	19	35	28.2%	1.12 [0.73, 1.71]
Subtotal (95% CI)		**28**		**35**	**28.2%**	**1.12 [0.73, 1.71]**
Total events	17		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.61)						
13.1.2 Maintenance combined IPT + imipramine versus maintenance imipramine + tapered IPT						
Frank 1990	10	25	15	28	16.0%	0.75 [0.41, 1.35]
Subtotal (95% CI)		**25**		**28**	**16.0%**	**0.75 [0.41, 1.35]**
Total events	10		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
13.1.3 IPT + maintenance escitalopram versus maintenance escitalopram						
Reynolds 2010	29	60	39	64	42.6%	0.79 [0.57, 1.10]
Subtotal (95% CI)		**60**		**64**	**42.6%**	**0.79 [0.57, 1.10]**
Total events	29		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.16)						
13.1.4 Maintenance combined IPT + nortriptyline versus maintenance nortriptyline + tapered IPT						
Reynolds 1999a	8	25	16	28	13.2%	0.56 [0.29, 1.08]
Subtotal (95% CI)		**25**		**28**	**13.2%**	**0.56 [0.29, 1.08]**
Total events	8		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
Total (95% CI)		**138**		**155**	**100.0%**	**0.83 [0.64, 1.06]**
Total events	64		89			
Heterogeneity: Tau² = 0.01; Chi² = 3.52, df = 3 (P = 0.32); I² = 15%						
Test for overall effect: Z = 1.50 (P = 0.13)						
Test for subgroup differences: Chi² = 3.47, df = 3 (P = 0.32), I² = 13.5%						

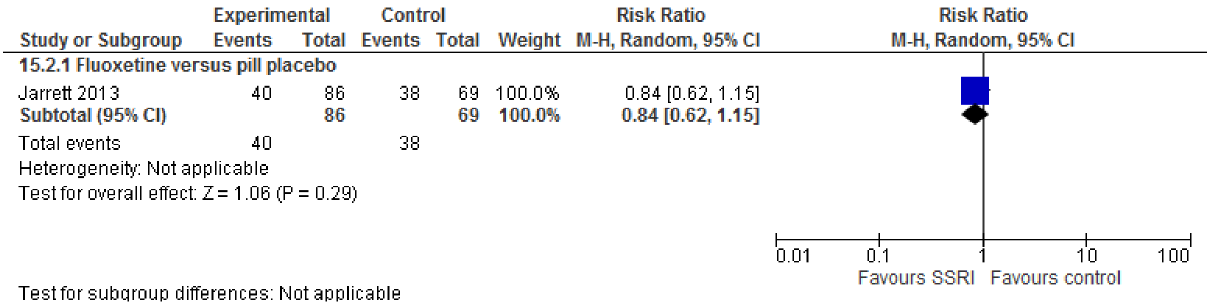
SSRIs versus control

Relapse at endpoint

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.1.1 Maintenance paroxetine versus pill placebo						
Dobson 2008	11	28	16	21	3.7%	0.52 [0.31, 0.87]
Montgomery 1993a	11	68	29	67	3.1%	0.37 [0.20, 0.69]
Subtotal (95% CI)		**96**		**88**	**6.8%**	**0.45 [0.30, 0.67]**
Total events	22		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
15.1.2 Maintenance paroxetine + tapered IPT versus pill placebo						
Reynolds 2006	19	35	13	18	4.4%	0.75 [0.49, 1.14]
Subtotal (95% CI)		**35**		**18**	**4.4%**	**0.75 [0.49, 1.14]**
Total events	19		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
15.1.3 (Maintenance) sertraline versus pill placebo						
Doogan 1992	25	185	53	110	4.4%	0.28 [0.19, 0.42]
Lepine 2004	74	189	49	99	5.6%	0.79 [0.61, 1.03]
Wilson 2003	39	56	43	57	5.9%	0.92 [0.74, 1.16]
Subtotal (95% CI)		**430**		**266**	**16.0%**	**0.60 [0.32, 1.14]**
Total events	138		145			
Heterogeneity: Tau² = 0.29; Chi² = 28.53, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 1.56 (P = 0.12)						
15.1.4 (Maintenance) fluoxetine versus pill placebo						
Gilaberte 2001	23	72	44	73	4.7%	0.53 [0.36, 0.78]
Jarrett 2013	35	86	36	69	5.0%	0.78 [0.55, 1.10]
McGrath 2006	88	131	104	131	6.5%	0.85 [0.73, 0.98]
Montgomery 1988	43	108	72	112	5.6%	0.62 [0.47, 0.81]
Reimherr 1998	77	102	68	96	6.3%	1.07 [0.90, 1.26]
Schmidt 2000	105	189	87	122	6.3%	0.78 [0.66, 0.92]
Subtotal (95% CI)		**688**		**603**	**34.4%**	**0.78 [0.65, 0.93]**
Total events	371		411			
Heterogeneity: Tau² = 0.04; Chi² = 20.08, df = 5 (P = 0.001); I² = 75%						
Test for overall effect: Z = 2.72 (P = 0.007)						
15.1.5 Maintenance escitalopram versus pill placebo						
Gorwood 2007	23	152	63	153	4.4%	0.37 [0.24, 0.56]
Kornstein 2006	36	73	54	66	5.7%	0.60 [0.47, 0.78]
Rapaport 2004	89	181	62	93	6.1%	0.74 [0.60, 0.91]
Subtotal (95% CI)		**406**		**312**	**16.1%**	**0.57 [0.40, 0.81]**
Total events	148		179			
Heterogeneity: Tau² = 0.08; Chi² = 9.60, df = 2 (P = 0.008); I² = 79%						
Test for overall effect: Z = 3.09 (P = 0.002)						
15.1.6 Maintenance citalopram versus pill placebo						
Hochstrasser 2001	24	132	64	137	4.5%	0.39 [0.26, 0.58]
Klysner 2002	37	60	55	61	6.0%	0.68 [0.55, 0.85]
Montgomery 1993b	40	105	23	42	4.8%	0.70 [0.48, 1.00]
Robert 1995	21	152	18	74	3.4%	0.57 [0.32, 1.00]
Subtotal (95% CI)		**449**		**314**	**18.7%**	**0.58 [0.44, 0.78]**
Total events	122		160			
Heterogeneity: Tau² = 0.05; Chi² = 7.56, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
15.1.7 Maintenance fluvoxamine versus pill placebo						
Terra 1998	16	110	33	94	3.6%	0.41 [0.24, 0.70]
Subtotal (95% CI)		**110**		**94**	**3.6%**	**0.41 [0.24, 0.70]**
Total events	16		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.26 (P = 0.001)						
Total (95% CI)		**2214**		**1695**	**100.0%**	**0.63 [0.55, 0.73]**
Total events	836		986			
Heterogeneity: Tau² = 0.08; Chi² = 97.55, df = 19 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 6.18 (P < 0.00001)						
Test for subgroup differences: Chi² = 11.53, df = 6 (P = 0.07), I² = 48.0%						



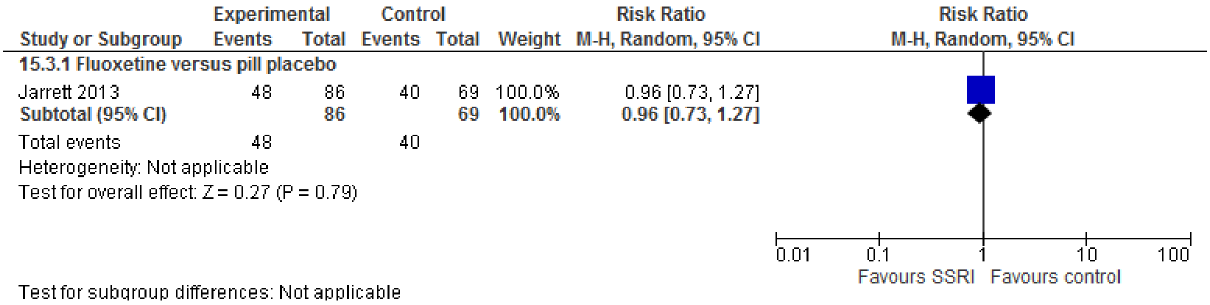
Relapse at 2-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.2.1 Fluoxetine versus pill placebo						
Jarrett 2013	40	86	38	69	100.0%	0.84 [0.62, 1.15]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.84 [0.62, 1.15]**
Total events	40		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

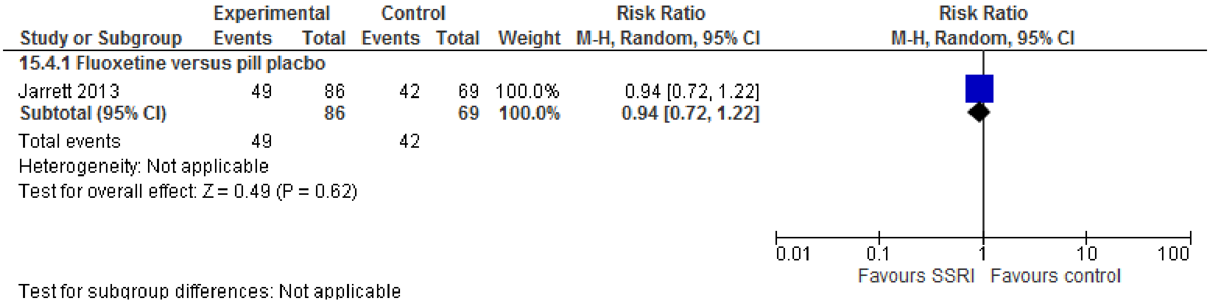
Relapse at 5-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.3.1 Fluoxetine versus pill placebo						
Jarrett 2013	48	86	40	69	100.0%	0.96 [0.73, 1.27]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.96 [0.73, 1.27]**
Total events	48		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

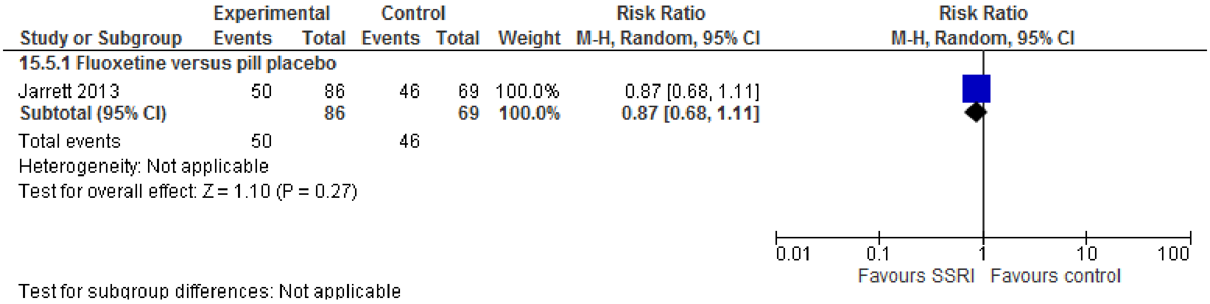
Relapse at 8-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.4.1 Fluoxetine versus pill placbo						
Jarrett 2013	49	86	42	69	100.0%	0.94 [0.72, 1.22]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.94 [0.72, 1.22]**
Total events	49		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

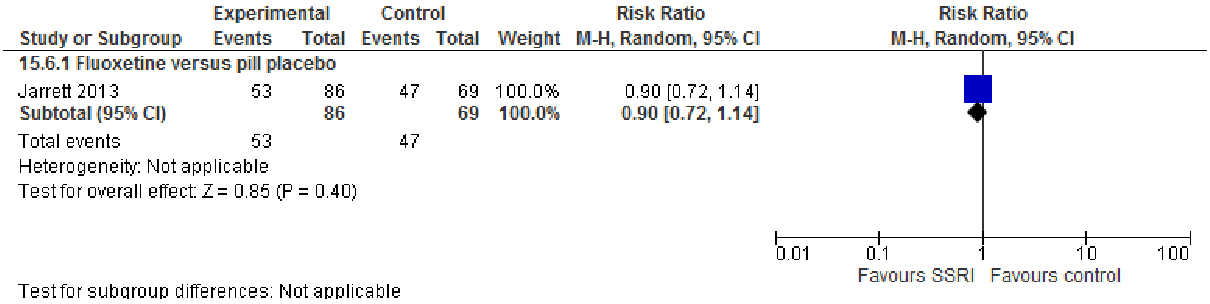
Relapse at 11-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.5.1 Fluoxetine versus pill placebo						
Jarrett 2013	50	86	46	69	100.0%	0.87 [0.68, 1.11]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.87 [0.68, 1.11]**
Total events	50		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

