Forest plots for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an

# inadequate response to at least one previous intervention for the current episode?

# Comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus continuing with antidepressant (+/ waitlist or attention-placebo)

Study or Subgroup	Expe Mean	rimen SD		C Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% CI
1.1.1 CBT individual									
Dozois 2009	6.43	6.95	21	9.33	7.21	21	7.7%	-0.40 [-1.01, 0.21]	+
Dunn 1979	9.5	4.81	10	20.3	6.18	10	4.4%	-1.87 [-2.96, -0.78]	
Nakagawa 2017	8.2	4.7	40	13.2	6.9	40	9.0%	-0.84 [-1.30, -0.38]	
Paykel 1999/Scott 2000	8.7	5.3	80	9.4	5.2	78	10.3%	-0.13 [-0.44, 0.18]	4
Viles 2013/2016 Subtotal (95% Cl)	18.9	14.2	206 <mark>357</mark>	24.5	13.1	213 <mark>362</mark>	11.1% <b>42.5%</b>	-0.41 [-0.60, -0.22] - <b>0.54 [-0.88, -0.20]</b>	•
Heterogeneity: Tau² = 0.0 Fest for overall effect: Z =				(P = 0.0	1);  ² =	70%			
1.1.2 Rumination-focuse	d CBT								
Watkins 2011a Subtotal (95% CI)	5.48	5.15	21 <b>21</b>	9.05	5.25	21 <b>21</b>	7.6% <b>7.6%</b>	-0.67 [-1.30, -0.05] - <b>0.67 [-1.30, -0.05]</b>	•
Heterogeneity: Not applic Fest for overall effect: Z =		0.03)							
1.1.3 Cognitive behaviora	al analysi	s syst	em of j	osycho	therap	y (CBA	SP)		
Kocsis 2009/Klein 2011 Subtotal (95% Cl)	11.29	8.3	174 <b>174</b>	12.28	8.44	76 <b>76</b>	10.6% <b>10.6%</b>	-0.12 [-0.39, 0.15] - <b>0.12 [-0.39, 0.15]</b>	4
Heterogeneity: Not applic Fest for overall effect: Z =		0.39)							
1.1.4 Dialectical behavio			-						
_ynch 2007_study 2 Subtotal (95% Cl)	7.88	4.35	21 <b>21</b>	11.26	9.22	10 <b>10</b>	6.4% <mark>6.4%</mark>	-0.52 [-1.29, 0.24] -0.52 [-1.29, 0.24]	•
Heterogeneity: Not applic Fest for overall effect: Z =		0.18)							
1.1.5 Blended CCBT & inc	dividual C	BT							
Nakao 2018 Subtotal (95% CI)	9.4	5.1	20 <b>20</b>	15.5	6.3	20 <b>20</b>	7.2% <b>7.2%</b>	-1.04 [-1.71, -0.38] - <b>1.04 [-1.71, -0.38]</b>	•
Heterogeneity: Not applic Fest for overall effect: Z =		0.002	)						
1.1.6 CBT group									
Chan 2012	6.82	5.73	17	10	4.41	16	6.9%	-0.60 [-1.30, 0.10]	
Embling 2002 Subtotal (95% CI)	15.17	5.15	19 <b>36</b>	32.17	8.01	19 <b>35</b>	5.7% <b>12.6%</b>	-2.47 [-3.34, -1.61] -1.52 [-3.35, 0.31]	-
Heterogeneity: Tau² = 1.5 Fest for overall effect: Z =			df = 1 (	(P = 0.0	01); I²:	= 91%			
1.1.7 Mindfulness-based	cognitive	e thera	apy (Mi	BCT) gr	oup				
Chiesa 2015 <b>Subtotal (95% CI)</b>	9.82	7.35	23 <b>23</b>	13.8	7.32	20 <b>20</b>	7.7% <b>7.7%</b>	-0.53 [-1.14, 0.08] - <b>0.53 [-1.14, 0.08]</b>	
Heterogeneity: Not applic Fest for overall effect: Z =		0.09)							
1.1.8 Person-based cogr	nitive ther	apy (F	BCT)	ILOND					
Strauss 2012 Subtotal (95% CI)	27.93				8.58	14 <b>14</b>	5.4% <b>5.4%</b>	-1.83 [-2.73, -0.92] - <b>1.83 [-2.73, -0.92]</b>	<b>→</b>
Heterogeneity: Not applic Fest for overall effect: Z =		0.000							-
Fotal (95% CI)			666			558	100.0%	-0.74 [-1.03, -0.45]	•
Heterogeneity: Tau² = 0.1 Fest for overall effect: Z = Fest for subgroup differer	5.06 (P <	0.000	df = 12 01)			); <b> ²</b> = 71	7%		-10 -5 0 5 Favours CBT + AD Favours AD

# Figure 2: Depression symptomatology endpoint

# Figure 3: Depression symptomatology change score

Chudu an Cubanaur	-	rimen			ontrol	Tetal		Std. Mean Difference	Std. Mean Difference
Study or Subgroup 1.2.1 CBT individual	Mean	50	Total	Mean	50	lotal	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
	10.05	100	24	0.70	4.00	- 24	10.00	0.071454 0.042	-
Dozois 2009	-13.95		21	-9.72		21	10.6%	-0.87 [-1.51, -0.24]	
Dunn 1979	-13.4		10	-1.8	4.5	10	7.1%	-2.60 [-3.85, -1.34]	
Nakagawa 2017	-12.7		40	-7.6	4.9	40	11.4%	-1.23 [-1.71, -0.75]	*
Paykel 1999/Scott 2000 Subtotal (95% CI)	-3.4	3.73	80 151	-2.8	3.58	78 <b>149</b>	12.1% <b>41.2%</b>	-0.16 [-0.48, 0.15] - <b>1.06 [-1.86, -0.27]</b>	◆
Heterogeneity: Tau² = 0.5 Fest for overall effect: Z =	•			P < 0.00	001); P	'= 88%			
1.2.2 Rumination-focuse	d CBT								
Watkins 2011a <b>Subtotal (95% CI)</b>	-7.81	3.45	21 <b>21</b>	-3.14	3.65	21 <b>21</b>	10.4% <b>10.4%</b>	-1.29 [-1.96, -0.62] - <b>1.29 [-1.96, -0.62]</b>	<b>→</b>
Heterogeneity: Not applic Test for overall effect: Z =		0.000	2)						
1.2.3 Blended CCBT & in	dividual C	BT							
Nakao 2018 Subtotal (95% CI)	-8.9	3.38	20 <b>20</b>	-3	4.32	20 <b>20</b>	10.1% <b>10.1%</b>	-1.49 [-2.20, -0.78] - <b>1.49 [-2.20, -0.78]</b>	$\bullet$
Heterogeneity: Not applic Fest for overall effect: Z =		0.000	1)						
1.2.4 CBT group									
Chan 2012	-5.42	3.81	17	-1.56	3.67	16	10.0%	-1.01 [-1.74, -0.28]	
Embling 2002	-16.5		19	1.84		19	9.0%	-2.68 [-3.58, -1.78]	
Subtotal (95% CI)			36			35	19.1%	-1.82 [-3.46, -0.18]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 1.2 Fest for overall effect: Z =			f=1 (F	= 0.00\$	5); <b>I²</b> =	88%			
1.2.5 Mindfulness-based	cognitive	e thera	apy (ME	BCT) gro	oup				
Chiesa 2015	-6.41	4.59	23	-1.35	4.49	20	10.5%	-1.09 [-1.74, -0.45]	
Subtotal (95% CI)			23			20	10.5%	-1.09 [-1.74, -0.45]	◆
Heterogeneity: Not applic Fest for overall effect: Z =		0.000	9)						
1.2.6 Person-based cog	nitive the	apy (F	BCT) (	roup					
Strauss 2012	-9.81	5.4	14	2.71	6.11	14	8.8%	-2.11 [-3.06, -1.16]	
Subtotal (95% CI)			14			14	8.8%	-2.11 [-3.06, -1.16]	◆
Heterogeneity: Not applic Fest for overall effect: Z =		0.000	1)						
Fotal (95% CI)			265			259	100.0%	-1.36 [-1.87, -0.86]	•
Heterogeneity: Tau <sup>2</sup> = 0.5	2: Chi <b>²</b> = 4	55.66		P < 0.00	1001)			,	
Test for overall effect: Z =				, 0.00		04.	~		-10 -5 0 5
Fest for subgroup differen				5 (P = 0	54) P	= 0%			Favours CBT + AD Favours AD
rearior subgroup differen	nces. Off	- 4.0	5, ui – t	$y_{10} = 0.$	547.1	- 0 %			