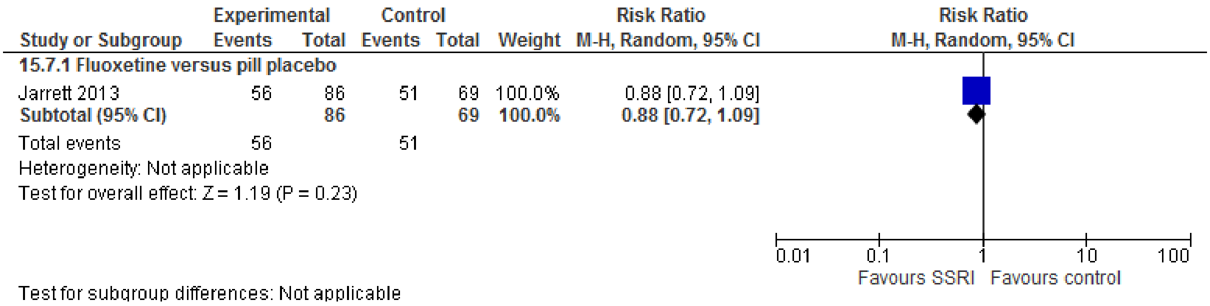
Relapse at 15-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.6.1 Fluoxetine versus pill placebo						
Jarrett 2013	53	86	47	69	100.0%	0.90 [0.72, 1.14]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.90 [0.72, 1.14]**
Total events	53		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

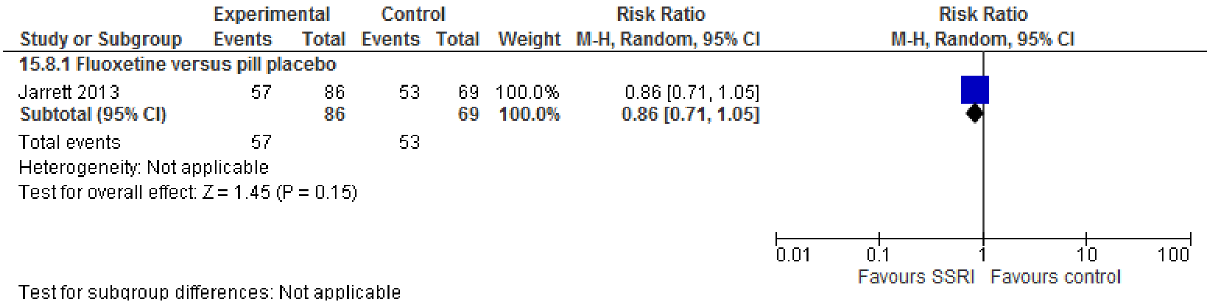
Relapse at 18-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.7.1 Fluoxetine versus pill placebo						
Jarrett 2013	56	86	51	69	100.0%	0.88 [0.72, 1.09]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.88 [0.72, 1.09]**
Total events	56		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.23)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

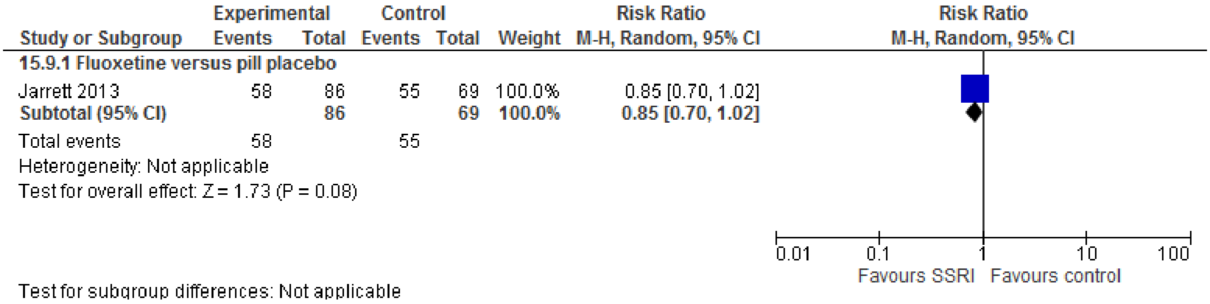
Relapse at 21-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.8.1 Fluoxetine versus pill placebo						
Jarrett 2013	57	86	53	69	100.0%	0.86 [0.71, 1.05]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.86 [0.71, 1.05]**
Total events	57		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

Relapse at 2-year follow-up

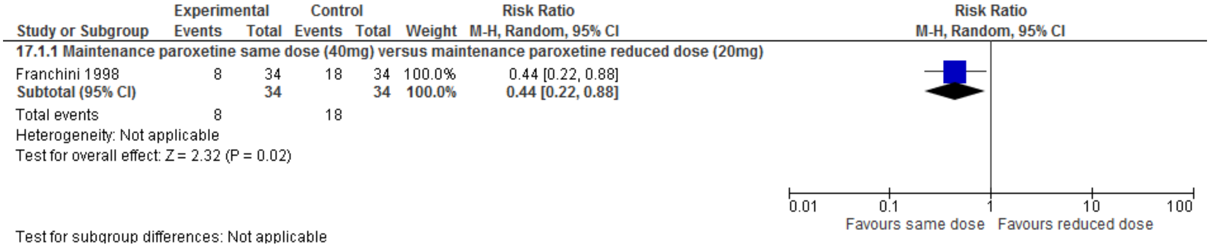


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
15.9.1 Fluoxetine versus pill placebo						
Jarrett 2013	58	86	55	69	100.0%	0.85 [0.70, 1.02]
Subtotal (95% CI)		**86**		**69**	**100.0%**	**0.85 [0.70, 1.02]**
Total events	58		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours SSRI
Favours control

SSRI maintenance same dose versus SSRI maintenance reduced dose

Relapse at endpoint

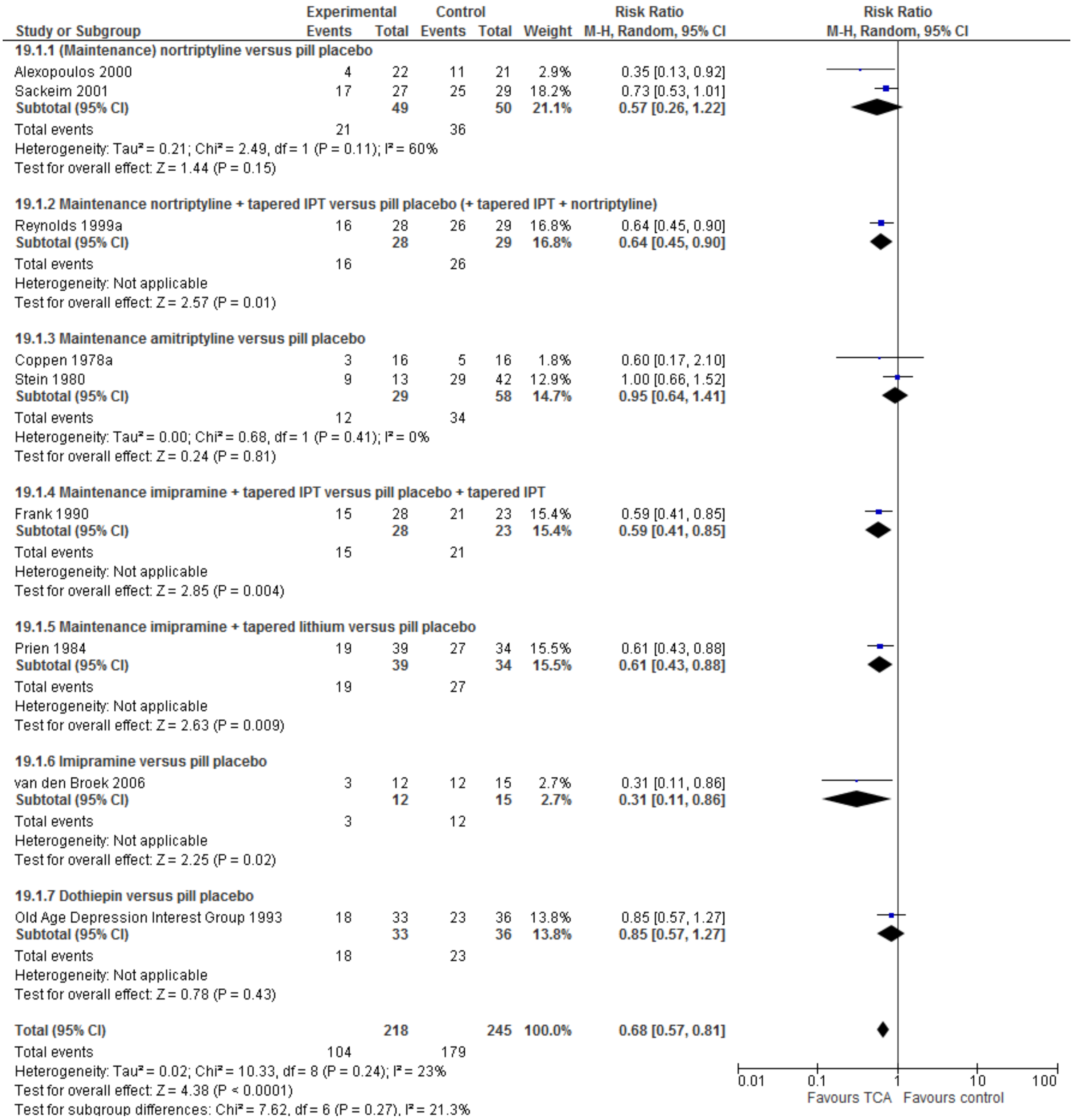


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
17.1.1 Maintenance paroxetine same dose (40mg) versus maintenance paroxetine reduced dose (20mg)						
Franchini 1998	8	34	18	34	100.0%	0.44 [0.22, 0.88]
Subtotal (95% CI)		**34**		**34**	**100.0%**	**0.44 [0.22, 0.88]**
Total events	8		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Not applicable						

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours same dose
Favours reduced dose

TCAs versus control

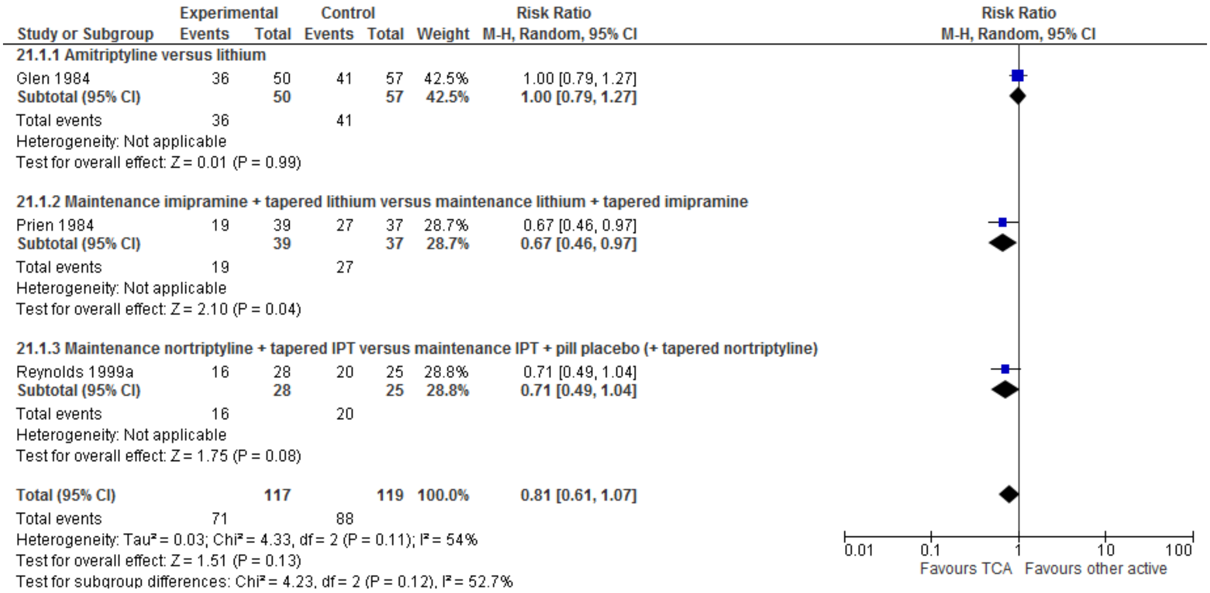
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
19.1.1 (Maintenance) nortriptyline versus pill placebo						
Alexopoulos 2000	4	22	11	21	2.9%	0.35 [0.13, 0.92]
Sackeim 2001	17	27	25	29	18.2%	0.73 [0.53, 1.01]
Subtotal (95% CI)		**49**		**50**	**21.1%**	**0.57 [0.26, 1.22]**
Total events	21		36			
Heterogeneity: Tau² = 0.21; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 1.44 (P = 0.15)						
19.1.2 Maintenance nortriptyline + tapered IPT versus pill placebo (+ tapered IPT + nortriptyline)						
Reynolds 1999a	16	28	26	29	16.8%	0.64 [0.45, 0.90]
Subtotal (95% CI)		**28**		**29**	**16.8%**	**0.64 [0.45, 0.90]**
Total events	16		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.57 (P = 0.01)						
19.1.3 Maintenance amitriptyline versus pill placebo						
Coppen 1978a	3	16	5	16	1.8%	0.60 [0.17, 2.10]
Stein 1980	9	13	29	42	12.9%	1.00 [0.66, 1.52]
Subtotal (95% CI)		**29**		**58**	**14.7%**	**0.95 [0.64, 1.41]**
Total events	12		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
19.1.4 Maintenance imipramine + tapered IPT versus pill placebo + tapered IPT						
Frank 1990	15	28	21	23	15.4%	0.59 [0.41, 0.85]
Subtotal (95% CI)		**28**		**23**	**15.4%**	**0.59 [0.41, 0.85]**
Total events	15		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.85 (P = 0.004)						
19.1.5 Maintenance imipramine + tapered lithium versus pill placebo						
Prien 1984	19	39	27	34	15.5%	0.61 [0.43, 0.88]
Subtotal (95% CI)		**39**		**34**	**15.5%**	**0.61 [0.43, 0.88]**
Total events	19		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
19.1.6 Imipramine versus pill placebo						
van den Broek 2006	3	12	12	15	2.7%	0.31 [0.11, 0.86]
Subtotal (95% CI)		**12**		**15**	**2.7%**	**0.31 [0.11, 0.86]**
Total events	3		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						
19.1.7 Dothiepin versus pill placebo						
Old Age Depression Interest Group 1993	18	33	23	36	13.8%	0.85 [0.57, 1.27]
Subtotal (95% CI)		**33**		**36**	**13.8%**	**0.85 [0.57, 1.27]**
Total events	18		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
Total (95% CI)		**218**		**245**	**100.0%**	**0.68 [0.57, 0.81]**
Total events	104		179			
Heterogeneity: Tau² = 0.02; Chi² = 10.33, df = 8 (P = 0.24); I² = 23%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
Test for subgroup differences: Chi² = 7.62, df = 6 (P = 0.27), I² = 21.3%						