# Figure 4: Depression symptomatology at 2-3 month follow-up

	Experimental Control							Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD		Mean	SD		Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.7.1 CBT individual									
Nakagawa 2017 Subtotal (95% CI)	7.8	5.2	40 <b>40</b>	11.3	7.2	40 <b>40</b>	64.8% <mark>64.8%</mark>	-0.55 [-1.00, -0.10] - <b>0.55 [-1.00, -0.10]</b>	•
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=2.42	(P = 0	1.02)						
1.7.2 Mindfulness-ba	sed cogr	nitive	therap	y (MBC1	r) grou	р			
Chiesa 2015 Subtotal (95% CI)	9.32	8.45	23 23	12.8	7.73	20 <b>20</b>	35.2% <b>35.2%</b>	-0.42 [-1.03, 0.19] - <b>0.42 [-1.03, 0.19]</b>	- <b>-</b>
Heterogeneity: Not ap Test for overall effect:	•	(P = 0	.17)						
Total (95% CI)			63			60	100.0%	-0.51 [-0.87, -0.15]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff AD: antidepressa	Z = 2.75 erences:	(P = 0	1.006)					-10 -5 0 5 10 Favours CBT + AD Favours AD	

# Figure 5: Depression symptomatology at 4-6 month follow-up

	Experimental Control Std							Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.10.1 CBT individual									
Dunn 1979	11	4.71	10	20.6	6.02	10	5.4%	-1.70 [-2.76, -0.65]	
Nakagawa 2017	6.1	4.5	40	9.3	6.9	40	19.4%	-0.54 [-0.99, -0.10]	-
Paykel 1999/Scott 2000	7.6	4.7	80	9.2	5.2	78	27.1%	-0.32 [-0.64, -0.01]	-
Wiles 2013/2016	17	14	197	21.7	12.9	198	35.3%	-0.35 [-0.55, -0.15]	
Subtotal (95% CI)			327			326	87.3%	-0.47 [-0.76, -0.18]	◆
Heterogeneity: Tau <sup>2</sup> = 0.0-	4; Chi <sup>2</sup> =	6.73,	df = 3 (l	P = 0.08	3); <b>i</b> ² = 9	55%			
Test for overall effect: Z =	3.23 (P =	= 0.001	1)						
1.10.2 Mindfulness-base	d cognit	ive the	erapy (I	MBCT) (	group				
Chiesa 2015	8.04	6.18	23	13.25	6.98	20	12.7%	-0.78 [-1.40, -0.16]	
Subtotal (95% CI)			23			20	12.7%	-0.78 [-1.40, -0.16]	•
Heterogeneity: Not applica	able								
Test for overall effect: Z =	2.45 (P =	= 0.01)							
Total (95% CI)			350			346	100.0%	-0.51 [-0.77, -0.24]	•
Heterogeneity: Tau <sup>2</sup> = 0.0-	4; Chi <sup>2</sup> =	8.10,	df = 4 (l	P = 0.09	3); l² = 9	51%			
Test for overall effect: Z =	3.78 (P =	= 0.000	)2)						-10 -5 0 5 10 Favours CBT + AD Favours AD
Test for subgroup differer	nces: Ch	i² = 0.7	'8, df =	1 (P = 0	).38), P	²= 0%			Favours CBT + AD Favours AD
AD: antidepressant									

### Figure 6: Depression symptomatology at 11-12 month follow-up

	Expe	rimen	tal	Co	ontro	I I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.13.1 CBT individual + a	ny AD								
Nakagawa 2017	5.4	5.9	40	10.1	8.4	40	46.7%	-0.64 [-1.09, -0.19]	-
Paykel 1999/Scott 2000	7.2	5.3	80	7.2	4.7	78	53.3%	0.00 [-0.31, 0.31]	•
Subtotal (95% CI)			120			118	100.0%	-0.30 [-0.93, 0.33]	•
Heterogeneity: Tau <sup>2</sup> = 0.1	7; Chi <sup>z</sup> =	5.27, (	df = 1 (l	P = 0.02	?); <b> </b> ² =	81%			
Test for overall effect: Z =	0.94 (P =	0.35)							
									-10 -5 0 5 10 Favours CBT + AD Favours AD
Test for subgroup differences: Not applicable									Favours CET FAD Favours AD
D <sup>.</sup> antidepressant									

AD: antidepressant

# Figure 7: Depression symptomatology at 40-month follow-up

	Expe	rimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.16.1 CBT individual	l + any AC	)							
Wiles 2013/2016 Subtotal (95% CI)	19.2	13.8	136 <b>136</b>	23.4	13.2	112 <b>112</b>	100.0% <b>100.0%</b>	-0.31 [-0.56, -0.06] - <b>0.31 [-0.56, -0.06]</b>	
Heterogeneity: Not ap	•								
Test for overall effect:	: Z = 2.41	(P = 0	).02)						
T	~								Favours CBT + AD Favours AD

Test for subgroup differences: Not applicable AD: antidepressant

# Figure 8: Remission (ITT)

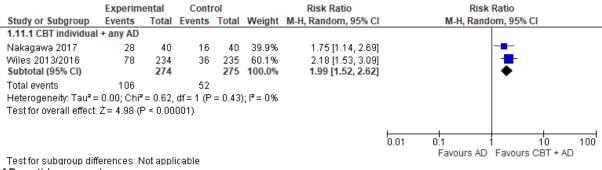
tudy or Subgroup							
A 4 APT 1 1 1 1	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
.3.1 CBT individual							
lakagawa 2017	17	40	8	40	11.3%	2.13 [1.04, 4.35]	
aykel 1999/Scott 2000	19	80	9	78	11.0%	2.06 [0.99, 4.27]	
Viles 2013/2016 S <b>ubtotal (95% CI)</b>	57	234 354	32	235 353	21.6% <b>43.9%</b>	1.79 [1.21, 2.65] 1.90 [1.39, 2.59]	
otal events	93	554	49	333	43.370	1.50 [1.55, 2.55]	•
leterogeneity: Tau² = 0.00 est for overall effect: Z = 4	; Chi <b>ř</b> = 0.2	•		9); I² =	0%		
.3.2 Rumination-focused	CBT						
Vatkins 2011a	13	21	4	21	7.5%	3.25 [1.27, 8.35]	
ubtotal (95% CI)		21		21	7.5%	3.25 [1.27, 8.35]	-
otal events	13		4				
leterogeneity: Not applica est for overall effect: Z = 2		01)					
.3.3 Cognitive behavioral	analysis	system	of psych	othera	py (CBAS	SP)	
ocsis 2009/Klein 2011	67	200	30	96	23.3%	1.07 [0.75, 1.53]	±
ubtotal (95% CI)		200		96	23.3%	1.07 [0.75, 1.53]	◆
otal events	67		30				
leterogeneity: Not applica		70)					
est for overall effect: Z = 0	.38 (P = 0.	70)					
.3.4 Dialectical behaviou		(DBT)					
ynch 2007_study 2	15	21	5	14	10.5%	2.00 [0.94, 4.25]	
ubtotal (95% CI)		21	-	14	10.5%	2.00 [0.94, 4.25]	
otal events Istorogonaitir Not applica	15 No		5				
leterogeneity: Not applica 'est for overall effect: Z = 1		07)					
.3.5 Blended CCBT & indi	vidual CB	г					
lakao 2018	8	20	1	20	2.0%	8.00 [1.10, 58.19]	
ubtotal (95% CI)		20		20	2.0%	8.00 [1.10, 58.19]	
otal events	8		1				
leterogeneity: Not applica							
est for overall effect: Z = 2	.05 (P = 0.	04)					
.3.6 Mindfulness-based o	cognitive t	herapy	(MBCT) g	roup			
isendrath 2016	19	87	12	86	12.6%	1.57 [0.81, 3.02]	
ubtotal (95% CI)		87		86	12.6%	1.57 [0.81, 3.02]	★
otal events	19		12				
leterogeneity: Not applica							
est for overall effect: Z = 1	.33 (P = 0.	18)					
otal (95% CI)		703		590	100.0%	1.76 [1.32, 2.36]	◆
otal events	215		101				
leterogeneity: Tau² = 0.06	; Chi² = 11	.42, df=	7 (P = 0.	12); I²:	= 39%		0.01 0.1 1 10
est for overall effect: Z = 3							Favours AD Favours CBT + AD
est for subgroup differend D: antidepressant	es: Chi <b>=</b> =	11.06,	df = 5 (P :	= 0.05)	, I² = 54.8	%	, creater to ratione obt - Ab