TCAs versus active intervention

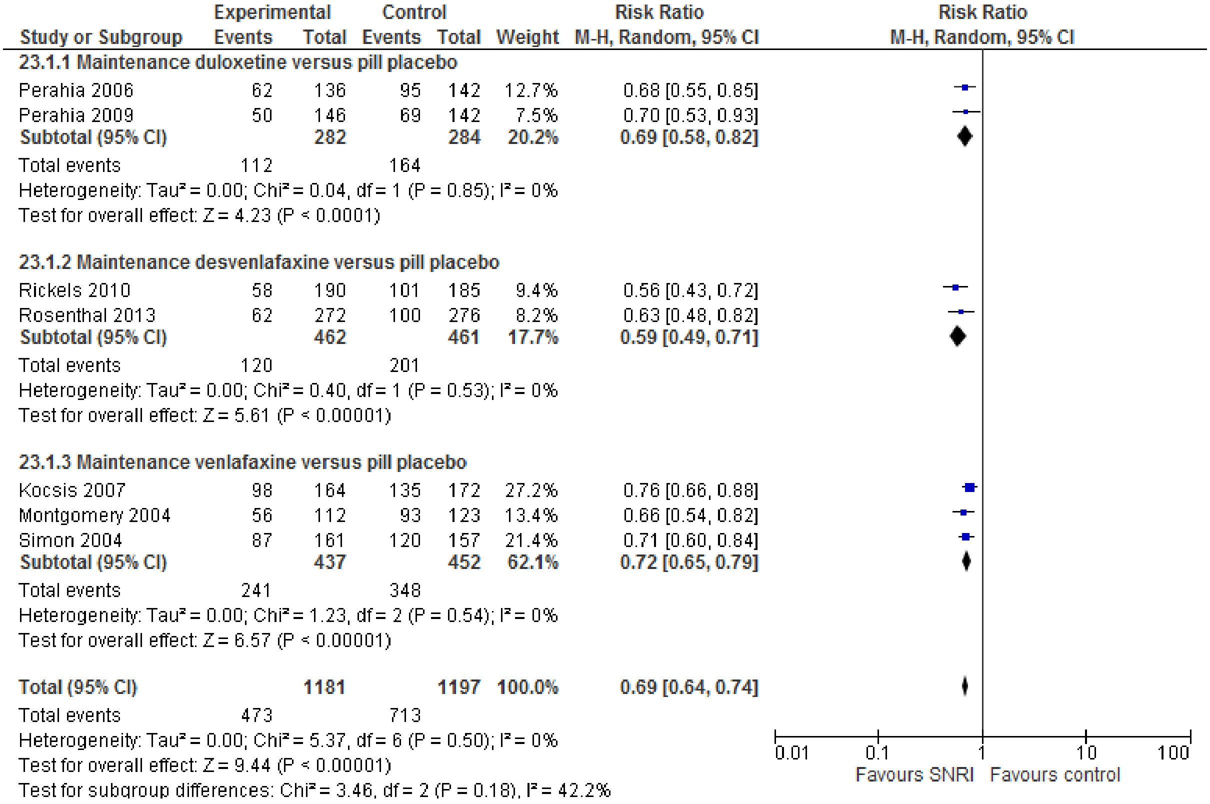
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 Amitriptyline versus lithium						
Glen 1984	36	50	41	57	42.5%	1.00 [0.79, 1.27]
Subtotal (95% CI)		**50**		**57**	**42.5%**	**1.00 [0.79, 1.27]**
Total events	36		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
21.1.2 Maintenance imipramine + tapered lithium versus maintenance lithium + tapered imipramine						
Prien 1984	19	39	27	37	28.7%	0.67 [0.46, 0.97]
Subtotal (95% CI)		**39**		**37**	**28.7%**	**0.67 [0.46, 0.97]**
Total events	19		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						
21.1.3 Maintenance nortriptyline + tapered IPT versus maintenance IPT + pill placebo (+ tapered nortriptyline)						
Reynolds 1999a	16	28	20	25	28.8%	0.71 [0.49, 1.04]
Subtotal (95% CI)		**28**		**25**	**28.8%**	**0.71 [0.49, 1.04]**
Total events	16		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**117**		**119**	**100.0%**	**0.81 [0.61, 1.07]**
Total events	71		88			
Heterogeneity: Tau² = 0.03; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Chi² = 4.23, df = 2 (P = 0.12), I² = 52.7%						

SNRIs versus control

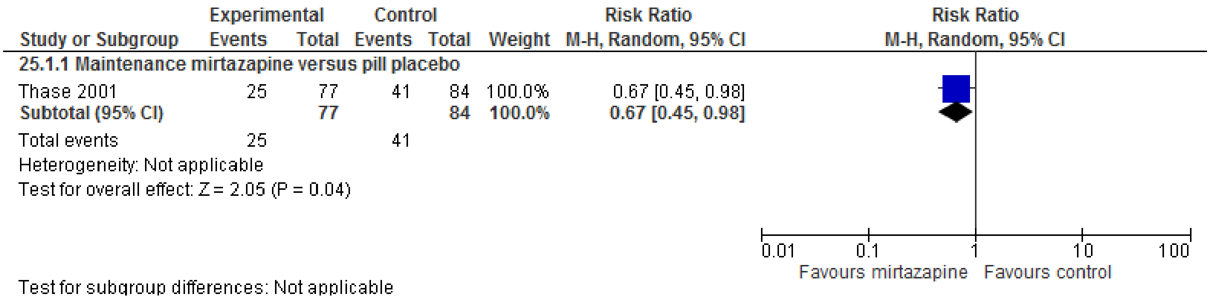
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
23.1.1 Maintenance duloxetine versus pill placebo						
Perahia 2006	62	136	95	142	12.7%	0.68 [0.55, 0.85]
Perahia 2009	50	146	69	142	7.5%	0.70 [0.53, 0.93]
Subtotal (95% CI)		**282**		**284**	**20.2%**	**0.69 [0.58, 0.82]**
Total events	112		164			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
23.1.2 Maintenance desvenlafaxine versus pill placebo						
Rickels 2010	58	190	101	185	9.4%	0.56 [0.43, 0.72]
Rosenthal 2013	62	272	100	276	8.2%	0.63 [0.48, 0.82]
Subtotal (95% CI)		**462**		**461**	**17.7%**	**0.59 [0.49, 0.71]**
Total events	120		201			
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 5.61 (P < 0.00001)						
23.1.3 Maintenance venlafaxine versus pill placebo						
Kocsis 2007	98	164	135	172	27.2%	0.76 [0.66, 0.88]
Montgomery 2004	56	112	93	123	13.4%	0.66 [0.54, 0.82]
Simon 2004	87	161	120	157	21.4%	0.71 [0.60, 0.84]
Subtotal (95% CI)		**437**		**452**	**62.1%**	**0.72 [0.65, 0.79]**
Total events	241		348			
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 6.57 (P < 0.00001)						
Total (95% CI)		**1181**		**1197**	**100.0%**	**0.69 [0.64, 0.74]**
Total events	473		713			
Heterogeneity: Tau² = 0.00; Chi² = 5.37, df = 6 (P = 0.50); I² = 0%						
Test for overall effect: Z = 9.44 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.46, df = 2 (P = 0.18), I² = 42.2%						

Mirtazapine versus control

Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
25.1.1 Maintenance mirtazapine versus pill placebo						
Thase 2001	25	77	41	84	100.0%	0.67 [0.45, 0.98]
Subtotal (95% CI)		**77**		**84**	**100.0%**	**0.67 [0.45, 0.98]**
Total events	25		41			

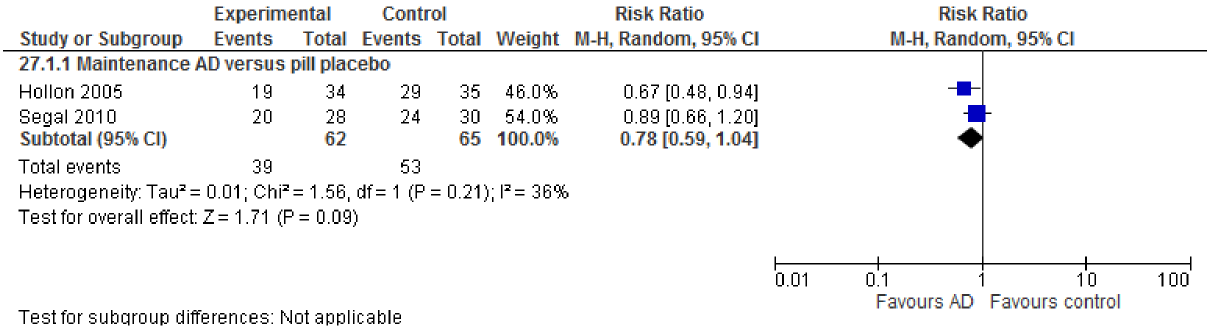
Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours mirtazapine
Favours control

Any AD versus control

Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
27.1.1 Maintenance AD versus pill placebo						
Hollon 2005	19	34	29	35	46.0%	0.67 [0.48, 0.94]
Segal 2010	20	28	24	30	54.0%	0.89 [0.66, 1.20]
Subtotal (95% CI)		**62**		**65**	**100.0%**	**0.78 [0.59, 1.04]**
Total events	39		53			

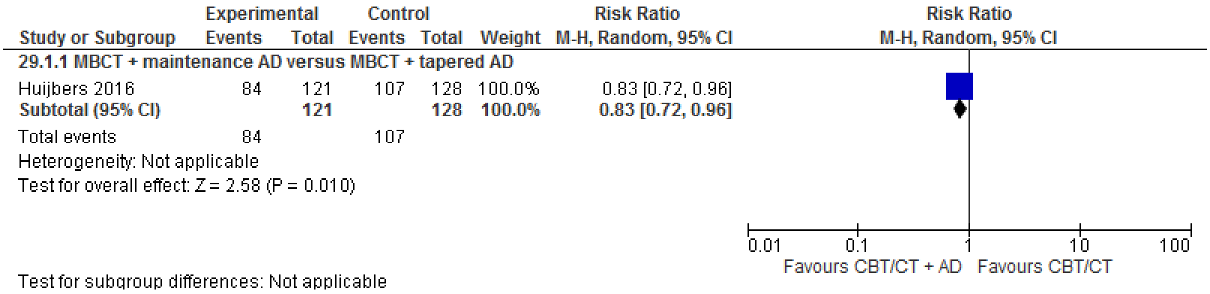
Heterogeneity: Tau² = 0.01; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 1.71 (P = 0.09)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours AD
Favours control

Combined CT/CBT + AD versus CT/CBT

Relapse at 13-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
29.1.1 MBCT + maintenance AD versus MBCT + tapered AD						
Huijbers 2016	84	121	107	128	100.0%	0.83 [0.72, 0.96]
Subtotal (95% CI)		**121**		**128**	**100.0%**	**0.83 [0.72, 0.96]**
Total events	84		107			