# Figure 9: Remission (ITT) at 3-month follow-up

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.8.1 CBT individual	+ any AD						
Nakagawa 2017 Subtotal (95% CI)	20	40 <b>40</b>	12	40 <b>40</b>	100.0% <b>100.0%</b>	1.67 [0.95, 2.93] <b>1.67 [0.95, 2.93]</b>	
Total events Heterogeneity: Not ap Test for overall effect:	•	9 = 0.08	12 )				
Test for subgroup dif		lot appl	icable				0.01 0.1 1 10 100 Favours AD Favours CBT + AD

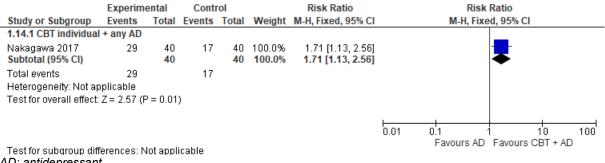
AD: antidepressant

#### Figure 10: Remission (ITT) at 6-month follow-up



AD: antidepressant

#### Figure 11: Remission (ITT) at 12-month follow-up



AD: antidepressant

#### Figure 12: Remission (ITT) at 40-month follow-up

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M-H, Fixed, 95% CI
1.17.1 CBT individua	l + any AD						
Wiles 2013/2016 Subtotal (95% CI)	38	234 <b>234</b>	20	235 <b>235</b>	100.0% <b>100.0%</b>	1.91 [1.15, 3.18] <b>1.91 [1.15, 3.18]</b>	
Total events Heterogeneity: Not a Test for overall effect		° = 0.01	20				
Test for subgroup dit	fferences: N	lot appl	icable				0.01 0.1 1 10 100 Favours AD Favours CBT + AD

AD: antidepressant

# Figure 13: Response (ITT)

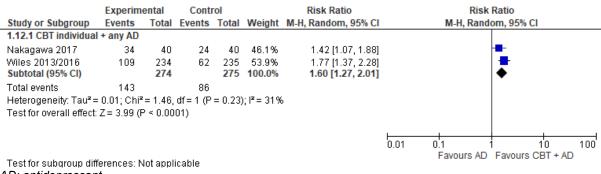
	Experim		Cont			Risk Ratio	Risk Ratio
Study or Subgroup 1.4.1 CBT individual	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Nakagawa 2017	31	40	13	40	20.9%	2.38 [1.48, 3.84]	
Wiles 2008	8	14	0	11	0.6%	13.60 [0.87, 212.59]	+
Wiles 2013/2016	95	234	46	235	52.1%	2.07 [1.53, 2.81]	🛨
Subtotal (95% CI)		288		286	73.7%	2.19 [1.70, 2.83]	•
Total events Heterogeneity: Tau <sup>2</sup> =	134 0.00: Chia	- 1 00	59 df = 270	- 0.27			
Test for overall effect:				= 0.37,	), 1- = 0%		
1.4.2 Rumination-foc	usod CDT						
Watkins 2011a	17	21	5	21	7.6%	3.40 [1.54, 7.51]	
Subtotal (95% CI)		21	5	21	7.6%	3.40 [1.54, 7.51] 3.40 [1.54, 7.51]	
Total events	17		5				-
Heterogeneity: Not ap	plicable		-				
Test for overall effect:	Z = 3.03 (F	P = 0.00	2)				
1.4.3 Blended CCBT &	& individua	I CBT					
Nakao 2018	11	20	4	20	5.1%	2.75 [1.05, 7.20]	
Subtotal (95% CI)		20		20	5.1%	2.75 [1.05, 7.20]	-
Total events	. 11		4				
Heterogeneity: Not ap Test for overall effect:	•	2 – O OA	\ \				
			·				
1.4.4 Mindfulness-ba	-			CT) gro			
Eisendrath 2016	27	87	13	86	13.6%	2.05 [1.14, 3.71]	-
Subtotal (95% CI)		87	4.0	86	13.6%	2.05 [1.14, 3.71]	-
Total events Heterogeneity: Not ap	27 Inliaghla		13				
Test for overall effect:	•	P = 0 02	)				
		0.02	,				
Total (95% CI)		416		413	100.0%	2.27 [1.83, 2.83]	▲
Total events	189		81				
Heterogeneity: Tau <sup>2</sup> =	•			= 0.65)	); I² = 0%		
Test for overall effect:					700 17. 0	00	Favours AD Favours CBT + AD
Test for subgroup diff AD: antidepressan		/nl*=1.	33, at = 3	(P = 0.	.72), if = l	170	
ne. undepressan	•						

# Figure 14: Response (ITT) at 3-month follow-up

	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% C	I
1.9.1 CBT individual	+ any AD								
Nakagawa 2017 Subtotal (95% CI)	28	40 <b>40</b>	17	40 <b>40</b>	100.0% <b>100.0%</b>	1.65 [1.09, 2.49] <b>1.65 [1.09, 2.49]</b>		-	
Total events Heterogeneity: Not a Test for overall effect		<sup>o</sup> = 0.02	17 )						
Toot for outparous di	forence: h	lot onni	isabla				L C.01 0.1	1 1 avours AD Favours	10 100 CBT + AD

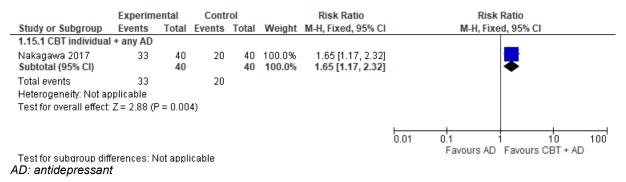
Test for subgroup differences: Not applicable AD: antidepressant

# Figure 15: Response (ITT) at 6-month follow-up



AD: antidepressant

#### Figure 16: Response (ITT) at 12-month follow-up



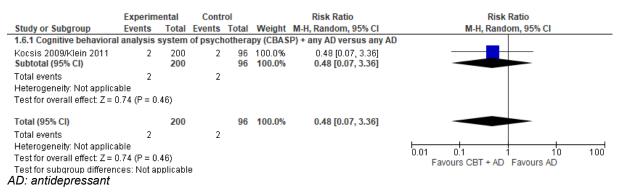
#### Figure 17: Response (ITT) at 40-month follow-up

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.18.1 CBT individual	+ any AD						
Wiles 2013/2016 Subtotal (95% CI)	59	234 <b>234</b>	30	235 <b>235</b>	100.0% <b>100.0%</b>	1.98 [1.32, 2.95] <b>1.98 [1.32, 2.95]</b>	
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.00	30 09)				
Test for subgroup diff AD: antidepressant		lot appl	icable				0.01 0.1 1 10 100 Favours AD Favours CBT + AD