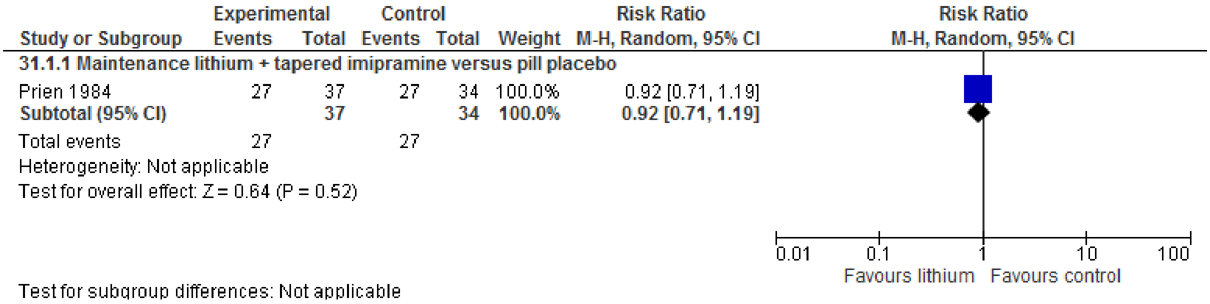
Heterogeneity: Not applicable
Test for overall effect: Z = 2.58 (P = 0.010)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours CBT/CT + AD
Favours CBT/CT

Lithium versus control

Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
31.1.1 Maintenance lithium + tapered imipramine versus pill placebo						
Prien 1984	27	37	27	34	100.0%	0.92 [0.71, 1.19]
Subtotal (95% CI)		**37**		**34**	**100.0%**	**0.92 [0.71, 1.19]**
Total events	27		27			

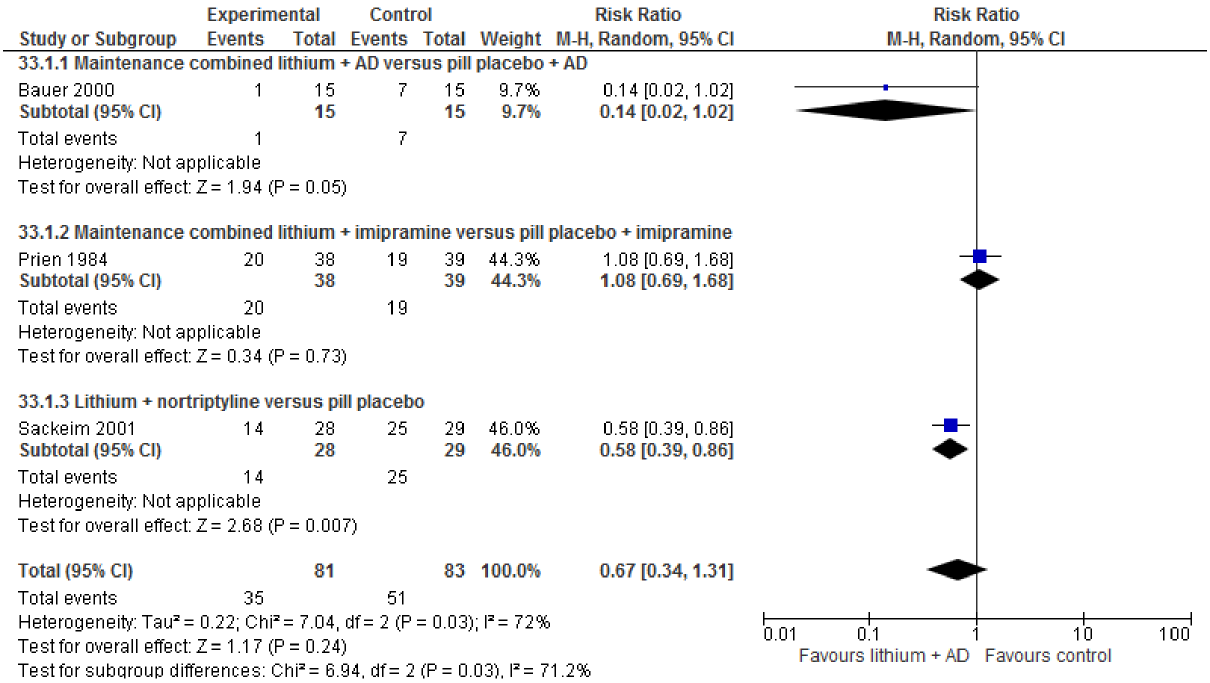
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

Risk Ratio
M-H, Random, 95% CI
0.01
0.1
1
10
100
Favours lithium
Favours control

Lithium augmentation versus control

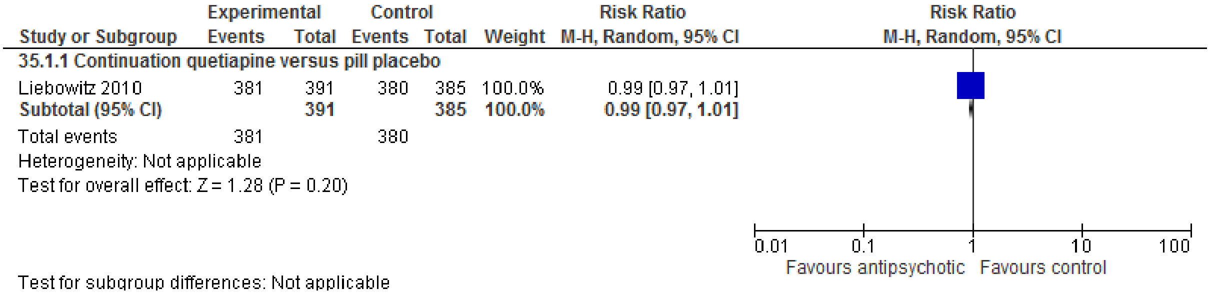
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
33.1.1 Maintenance combined lithium + AD versus pill placebo + AD						
Bauer 2000	1	15	7	15	9.7%	0.14 [0.02, 1.02]
Subtotal (95% CI)		**15**		**15**	**9.7%**	**0.14 [0.02, 1.02]**
Total events	1		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
33.1.2 Maintenance combined lithium + imipramine versus pill placebo + imipramine						
Prien 1984	20	38	19	39	44.3%	1.08 [0.69, 1.68]
Subtotal (95% CI)		**38**		**39**	**44.3%**	**1.08 [0.69, 1.68]**
Total events	20		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
33.1.3 Lithium + nortriptyline versus pill placebo						
Sackeim 2001	14	28	25	29	46.0%	0.58 [0.39, 0.86]
Subtotal (95% CI)		**28**		**29**	**46.0%**	**0.58 [0.39, 0.86]**
Total events	14		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.68 (P = 0.007)						
Total (95% CI)		**81**		**83**	**100.0%**	**0.67 [0.34, 1.31]**
Total events	35		51			
Heterogeneity: Tau² = 0.22; Chi² = 7.04, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 6.94, df = 2 (P = 0.03), I² = 71.2%						

Antipsychotic versus control

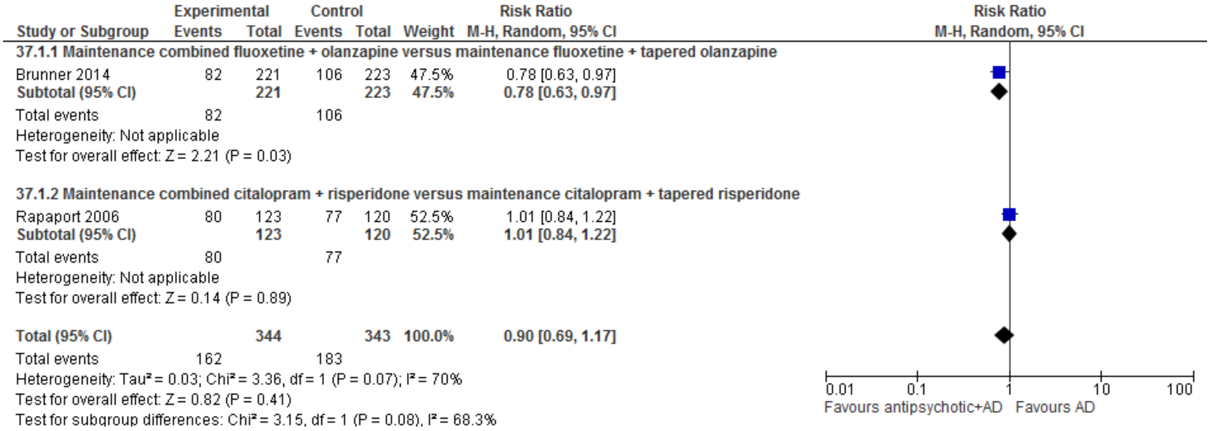
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
35.1.1 Continuation quetiapine versus pill placebo						
Liebowitz 2010	381	391	380	385	100.0%	0.99 [0.97, 1.01]
Subtotal (95% CI)		**391**		**385**	**100.0%**	**0.99 [0.97, 1.01]**
Total events	381		380			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
Test for subgroup differences: Not applicable						

Antipsychotic augmentation versus AD monotherapy

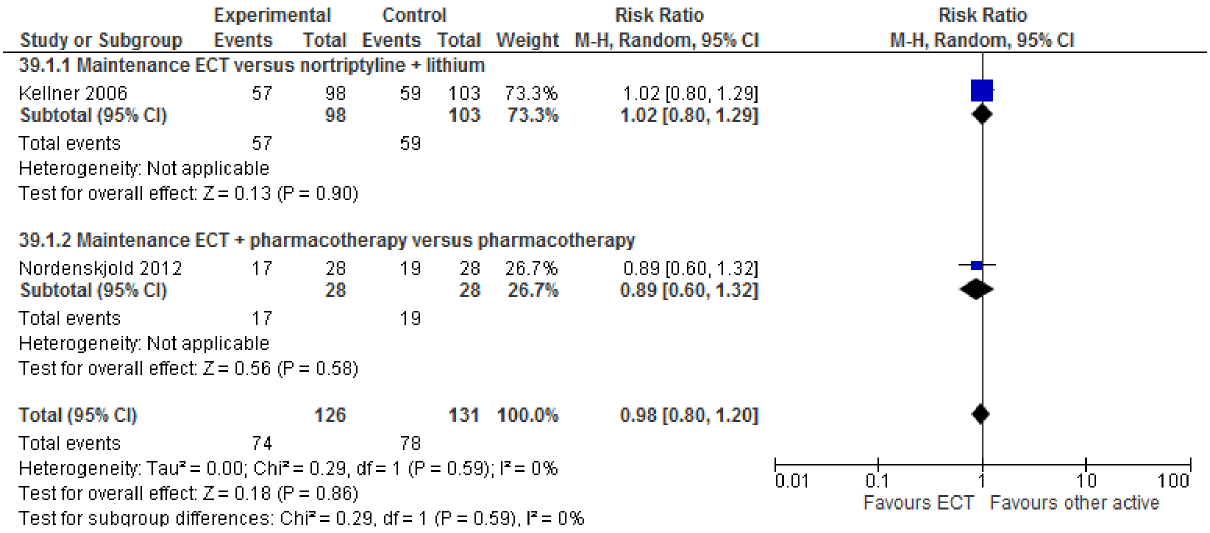
Relapse at endpoint



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
37.1.1 Maintenance combined fluoxetine + olanzapine versus maintenance fluoxetine + tapered olanzapine						
Brunner 2014	82	221	106	223	47.5%	0.78 [0.63, 0.97]
Subtotal (95% CI)		**221**		**223**	**47.5%**	**0.78 [0.63, 0.97]**
Total events	82		106			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.21 (P = 0.03)						
37.1.2 Maintenance combined citalopram + risperidone versus maintenance citalopram + tapered risperidone						
Rapaport 2006	80	123	77	120	52.5%	1.01 [0.84, 1.22]
Subtotal (95% CI)		**123**		**120**	**52.5%**	**1.01 [0.84, 1.22]**
Total events	80		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**344**		**343**	**100.0%**	**0.90 [0.69, 1.17]**
Total events	162		183			
Heterogeneity: Tau² = 0.03; Chi² = 3.36, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Chi² = 3.15, df = 1 (P = 0.08), I² = 68.3%						

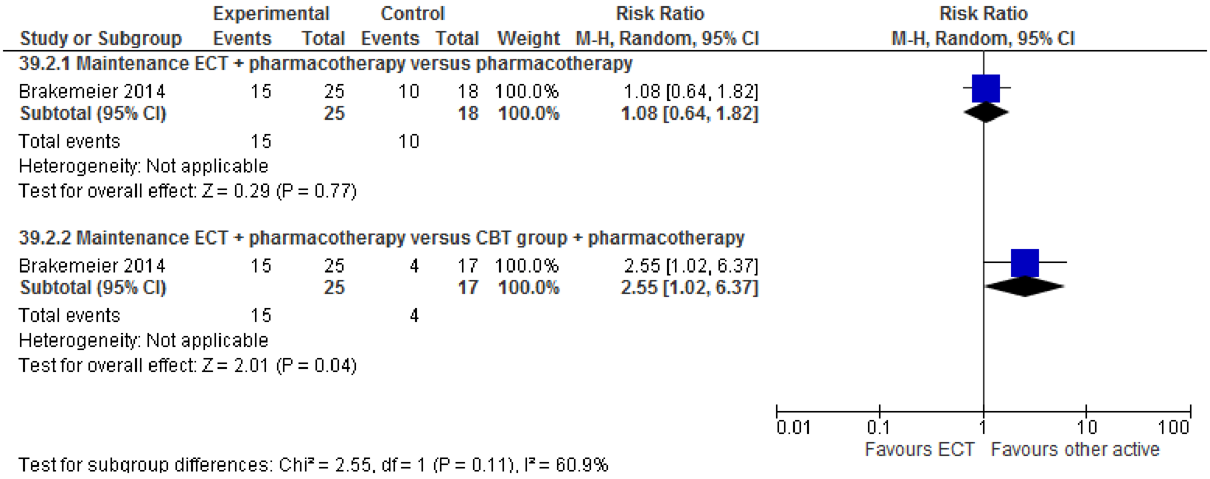
ECT versus active intervention

Relapse at endpoint



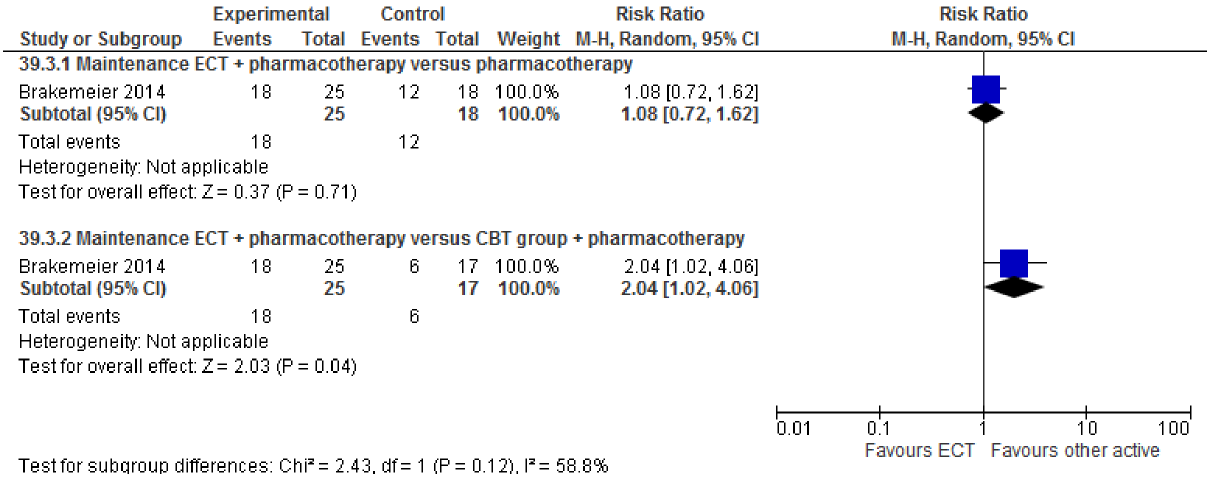
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
39.1.1 Maintenance ECT versus nortriptyline + lithium						
Kellner 2006	57	98	59	103	73.3%	1.02 [0.80, 1.29]
Subtotal (95% CI)		**98**		**103**	**73.3%**	**1.02 [0.80, 1.29]**
Total events	57		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
39.1.2 Maintenance ECT + pharmacotherapy versus pharmacotherapy						
Nordenskjold 2012	17	28	19	28	26.7%	0.89 [0.60, 1.32]
Subtotal (95% CI)		**28**		**28**	**26.7%**	**0.89 [0.60, 1.32]**
Total events	17		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
Total (95% CI)		**126**		**131**	**100.0%**	**0.98 [0.80, 1.20]**
Total events	74		78			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						

Relapse at 3-month follow-up



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
39.2.1 Maintenance ECT + pharmacotherapy versus pharmacotherapy						
Brakemeier 2014	15	25	10	18	100.0%	1.08 [0.64, 1.82]
Subtotal (95% CI)		**25**		**18**	**100.0%**	**1.08 [0.64, 1.82]**
Total events	15		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
39.2.2 Maintenance ECT + pharmacotherapy versus CBT group + pharmacotherapy						
Brakemeier 2014	15	25	4	17	100.0%	2.55 [1.02, 6.37]
Subtotal (95% CI)		**25**		**17**	**100.0%**	**2.55 [1.02, 6.37]**
Total events	15		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
Test for subgroup differences: Chi² = 2.55, df = 1 (P = 0.11), I² = 60.9%						

Relapse at 9-month follow-up

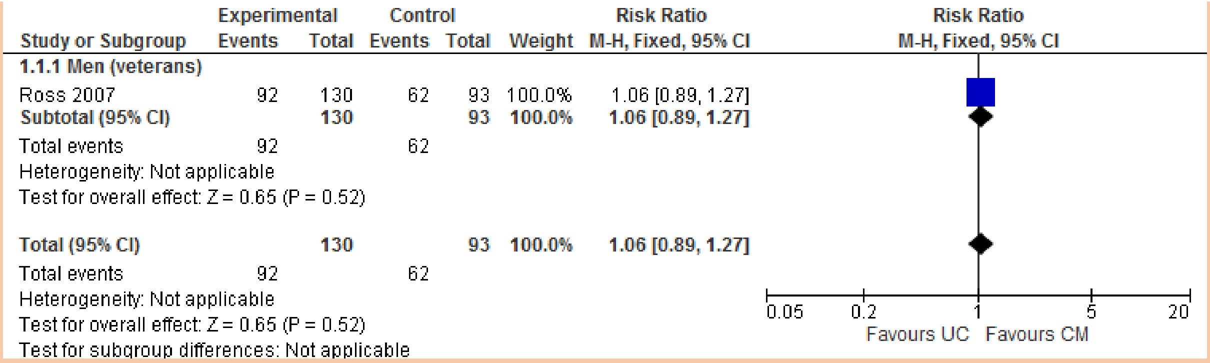


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
39.3.1 Maintenance ECT + pharmacotherapy versus pharmacotherapy						
Brakemeier 2014	18	25	12	18	100.0%	1.08 [0.72, 1.62]
Subtotal (95% CI)		**25**		**18**	**100.0%**	**1.08 [0.72, 1.62]**
Total events	18		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
39.3.2 Maintenance ECT + pharmacotherapy versus CBT group + pharmacotherapy						
Brakemeier 2014	18	25	6	17	100.0%	2.04 [1.02, 4.06]
Subtotal (95% CI)		**25**		**17**	**100.0%**	**2.04 [1.02, 4.06]**
Total events	18		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.03 (P = 0.04)						
Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.8%						

Access to services (chapter 12)

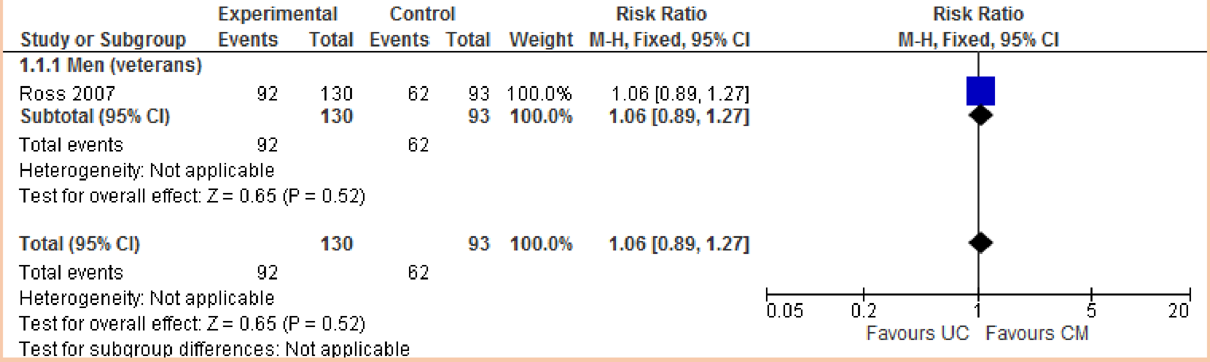
Close monitoring versus usual care (men [veterans])

Number attending primary care visits during study period (case review)



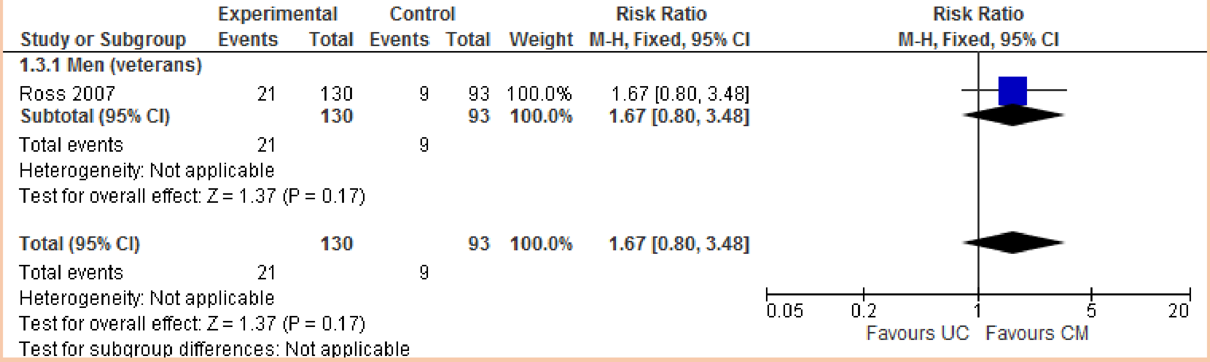
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Men (veterans)						
Ross 2007	92	130	62	93	100.0%	1.06 [0.89, 1.27]
Subtotal (95% CI)		**130**		**93**	**100.0%**	**1.06 [0.89, 1.27]**
Total events	92		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**130**		**93**	**100.0%**	**1.06 [0.89, 1.27]**
Total events	92		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Not applicable						

Number who had any MH care [including behavioural health specialist] during the study period (case review)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Men (veterans)						
Ross 2007	92	130	62	93	100.0%	1.06 [0.89, 1.27]
Subtotal (95% CI)		**130**		**93**	**100.0%**	**1.06 [0.89, 1.27]**
Total events	92		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**130**		**93**	**100.0%**	**1.06 [0.89, 1.27]**
Total events	92		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Not applicable						

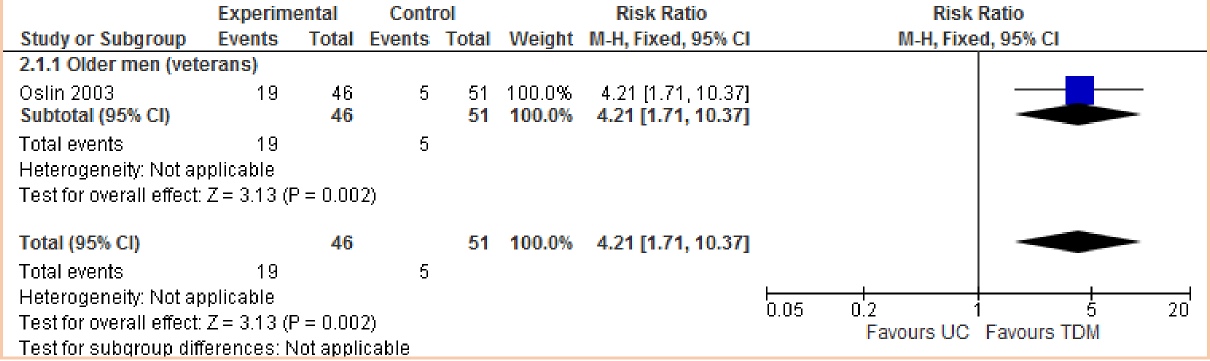
Number who started an antidepressant during the study period (case review)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Men (veterans)						
Ross 2007	21	130	9	93	100.0%	1.67 [0.80, 3.48]
Subtotal (95% CI)		**130**		**93**	**100.0%**	**1.67 [0.80, 3.48]**
Total events	21		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		**130**		**93**	**100.0%**	**1.67 [0.80, 3.48]**
Total events	21		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: Not applicable						

Telephone disease management versus usual care (older men [veterans])