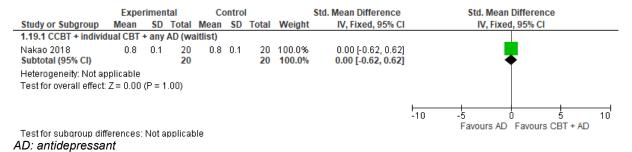
# Figure 18: Discontinuation due to any reason

Study on Submerry	Experime		Contro		Mainht	Risk Ratio	Risk Ratio
Study or Subgroup 1.5.1 CBT individual	Events	Total	events	rotal	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Dozois 2009	4	25	2	23	2.4%	1.84 [0.37, 9.11]	<b>_</b>
Nakagawa 2017	1	40	1	40	0.8%	1.00 [0.06, 15.44]	
Paykel 1999/Scott 2000	19	80	12	78	14.2%	1.54 [0.80, 2.96]	
Wiles 2008	0	14	2	11	0.7%	0.16 [0.01, 3.03]	•
Wiles 2013/2016	25	234	22	235	20.4%	1.14 [0.66, 1.97]	
Subtotal (95% CI)	40	393	20	387	38.5%	1.26 [0.85, 1.88]	<b>—</b>
Total events Heterogeneity: Tau² = 0.00 Test for overall effect: Z = 1			39 (P = 0.6)	2); <b>I²</b> =	0%		
1.5.2 Rumination-focused	CBT						
Watkins 2011a	0	21	2	21	0.7%	0.20 [0.01, 3.93]	
Subtotal (95% CI)		21		21	0.7%	0.20 [0.01, 3.93]	
Total events	0		2				
Heterogeneity: Not applica Test for overall effect: Z = 1		9)					
1.5.3 Cognitive behavioral	analysis sy	stem	of psycho	othera	py (CBAS	(P)	
Kocsis 2009/Klein 2011	25	200	16	96	18.0%	0.75 [0.42, 1.34]	_ <b>_</b> +
Subtotal (95% CI)	-	200	-	96	18.0%	0.75 [0.42, 1.34]	◆
Fotal events	25		16				
Heterogeneity: Not applica Fest for overall effect: Z = 0		3)					
1.5.4 Dialectical behaviou	r therapy (D	BT)					
Lynch 2007_study 2	0	21	4	14	0.7%	0.08 [0.00, 1.31]	
Subtotal (95% CI)		21		14	0.7%	0.08 [0.00, 1.31]	
Total events	0		4				
Heterogeneity: Not applica Test for overall effect: Z = 1		8)					
1.5.5 Blended CCBT & indi	ividual CBT						
Nakao 2018	0	20	0	20		Not estimable	
Subtotal (95% CI)		20		20		Not estimable	
Total events	0		0				
Heterogeneity: Not applica Test for overall effect: Not a							
1.5.6 CBT group							
Chan 2012	8	25	9	25	10.1%	0.89 [0.41, 1.93]	
Subtotal (95% CI)	_	25	_	25	10.1%	0.89 [0.41, 1.93]	-
Total events Listeregeneity Meteopolise	8		9				
Heterogeneity: Not applica Test for overall effect: Z = 0		7)					
1.5.7 Mindfulness-based o	coanitive the	erapy (	MBCT) a	roud			
Chiesa 2015	6	26	9	24	8.0%	0.62 [0.26, 1.47]	<b>_</b> _
Eisendrath 2016	20	87	22	86	21.7%	0.90 [0.53, 1.52]	_ <b>_</b>
Subtotal (95% CI)		113		110	29.7%	0.81 [0.52, 1.27]	•
Total events Heterogeneity: Tau² = 0.00	26 : Chi≅ = 0.53	) df – 1	31 (P = 0.4)	7) · JZ	<b>N</b> %		
Heterogeneity: Tau+ = 0.00 Test for overall effect: Z = 0			(r = 0.4	0,1*=	070		
		(PBC)	F) group				
1.5.8 Person-based cogni	tive therapy		-	14	2.3%	1.50 [0.29, 7.65]	
Strauss 2012	tive therapy 3	14	2				
Strauss 2012 Subtotal (95% CI)	3			14	2.3%	1.50 [0.29, 7.65]	
Strauss 2012 <b>Subtotal (95% CI)</b> Total events	3 3	14	2 2		2.5%	1.50 [0.29, 7.65]	
Strauss 2012 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Not applica	3 3 ble	14 <b>14</b>			2.3%	1.50 [0.29, 7.65]	
Strauss 2012 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Not applica Test for overall effect: Z = 0	3 3 ble	14 <b>14</b> 3)		14			
Strauss 2012 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 0 Total (95% CI)	3 3 ble 1.49 (P = 0.6	14 <b>14</b>	2	14	2.3%	1.50 [0.29, 7.65] 0.95 [0.74, 1.21]	•
Strauss 2012 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 0 Total (95% CI) Total events	3 3 ble 1.49 (P = 0.6 111	14 <b>14</b> 3) <b>807</b>	2 103	14 687	100.0%		
1.5.8 Person-based cogni Strauss 2012 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0	3 3 ble 1.49 (P = 0.6 111 ; Chi <sup>2</sup> = 10.7	14 <b>14</b> 3) <b>807</b> '3, df=	2 103	14 687	100.0%		0.01 0.1 1 10 100
Strauss 2012 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.00	3 3 ble 1.49 (P = 0.6 111 ; Chi <sup>2</sup> = 10.7 1.45 (P = 0.6	14 <b>14</b> 3) <b>807</b> '3, df = 5)	2 103 11 (P = 0	<b>14</b> <b>687</b> 0.47); F	<b>100.0%</b> ²= 0%	0.95 [0.74, 1.21]	0.01 0.1 1 10 100 Favours CBT + AD Favours AD

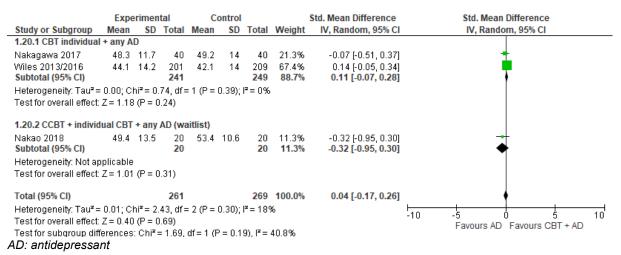
#### Figure 19: Discontinuation due to side effects



#### Figure 20: Quality of life endpoint



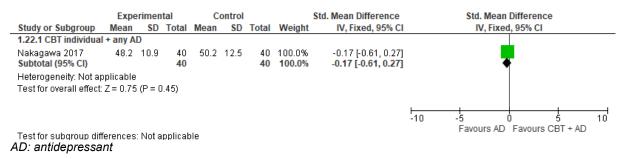
#### Figure 21: Quality of life physical component score (PCS) endpoint



#### Figure 22: Quality of life mental component score (MCS) endpoint

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI
1.21.1 CBT individual	+ any Al	D							
Nakagawa 2017	43.2	11.4	40	43.7	10.9	40	27.3%	-0.04 [-0.48, 0.39]	1 🕈
Wiles 2013/2016 Subtotal (95% CI)	39.1	14.1	201 <b>241</b>	33.7	12.6	209 <b>249</b>	56.2% 83.5%	0.40 [0.21, 0.60] 0.22 [-0.21, 0.65]	
Heterogeneity: Tau <sup>z</sup> =	0.07; Cł	ni <b>²</b> = 3.	35, df=	= 1 (P =	0.07);	l <sup>2</sup> = 709	6		
Test for overall effect:	Z=1.02	(P = 0	.31)						
1.21.2 CCBT + individ	ual CBT	+ any	AD (wa	aitlist)					
Nakao 2018 Subtotal (95% CI)	43.9	10.2	20 <b>20</b>	41.3	7.9	20 <b>20</b>	16.5% <b>16.5%</b>	0.28 [-0.34, 0.90] 0.28 [-0.34, 0.90]	
Heterogeneity: Not ap	plicable								
Test for overall effect:		(P = 0	.38)						
Total (95% CI)			261			269	100.0%	0.26 [-0.03, 0.55]	I +
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff AD: antidepressa	Z = 1.79 erences:	(P = 0	.07)						-10 -5 0 5 10 Favours AD Favours CBT + AD