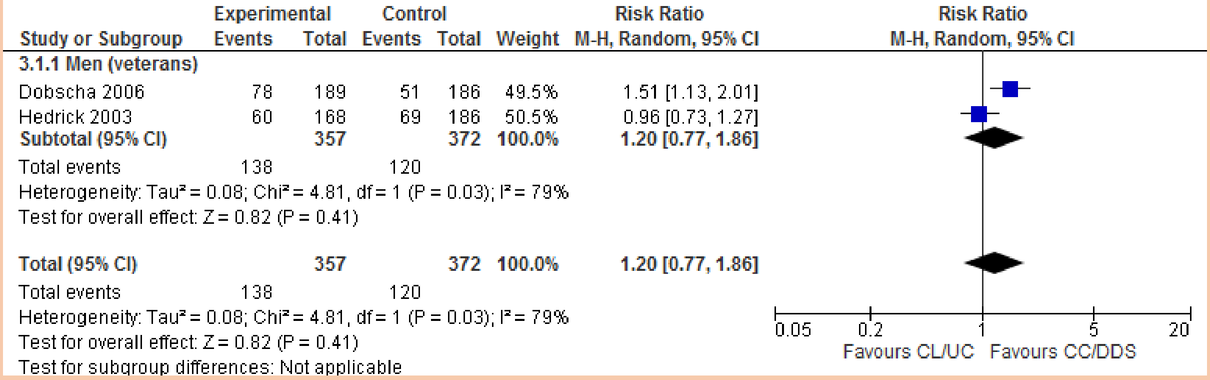
Number completing at least one mental health/substance abuse appointment (assessed by self-report)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Older men (veterans)						
Oslin 2003	19	46	5	51	100.0%	4.21 [1.71, 10.37]
Subtotal (95% CI)		**46**		**51**	**100.0%**	**4.21 [1.71, 10.37]**
Total events	19		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.13 (P = 0.002)						
Total (95% CI)		**46**		**51**	**100.0%**	**4.21 [1.71, 10.37]**
Total events	19		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.13 (P = 0.002)						
Test for subgroup differences: Not applicable						

Simple collaborative care versus usual care (men [veterans] and older adults)

Number who attended ≥1 appointment with mental health specialist

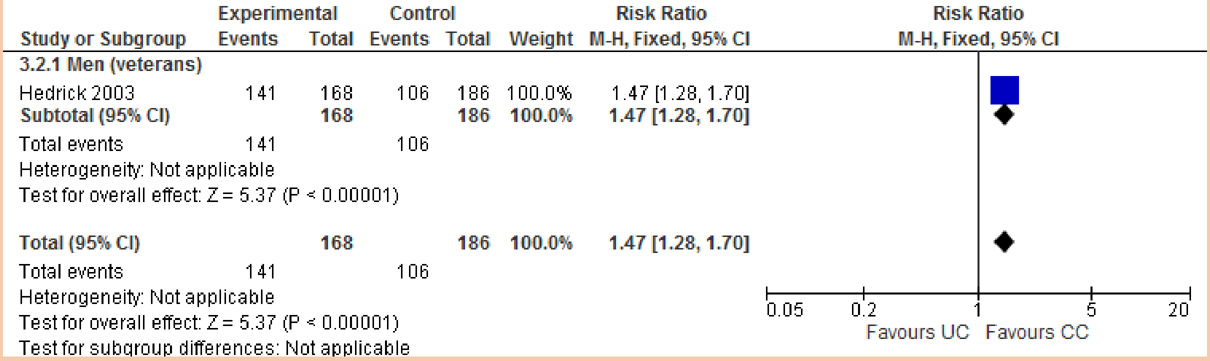


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Men (veterans)						
Dobscha 2006	78	189	51	186	49.5%	1.51 [1.13, 2.01]
Hedrick 2003	60	168	69	186	50.5%	0.96 [0.73, 1.27]
Subtotal (95% CI)		**357**		**372**	**100.0%**	**1.20 [0.77, 1.86]**
Total events	138		120			
Total (95% CI)		**357**		**372**	**100.0%**	**1.20 [0.77, 1.86]**
Total events	138		120			

Heterogeneity: Tau² = 0.08; Chi² = 4.81, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.82 (P = 0.41)

Heterogeneity: Tau² = 0.08; Chi² = 4.81, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable

Number who have had a depression-related primary care visit

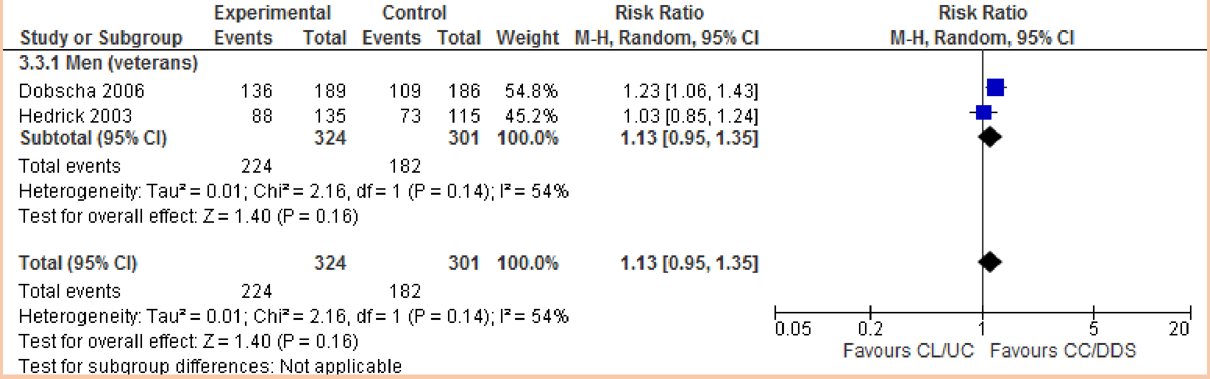


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Men (veterans)						
Hedrick 2003	141	168	106	186	100.0%	1.47 [1.28, 1.70]
Subtotal (95% CI)		**168**		**186**	**100.0%**	**1.47 [1.28, 1.70]**
Total events	141		106			
Total (95% CI)		**168**		**186**	**100.0%**	**1.47 [1.28, 1.70]**
Total events	141		106			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.37 (P < 0.00001)

Heterogeneity: Not applicable
Test for overall effect: Z = 5.37 (P < 0.00001)
Test for subgroup differences: Not applicable

Received ≥ 90 days of therapy with a minimally therapeutic dosage of antidepressant

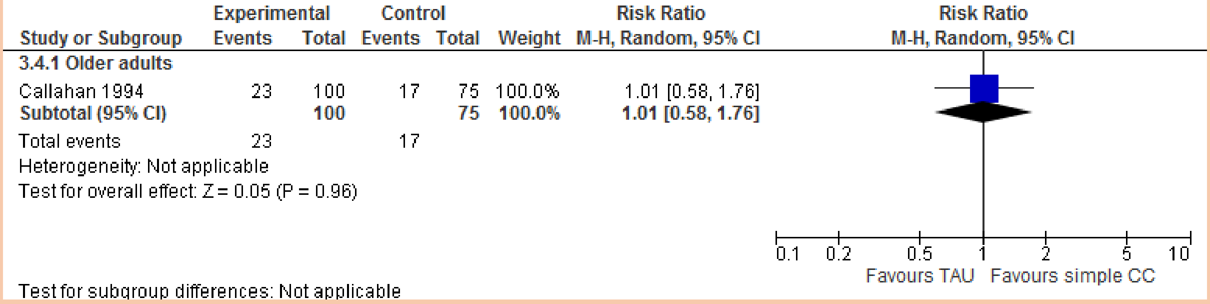


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Men (veterans)						
Dobscha 2006	136	189	109	186	54.8%	1.23 [1.06, 1.43]
Hedrick 2003	88	135	73	115	45.2%	1.03 [0.85, 1.24]
Subtotal (95% CI)		**324**		**301**	**100.0%**	**1.13 [0.95, 1.35]**
Total events	224		182			
Total (95% CI)		**324**		**301**	**100.0%**	**1.13 [0.95, 1.35]**
Total events	224		182			

Heterogeneity: Tau² = 0.01; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.40 (P = 0.16)

Heterogeneity: Tau² = 0.01; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable

Number of patients whose unhelpful medications (those potentially exacerbating depression) were terminated

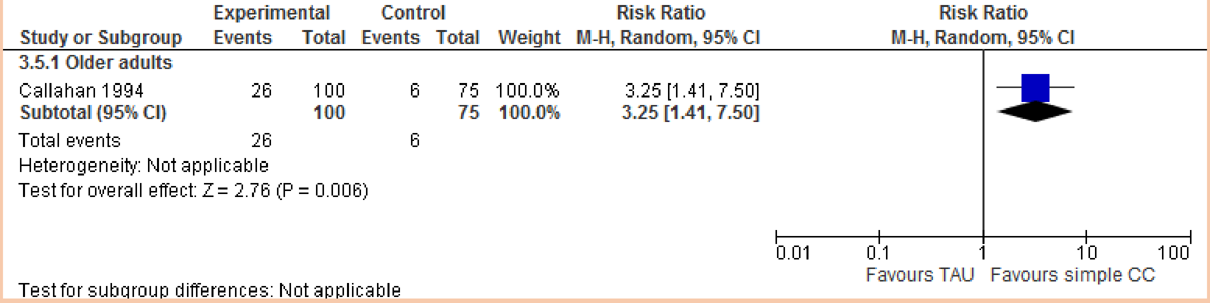


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Older adults						
Callahan 1994	23	100	17	75	100.0%	1.01 [0.58, 1.76]
Subtotal (95% CI)		**100**		**75**	**100.0%**	**1.01 [0.58, 1.76]**
Total events	23		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

Number of people starting an antidepressant

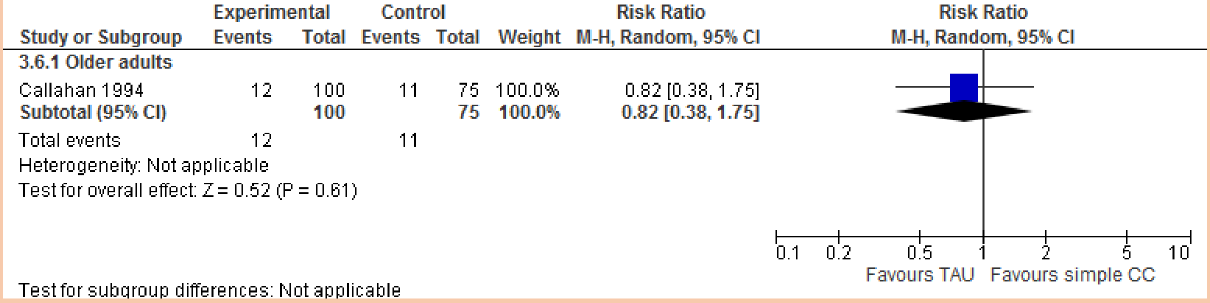


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Older adults						
Callahan 1994	26	100	6	75	100.0%	3.25 [1.41, 7.50]
Subtotal (95% CI)		**100**		**75**	**100.0%**	**3.25 [1.41, 7.50]**
Total events	26		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.76 (P = 0.006)

Test for subgroup differences: Not applicable

Number of patients for whom a psychiatric consultation was sought



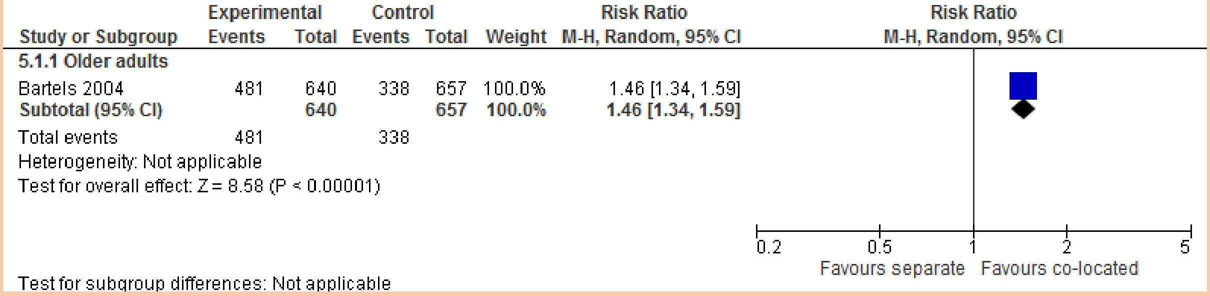
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Older adults						
Callahan 1994	12	100	11	75	100.0%	0.82 [0.38, 1.75]
Subtotal (95% CI)		**100**		**75**	**100.0%**	**0.82 [0.38, 1.75]**
Total events	12		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.61)

Test for subgroup differences: Not applicable

Co-located services versus geographically separate services (older adults)

Mean number of patients who engaged with treatment

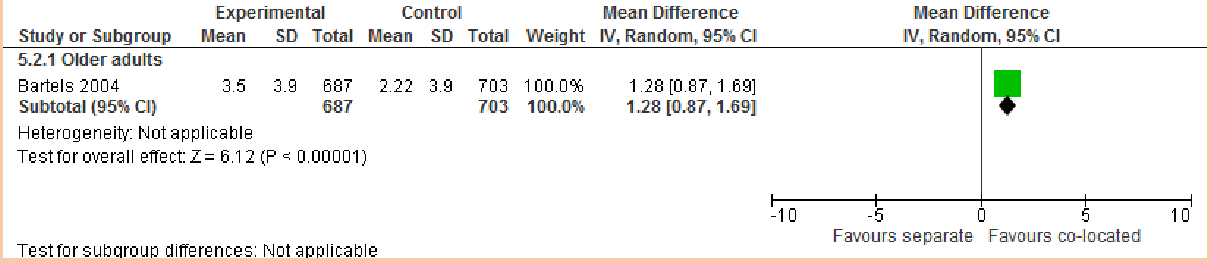


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Older adults						
Bartels 2004	481	640	338	657	100.0%	1.46 [1.34, 1.59]
Subtotal (95% CI)		**640**		**657**	**100.0%**	**1.46 [1.34, 1.59]**
Total events	481		338			