#### Figure 23: Quality of life physical component score (PCS) at 3-month follow-up



#### Figure 24: Quality of life mental component score (MCS) at 3-month follow-up

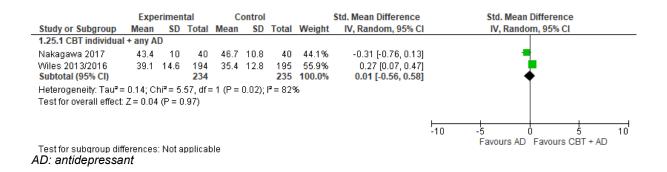
Study of Subgroup	Expe	rimen	tal	Control			9	Std. Mean Difference		Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	Mean SD		Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI		
1.23.1 CBT individual	+ any AD	)										
Nakagawa 2017 Subtotal (95% CI)	42.3	11.8	40 <b>40</b>	44	11.4	40 <b>40</b>	100.0% <b>100.0%</b>	-0.15 [-0.58, 0.29] - <b>0.15 [-0.58, 0.29]</b>				
Heterogeneity: Not ap Fest for overall effect: .		(P = 0	1.52)									
									⊢ -10			

AD: antidepressant

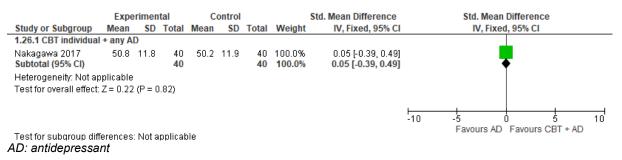
	Exper	Experimental			Control			Std. Mean Difference		Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 9	95% CI	
1.24.1 CBT individua	l + any AD	)										
Nakagawa 2017	47.9	7.4	40	50.2	14.1	40	40.7%	-0.20 [-0.64, 0.24]				
Wiles 2013/2016 Subtotal (95% CI)	44.6	13.2	194 <b>234</b>	41.1	13.5	195 <b>235</b>	59.3% <b>100.0%</b>	0.26 [0.06, 0.46] 0.07 [-0.37, 0.52]				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	•		•	= 1 (P =	0.06);	l² = 729	%					
									-10	-5 0 Favours AD Fa	5 5 vours CBT + Al	10
Test for subgroup dif AD: antidepressa		Not a	pplicat	ole								-

#### Figure 25: Quality of life physical component score (PCS) at 6-month follow-up

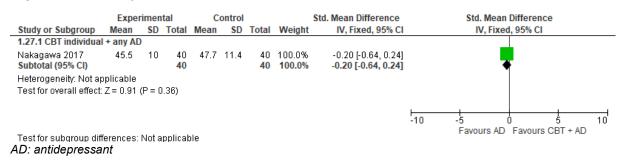
#### Figure 26: Quality of life mental component score (MCS) at 6-month follow-up



#### Figure 27: Quality of life physical component score (PCS) at 12-month follow-up



#### Figure 28: Quality of life mental component score (MCS) at 12-month follow-up



#### Control Std. Mean Difference Std. Mean Difference Experimental Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI 1.28.1 CBT individual + any AD 0.22 [-0.03, 0.47] 0.22 [-0.03, 0.47] Wiles 2013/2016 42.2 13.8 132 39.2 13.5 110 100.0% Subtotal (95% CI) 132 110 100.0% Heterogeneity: Not applicable Test for overall effect: Z = 1.69 (P = 0.09) -10 5 10 -5 Ó Favours AD Favours CBT + AD Test for subgroup differences: Not applicable AD: antidepressant

### Figure 29: Quality of life physical component score (PCS) at 40-month follow-up

#### Figure 30: Quality of life mental component score (MCS) at 40-month follow-up

	Expe	rimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean SD Total		Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.29.1 CBT individual	+ any Al	D							
Wiles 2013/2016 Subtotal (95% CI)	38.7	12.1	132 132	34.6	11.8	110 <b>110</b>	100.0% <b>100.0%</b>	0.34 [0.09, 0.60] 0.34 [0.09, 0.60]	*
Heterogeneity: Not ap Test for overall effect:	•		.009)					ł	10 -5 0 5 10
Test for subgroup diff AD: antidepressa		Not a	pplicat	ole					Favours AD Favours CBT + AD

#### Figure 31: Functional impairment endpoint

	Expe	erimen	tal	С	ontrol		:	Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% Cl	IV, Rando	om, 95% Cl	
1.30.1 CBT individual										1	
Paykel 1999/Scott 2000 Subtotal (95% Cl)	1.81	0.39	80 <mark>80</mark>	2.05	0.51	78 <b>78</b>	46.5% <b>46.5%</b>	-0.53 [-0.84, -0.21] - <b>0.53 [-0.84, -0.21]</b>	•	r •	
Heterogeneity: Not applica	able										
Test for overall effect: Z = 3	3.25 (P =	0.001	)								
1.30.2 Cognitive behavior	al analy	sis sys	stem of	f psych	othera	ру (СВ	ASP)				
Kocsis 2009/Klein 2011 Subtotal (95% Cl)	10.24	3.25	172 172	10.96	3.63	75 <b>75</b>	53.5% 53.5%	-0.21 [-0.48, 0.06] - <b>0.21 [-0.48, 0.06]</b>			
Heterogeneity: Not applica Test for overall effect: Z = 1		: 0.12)									
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03 Test for overall effect: Z = 3 Test for subgroup differen AD: antidepressant	2.29 (P =	0.02)		-0.36 [-0.67, -0.05]	-10 -5 Favours CBT + AD	0 5 Favours AD	10				

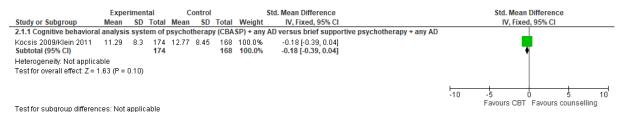
#### Figure 32: Functional impairment at 11-month follow-up

	Expe	erimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.31.1 CBT individual + a	ny AD								
Paykel 1999/Scott 2000 Subtotal (95% CI)	1.83	0.47	80 <mark>80</mark>	1.97	0.46	78 <b>78</b>	100.0% <b>100.0%</b>	-0.30 [-0.61, 0.01] - <b>0.30 [-0.61, 0.01]</b>	•
Heterogeneity: Not applic	able								
Test for overall effect: Z =	1.87 (P =	= 0.06)							
Test for subgroup different AD: antidepressant		t appli	able						Favours CBT + AD Favours AD

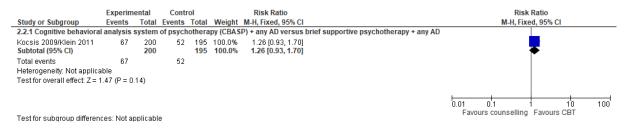
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#### Comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

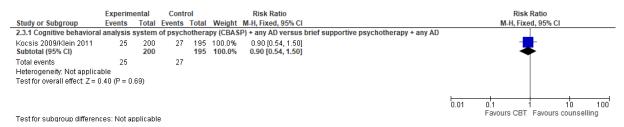
#### Figure 33: Depression symptomatology endpoint



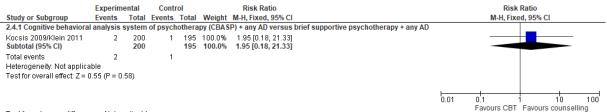
#### Figure 34: Remission (ITT)