Heterogeneity: Not applicable
Test for overall effect: Z = 8.58 (P < 0.00001)

Test for subgroup differences: Not applicable

Number of treatment visits

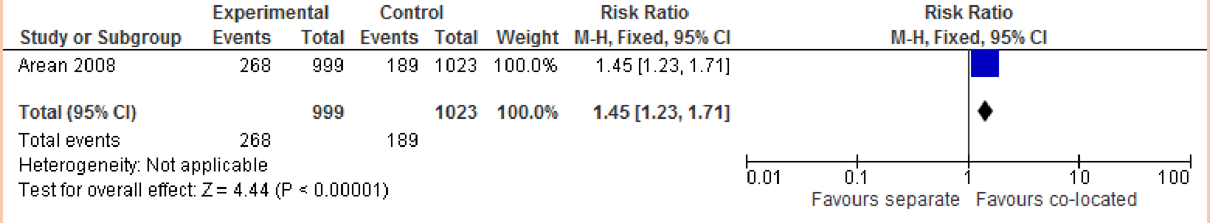


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.2.1 Older adults								
Bartels 2004	3.5	3.9	687	2.22	3.9	703	100.0%	1.28 [0.87, 1.69]
Subtotal (95% CI)			**687**			**703**	**100.0%**	**1.28 [0.87, 1.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.12 (P < 0.00001)

Test for subgroup differences: Not applicable

Proportion of patients who had at least one mental health visit

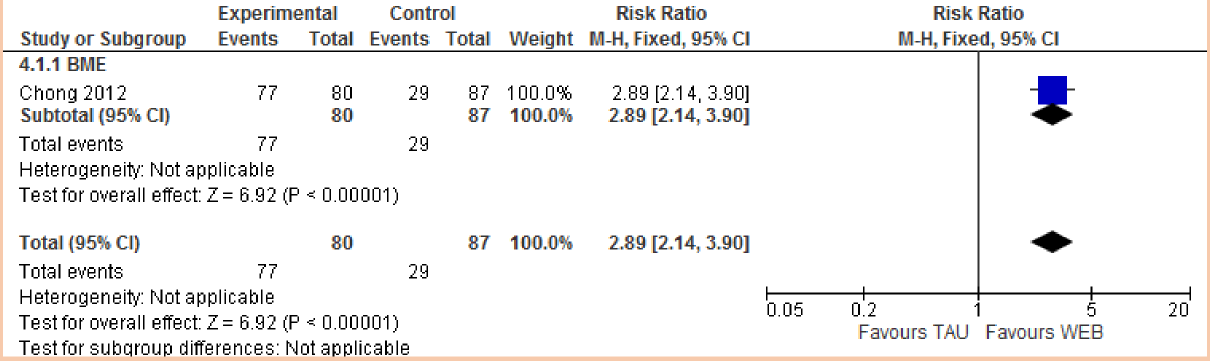


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arean 2008	268	999	189	1023	100.0%	1.45 [1.23, 1.71]
Total (95% CI)		**999**		**1023**	**100.0%**	**1.45 [1.23, 1.71]**
Total events	268		189			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.44 (P < 0.00001)

Clinic-based tele-psychiatry (using a webcam) versus TAU (BAME)

Number of subjects who made a mental health appointment



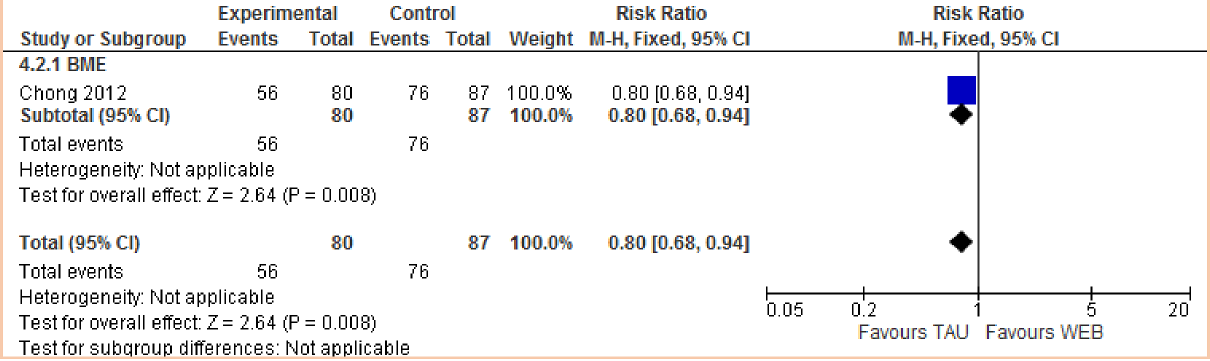
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 BME						
Chong 2012	77	80	29	87	100.0%	2.89 [2.14, 3.90]
Subtotal (95% CI)		**80**		**87**	**100.0%**	**2.89 [2.14, 3.90]**
Total events	77		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.92 (P < 0.00001)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**80**		**87**	**100.0%**	**2.89 [2.14, 3.90]**
Total events	77		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.92 (P < 0.00001)
Test for subgroup differences: Not applicable

Number of subjects who made a primary care appointment



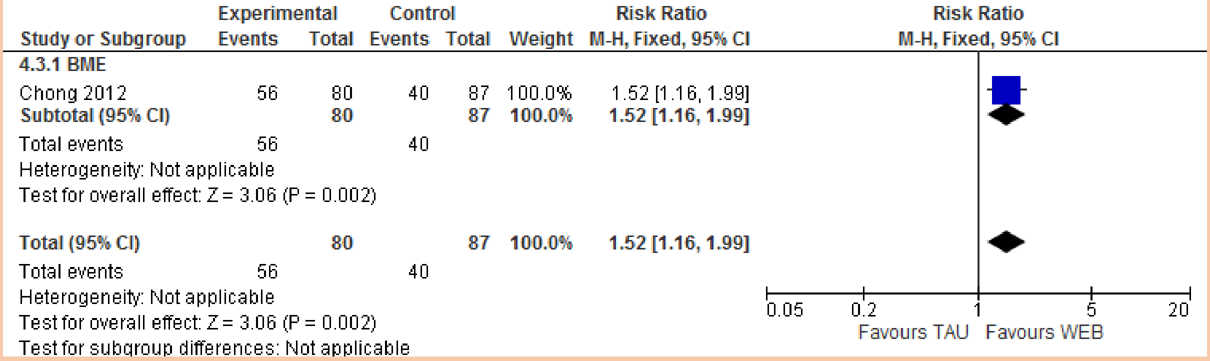
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 BME						
Chong 2012	56	80	76	87	100.0%	0.80 [0.68, 0.94]
Subtotal (95% CI)		**80**		**87**	**100.0%**	**0.80 [0.68, 0.94]**
Total events	56		76			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		**80**		**87**	**100.0%**	**0.80 [0.68, 0.94]**
Total events	56		76			

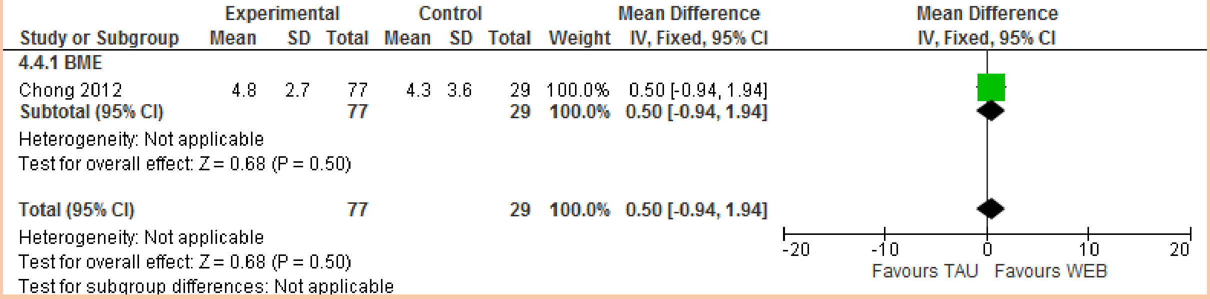
Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable

Number used antidepressants



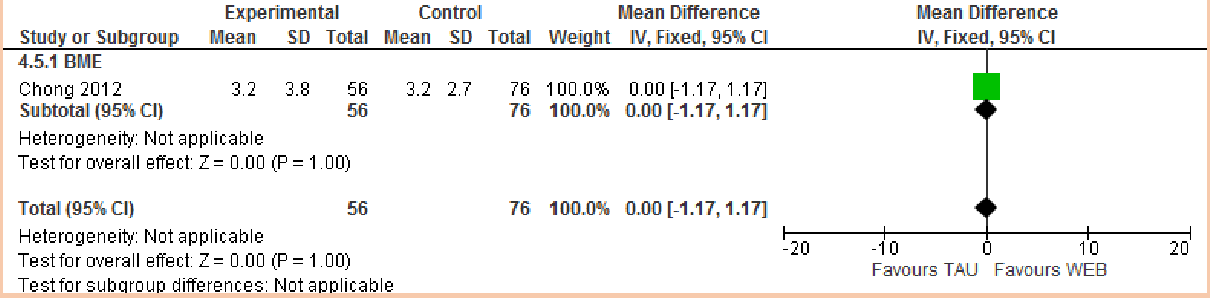
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 BME						
Chong 2012	56	80	40	87	100.0%	1.52 [1.16, 1.99]
Subtotal (95% CI)		**80**		**87**	**100.0%**	**1.52 [1.16, 1.99]**
Total events	56		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.06 (P = 0.002)						
Total (95% CI)		**80**		**87**	**100.0%**	**1.52 [1.16, 1.99]**
Total events	56		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.06 (P = 0.002)						
Test for subgroup differences: Not applicable						

Mean number of completed mental health appointments



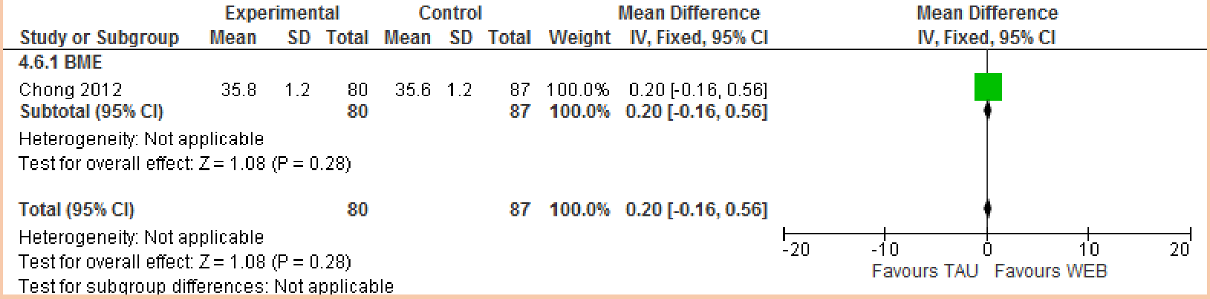
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 BME								
Chong 2012	4.8	2.7	77	4.3	3.6	29	100.0%	0.50 [-0.94, 1.94]
Subtotal (95% CI)			**77**			**29**	**100.0%**	**0.50 [-0.94, 1.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Total (95% CI)			**77**			**29**	**100.0%**	**0.50 [-0.94, 1.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
Test for subgroup differences: Not applicable								

Mean number of completed primary care appointments



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
4.5.1 BME								
Chong 2012	3.2	3.8	56	3.2	2.7	76	100.0%	0.00 [-1.17, 1.17]
Subtotal (95% CI)			**56**			**76**	**100.0%**	**0.00 [-1.17, 1.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**56**			**76**	**100.0%**	**0.00 [-1.17, 1.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								

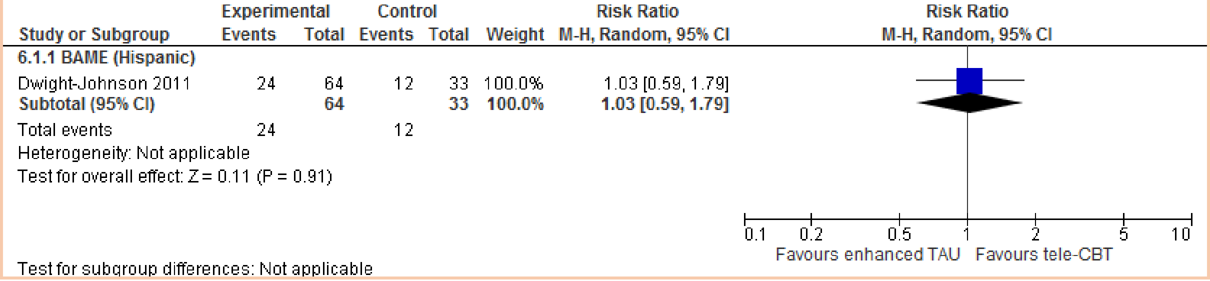
Satisfaction (visit specific satisfaction questionnaire [VSQ-9] range 0-36, higher better)



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
4.6.1 BME								
Chong 2012	35.8	1.2	80	35.6	1.2	87	100.0%	0.20 [-0.16, 0.56]
Subtotal (95% CI)			**80**			**87**	**100.0%**	**0.20 [-0.16, 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Total (95% CI)			**80**			**87**	**100.0%**	**0.20 [-0.16, 0.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Not applicable								

Telephone CBT versus enhanced usual care (BAME)

Number reporting they were satisfied with the treatment provided

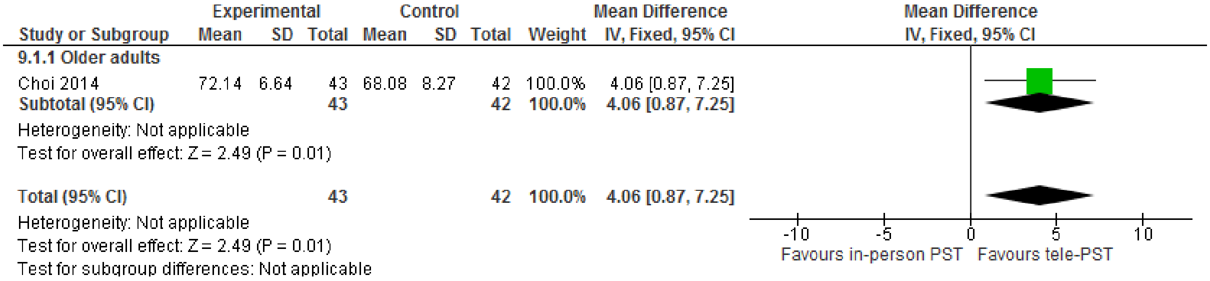


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 BAME (Hispanic)						
Dwight-Johnson 2011	24	64	12	33	100.0%	1.03 [0.59, 1.79]
Subtotal (95% CI)		**64**		**33**	**100.0%**	**1.03 [0.59, 1.79]**
Total events	24		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable

Tele-problem solving therapy versus in-person problem solving therapy



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
9.1.1 Older adults								
Choi 2014	72.14	6.64	43	68.08	8.27	42	100.0%	4.06 [0.87, 7.25]
Subtotal (95% CI)			**43**			**42**	**100.0%**	**4.06 [0.87, 7.25]**

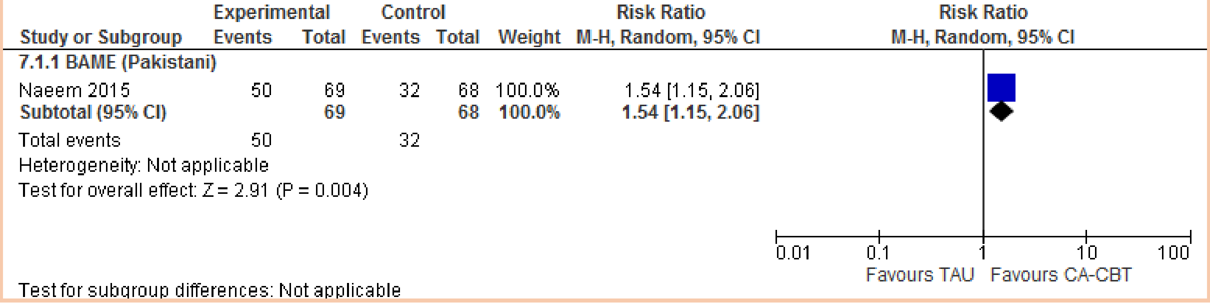
Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)

Total (95% CI)			**43**			**42**	**100.0%**	**4.06 [0.87, 7.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable

Culturally-adapted CBT versus TAU (BAME)

Number of participants stating they were ‘very satisfied’ with the treatment



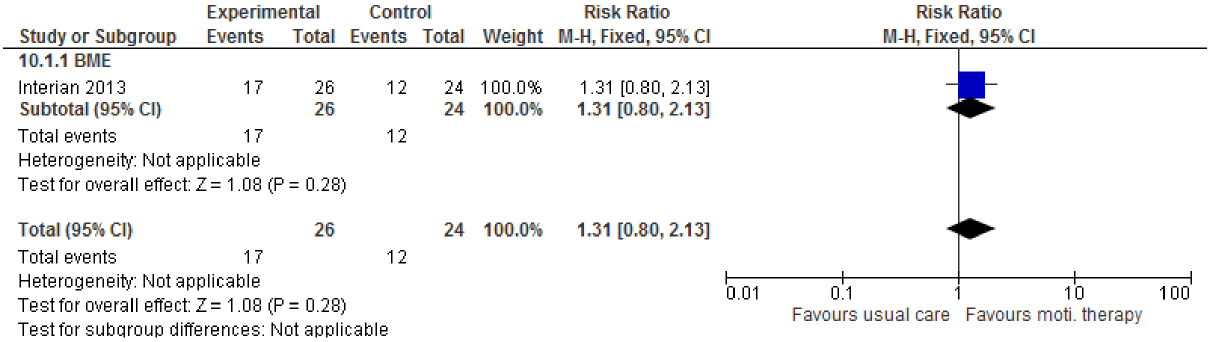
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 BAME (Pakistani)						
Naeem 2015	50	69	32	68	100.0%	1.54 [1.15, 2.06]
Subtotal (95% CI)		**69**		**68**	**100.0%**	**1.54 [1.15, 2.06]**
Total events	50		32			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.91 (P = 0.004)

Test for subgroup differences: Not applicable

Culturally adapted motivational therapy versus usual care (BAME)

Number of patients who attended at least one psychotherapy session



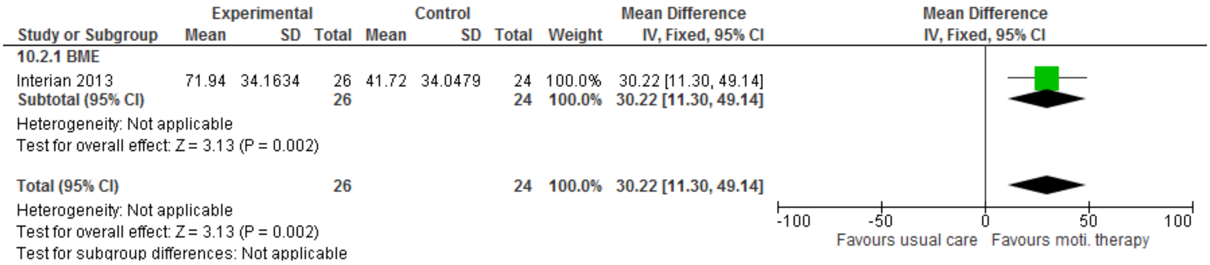
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 BME						
Interian 2013	17	26	12	24	100.0%	1.31 [0.80, 2.13]
Subtotal (95% CI)		**26**		**24**	**100.0%**	**1.31 [0.80, 2.13]**
Total events	17		12			

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

Total (95% CI)		**26**		**24**	**100.0%**	**1.31 [0.80, 2.13]**
Total events	17		12			

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

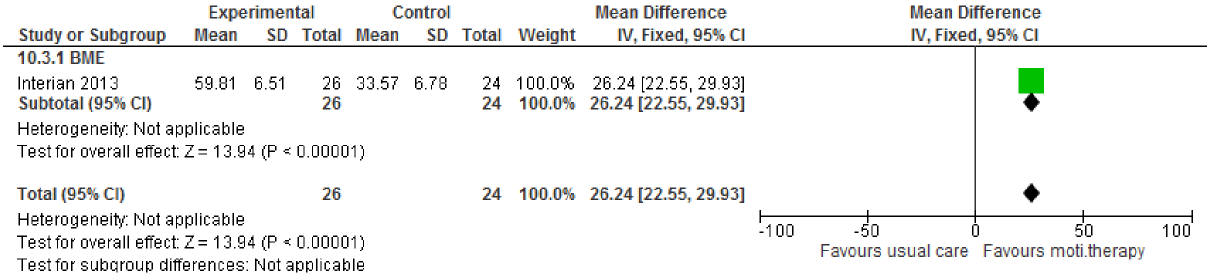
[Time 2] adherence score as measured by the Medication Event Monitoring System (MEMS)



	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
10.2.1 BME								
Interian 2013	71.94	34.1634	26	41.72	34.0479	24	100.0%	30.22 [11.30, 49.14]
Subtotal (95% CI)			**26**			**24**	**100.0%**	**30.22 [11.30, 49.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.13 (P = 0.002)								
Total (95% CI)			**26**			**24**	**100.0%**	**30.22 [11.30, 49.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.13 (P = 0.002)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-100
-50
0
50
100
Favours usual care
Favours moti. therapy

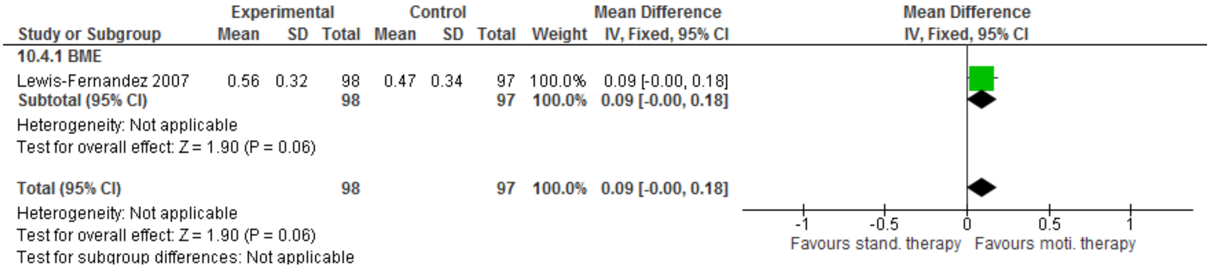
[Time 3] adherence score as measured by the Medication Event Monitoring System (MEMS)



	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
10.3.1 BME								
Interian 2013	59.81	6.51	26	33.57	6.78	24	100.0%	26.24 [22.55, 29.93]
Subtotal (95% CI)			**26**			**24**	**100.0%**	**26.24 [22.55, 29.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 13.94 (P < 0.00001)								
Total (95% CI)			**26**			**24**	**100.0%**	**26.24 [22.55, 29.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 13.94 (P < 0.00001)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-100
-50
0
50
100
Favours usual care
Favours moti.therapy

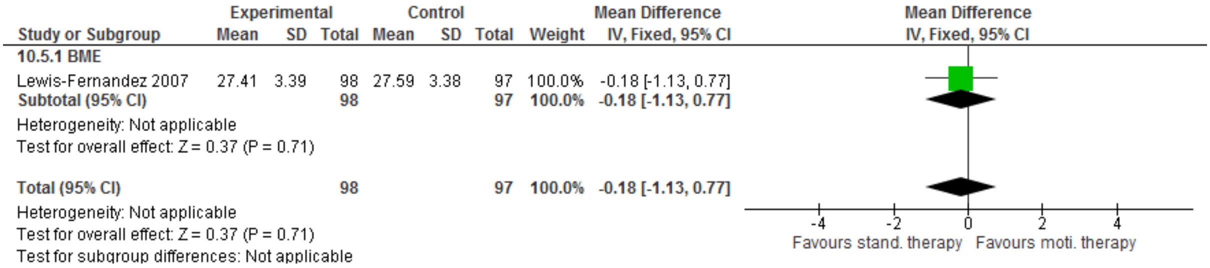
Proportion of fully attended days as measured by the Composite Adherence Score (CAS)



	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
10.4.1 BME								
Lewis-Fernandez 2007	0.56	0.32	98	0.47	0.34	97	100.0%	0.09 [-0.00, 0.18]
Subtotal (95% CI)			**98**			**97**	**100.0%**	**0.09 [-0.00, 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
Total (95% CI)			**98**			**97**	**100.0%**	**0.09 [-0.00, 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-1
-0.5
0
0.5
1
Favours stand. therapy
Favours moti. therapy

Patient satisfaction as assessed by the Client Satisfaction Questionnaire (CSQ)



	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
10.5.1 BME								
Lewis-Fernandez 2007	27.41	3.39	98	27.59	3.38	97	100.0%	-0.18 [-1.13, 0.77]
Subtotal (95% CI)			**98**			**97**	**100.0%**	**-0.18 [-1.13, 0.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Total (95% CI)			**98**			**97**	**100.0%**	**-0.18 [-1.13, 0.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
Test for subgroup differences: Not applicable								

Mean Difference
IV, Fixed, 95% CI
-4
-2
0
2
4
Favours stand. therapy
Favours moti. therapy