#### Figure 35: Discontinuation due to any reason



#### Figure 36: Discontinuation due to side effects



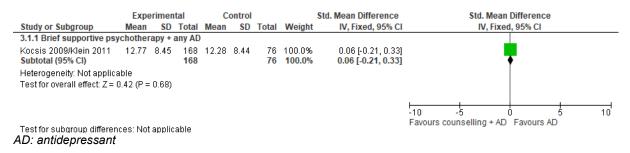
Test for subgroup differences: Not applicable

#### Experimental Std. Mean Difference Std. Mean Difference Control Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI 2.5.1 Cognitive behavioral analysis system of psychotherapy (CBASP) + any AD versus brief supportive psychotherapy + any AD 172 10.73 3.46 172 162 100.0% 162 100.0% Kocsis 2009/Klein 2011 10.24 3.25 -0.15 [-0.36, 0.07] -0.15 [-0.36, 0.07] Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 1.33 (P = 0.18) -10 10 Favours CBT Favours counselling Test for subgroup differences: Not applicable

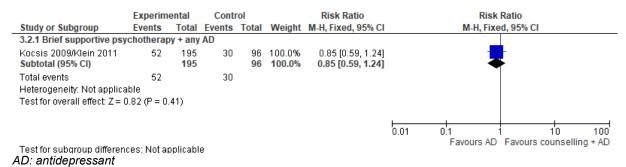
#### Figure 37: Functional impairment endpoint

#### Comparison 3. Augmenting with counselling versus continuing with antidepressant

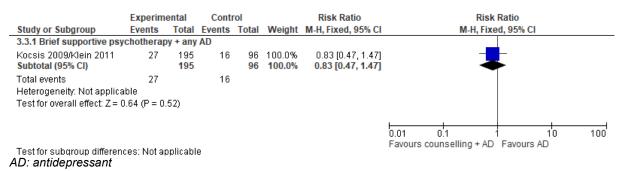
#### Figure 38: Depression symptomatology endpoint



#### Figure 39: Remission (ITT)

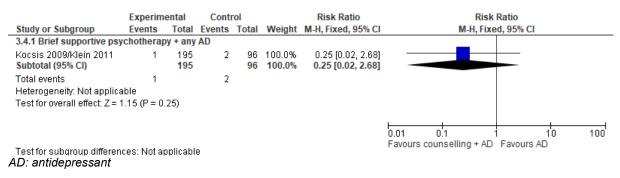


#### Figure 40: Discontinuation due to any reason

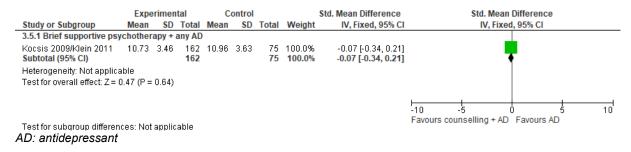


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#### Figure 41: Discontinuation due to side effects



#### Figure 42: Functional impairment endpoint

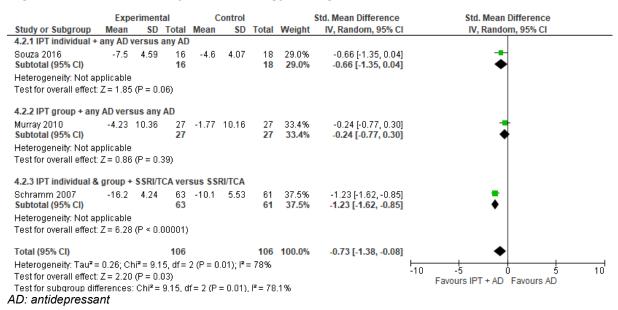


#### Comparison 4. Augmenting with IPT versus continuing with antidepressant

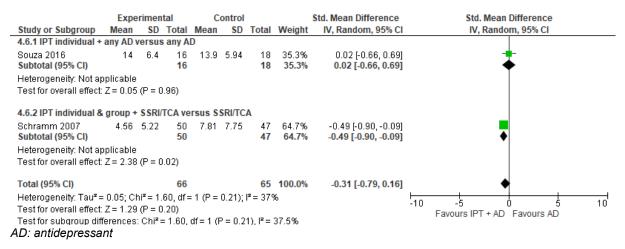
#### Figure 43: Depression symptomatology endpoint

	Experimental							Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	CI IV, Random, 95% CI
4.1.1 IPT individual +	any AD v	ersus	s any A	D					
Souza 2016 Subtotal (95% CI)	12.3	6.8	16 <b>16</b>	13.8	5.94	18 <b>18</b>	21.7% <b>21.7%</b>	-0.23 [-0.91, 0.45] - <b>0.23 [-0.91, 0.45]</b>	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.67	(P = 0	).50)						
4.1.2 IPT individual &	group +	S SRI/	TCA ve	rsus S	SRI/TC	A			
Schramm 2007 Subtotal (95% CI)	8.9	6.4	63 63	11.8	7.9	61 61	78.3% <b>78.3%</b>	-0.40 [-0.76, -0.05] - <b>0.40 [-0.76, -0.05]</b>	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.21	(P = 0	).03)						
Total (95% CI)			79			79	100.0%	-0.36 [-0.68, -0.05]	5] 🔶
Heterogeneity: Tau <sup>z</sup> =	0.00; Ch	$\mathbf{i}^{\mathbf{z}} = 0$	19, df=	= 1 (P =	0.66);	l <sup>z</sup> = 0%			
Test for overall effect:	Z = 2.27	(P = 0	).02)						Favours IPT + AD Favours AD
Test for subgroup diff	est for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), l² =					6), I²=	0%		
AD: antidepressa	nt								

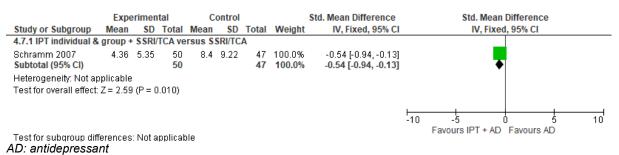
#### Figure 44: Depression symptomatology change score



#### Figure 45: Depression symptomatology at 1-3 month follow-up



#### Figure 46: Depression symptomatology at 12-month follow-up



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# Figure 47: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events					M-H, Random, 95% Cl		H, Random, 95% Cl
						italopram (dose increase)		
Reynolds 2010 Subtotal (95% CI)	35	60 <mark>60</mark>	29	64 <mark>64</mark>	55.2% <b>55.2%</b>	1.29 [0.91, 1.82] <b>1.29 [0.91, 1.82]</b>		•
Total events	35		29					
Heterogeneity: Not a Test for overall effect								
restior overall ellec	:1. ∠ = 1.44 (r	-= 0.15)						
4.3.2 IPT individual	+ any AD ve	rsus any	AD					
Souza 2016	5	17	3	23	3.9%	2.25 [0.62, 8.17]		+ • • •
Subtotal (95% CI)		17		23	3.9%	2.25 [0.62, 8.17]		
Total events	5		3					
Heterogeneity: Not a								
Test for overall effec	:T: Z = 1.24 (f	<sup>2</sup> = 0.22)						
4.3.3 IPT group + ar	ny AD versu	s any AD	)					
Murray 2010	12	34	4	30	6.3%	2.65 [0.95, 7.34]		
Subtotal (95% CI)		34		30	6.3%	2.65 [0.95, 7.34]		
Total events	12 nuliochio		4					
Heterogeneity: Not a Test for overall effec		/an n – c						
restion overall ellec	a. 2 – 1.07 (i	- 0.00)						
4.3.4 IPT individual	& group + S	SRI/TCA	versus	SSRI/T	CA			
Schramm 2007	31	65	21	65	34.6%	1.48 [0.96, 2.28]		
Subtotal (95% CI)		65		65	34.6%	1.48 [0.96, 2.28]		-
Total events	31		21					
Heterogeneity: Not a								
Test for overall effec	:т. Z = 1.76 (ł	-= 0.08)						
Total (95% CI)		176		182	100.0%	1.44 [1.12, 1.86]		◆
Total events	83		57					
Heterogeneity: Tau <sup>2</sup>				= 0.50)	; I <b>²</b> = 0%		0.01 0.1	1 10 1
Test for overall effec			·					ours AD Favours IPT + AD
Test for subaroup d		≎hi <b>²</b> = 2.2	!6. df = 3	(P = 0.	52), I <sup>2</sup> = 0	1%		
D: antidepressa	ant							

AD: antidepressant

# Figure 48: Response (ITT)

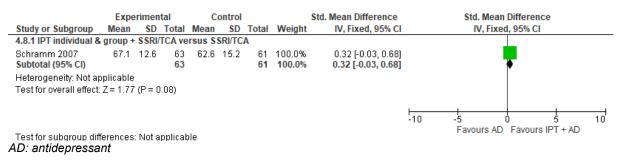
	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events			Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.4.1 IPT individual +	any AD vei	rsus an	y AD				
Souza 2016 Subtotal (95% CI)	6	17 <b>17</b>	4	23 <b>23</b>	6.5% <mark>6.5%</mark>	2.03 [0.68, 6.09] <b>2.03 [0.68, 6.09]</b>	
Total events	6		4				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z=1.26 (F	P = 0.21	)				
4.4.2 IPT group + any	AD versus	s any Al	D				
Murray 2010 Subtotal (95% CI)	12	34 <b>34</b>	5	30 <b>30</b>	9.2% <b>9.2%</b>	2.12 [0.84, 5.32] <b>2.12 [0.84, 5.32]</b>	•
Total events	12		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.60 (F	P = 0.11	)				
4.4.3 IPT individual &	group + S	SRI/TCA	versus	S SRI/T	CA		
Schramm 2007 <b>Subtotal (95% CI)</b>	44	65 65	31	65 65	84.3% <mark>84.3%</mark>	1.42 [1.05, 1.93] <b>1.42 [1.05, 1.93]</b>	●
Total events	44		31				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 2.25 (F	P = 0.02	)				
Total (95% CI)		116		118	100.0%	1.51 [1.14, 1.99]	◆
Total events	62		40				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 1.02,	df = 2 (P	= 0.60)	); I² = 0%		
Test for overall effect:	Z=2.87 (F	P = 0.00	4)				Favours AD Favours IPT + AD
Test for subgroup diffe		hi² = 0.	95. df = 2	(P = 0)	.62), I <sup>z</sup> = 0	%	
AD: antidepressant	t						

# Figure 49: Discontinuation due to any reason

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events					M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.5.1 IPT individual	+ escitalopi		se increa	ise) ve	rsus esc	italopram (dose increase)	
Reynolds 2010 Subtotal (95% CI)	7	60 60	5	64 64	21.4% <b>21.4%</b>	1.49 [0.50, 4.45] <b>1.49 [0.50, 4.45]</b>	
Total events	7		5	•••		110 [0100] 1110]	
Heterogeneity: Not a	applicable		-				
Test for overall effec	t: Z = 0.72 (F	P = 0.47)	1				
4.5.2 IPT individual	+ any AD ve	rsus an	y AD				
Souza 2016	5	17	2	23	11.2%	3.38 [0.74, 15.39]	
Subtotal (95% CI)		17		23	11.2%	3.38 [0.74, 15.39]	
Total events	5		2				
Heterogeneity: Not a							
Test for overall effec	t: Z = 1.58 (F	P = 0.11)	1				
4.5.3 IPT group + ar	ny AD versu	s any A[	)				
Murray 2010	7	34 <b>34</b>	3	30 30	16.1%	2.06 [0.58, 7.26]	
Subtotal (95% CI)	_	34		20	16.1%	2.06 [0.58, 7.26]	
Total events Heterogeneity: Not a	7 Annliachta		3				
Test for overall effec		- n 26					
restion overall ellec		- 0.20,					
4.5.4 IPT individual	& group + S	SRI/TCA	versus	SSRI/T	CA		
Schramm 2007	12	65	13	65	51.3%	0.92 [0.46, 1.87]	
Subtotal (95% CI)		65		65	51.3%	0.92 [0.46, 1.87]	-
Total events	12		13				
Heterogeneity: Not a							
Test for overall effec	:t: Z = 0.22 ()	P = 0.82)	1				
Total (95% CI)		176		182	100.0%	1.35 [0.81, 2.23]	◆
Total events	31		23				
Heterogeneity: Tau <sup>z</sup>	•			= 0.39)	; I² = 0%		
Test for overall effec							Favours IPT + AD Favours AD
Test for subaroup d		Chi <b>²</b> = 2.9	99. df = 3	(P = 0.	39), I <b>²</b> = 0	1%	
D: antidepressa	ant						

AD: antidepressant

#### Figure 50: Global functioning endpoint



#### Figure 51: Global functioning at 3-month follow-up

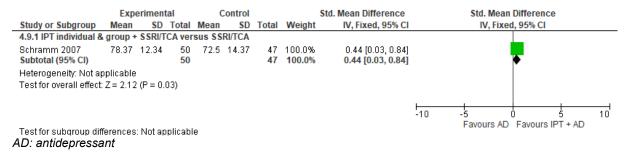
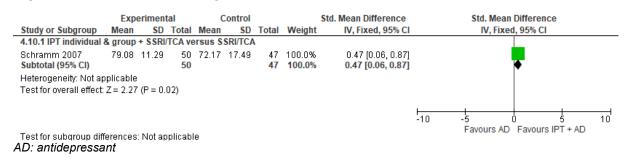
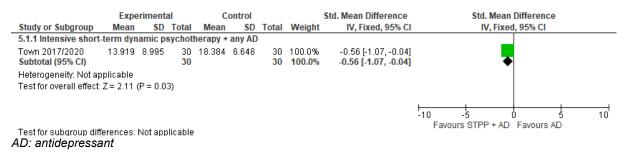


Figure 52: Global functioning at 12-month follow-up

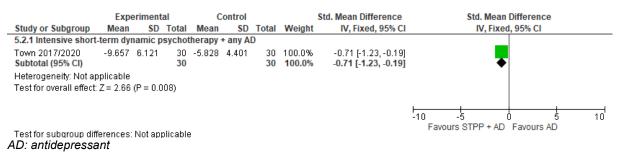


# Comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

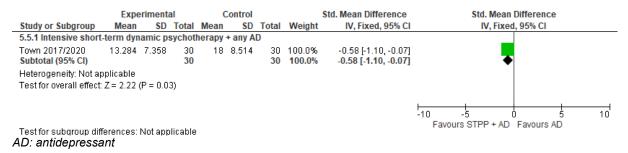
#### Figure 53: Depression symptomatology endpoint



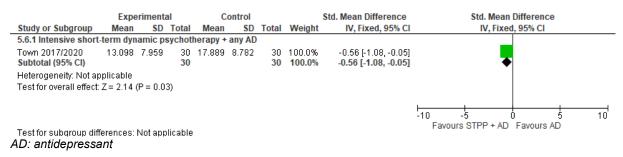
#### Figure 54: Depression symptomatology change score



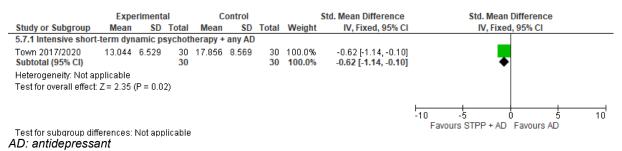
#### Figure 55: Depression symptomatology at 3-month follow-up



#### Figure 56: Depression symptomatology at 6-month follow-up



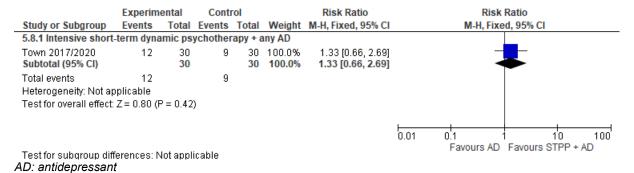
#### Figure 57: Depression symptomatology at 12-month follow-up



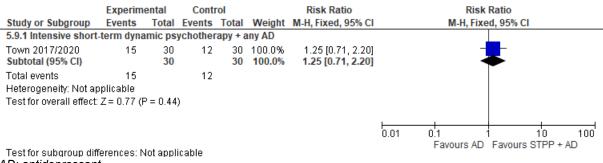
#### Figure 58: Remission (ITT)

	Experim	ental	Cont	ol		Risk Ratio		F			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H,	Fixed, 95% C	1	
5.3.1 Intensive short	term dyna	mic ps	ychother	apy + a	any AD						
Town 2017/2020 Subtotal (95% CI)	11	30 <b>30</b>	1	30 <b>30</b>		11.00 [1.51, 79.96] <b>11.00 [1.51, 79.96]</b>					
Total events Heterogeneity: Not a Test for overall effect	•	P = 0.02	1				H 0.01	0.1	1	<b> </b> 10	100
Test for subgroup dif AD: antidepressan		lot appl	icable					Favours	AD Favours	STPP +	AD

#### Figure 59: Remission (ITT) at 12-month follow-up



## Figure 60: Response (ITT) at 12-month follow-up



AD: antidepressant

#### Figure 61: Discontinuation due to any reason

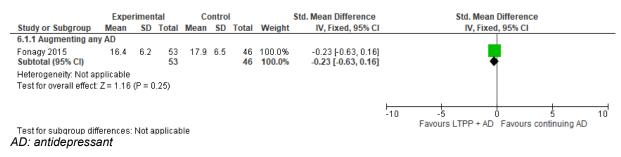
	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.4.1 Intensive short	t-term dyna	mic ps	ychothei	apy + a	any AD		
Town 2017/2020 Subtotal (95% CI)	5	30 <b>30</b>	3	30 <b>30</b>	100.0% <b>100.0%</b>	1.67 [0.44, 6.36] <b>1.67 [0.44, 6.36]</b>	
Total events Heterogeneity: Not a Test for overall effect		P = 0.45	3				
							0.01 0.1 1 10 100 Favours STPP + AD Favours AD

Test for subgroup differences: Not applicable

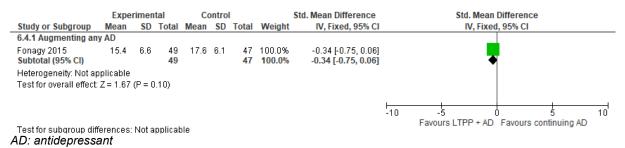
AD: antidepressant

#### Comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidepressant

#### Figure 62: Depression symptomatology endpoint



#### Figure 63: Depression symptomatology at 6-month follow-up

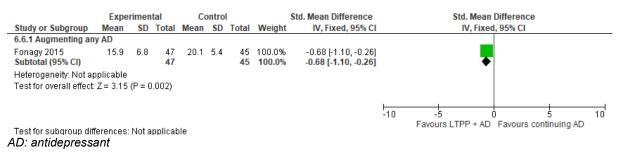


#### Figure 64: Depression symptomatology at 1-year follow-up

	Expe	rimen	ital	Co	ontro	I		Std. Mean Difference		Std. Mean I	Difference	
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI		IV, Fixed,	, 95% CI	
6.5.1 Augmenting an	iy AD											
Fonagy 2015 Subtotal (95% CI)	16.7	7.4	49 <b>49</b>	19.4	6.5	49 <b>49</b>	100.0% <b>100.0%</b>	-0.38 [-0.78, 0.02] -0.38 [-0.78, 0.02]		•		
Heterogeneity: Not ap Test for overall effect:			).06)									
									⊢ -10		5	10
Toot for cubaroup dif				-1-						Favours LTPP + AD	Favours continuing AD	

Test for subgroup differences: Not applicable AD: antidepressant

#### Figure 65: Depression symptomatology at 2-year follow-up

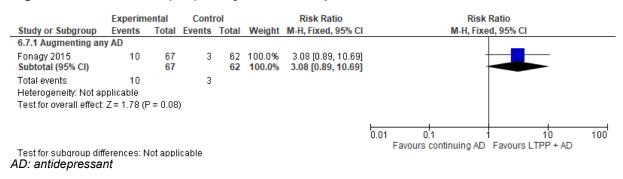


#### Figure 66: Remission (ITT)

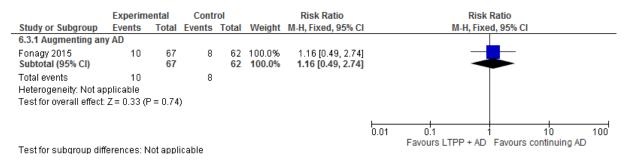
	Experim	ental	Cont	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
6.2.1 Augmenting an	iy AD						
Fonagy 2015 Subtotal (95% Cl)	6	67 67	4	62 62	100.0% <b>100.0%</b>	1.39 [0.41, 4.69] <b>1.39 [0.41, 4.69]</b>	
Total events Heterogeneity: Not a Test for overall effect		<sup>D</sup> = 0.60	4				
Test for subgroup dif		Vot appli	icable				0.01 0.1 1 10 100 Favours continuing AD Favours LTPP + AD

AD: antidepressant

#### Figure 67: Remission (ITT) at 2-year follow-up



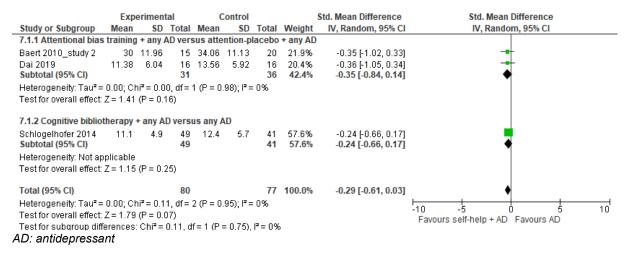
#### Figure 68: Discontinuation due to any reason



AD: antidepressant

#### Comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/attention-placebo)

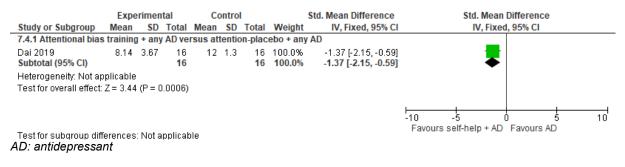
#### Figure 69: Depression symptomatology endpoint



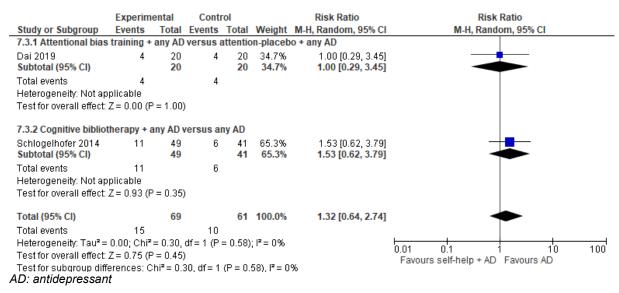
#### Figure 70: Depression symptomatology change score

	Expo	rimen	tal	6	ontrol			Std. Mean Difference	Std. Mean Difference
Study of Subgroup									
Study or Subgroup	Mean			Mean			Weight	IV, Random, 95% CI	IV, Random, 95% CI
7.2.1 Attentional bias	training	+ any	AD ver	sus atte	ention	-placeb	io + any Al	)	
Baert 2010_study 2	-5	8.06	15	-2.5	7.36	20	22.2%	-0.32 [-0.99, 0.36]	
Dai 2019	-11.75	4.45	16	-9.32	4.3	16	20.2%	-0.54 [-1.25, 0.17]	
Subtotal (95% CI)			31			36	42.4%	-0.42 [-0.91, 0.06]	◆
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i² = 0.2	0. df=	1 (P = 0	.66); P	²=0%			
Test for overall effect: 2			•						
			,						
7.2.2 Cognitive bibliot	herapy +	any A	D vers	us any i	AD				
Schlogelhofer 2014	-1.5	3.38	49	-0.1	4.17	41	57.6%	-0.37 [-0.79, 0.05]	
Subtotal (95% CI)			49			41	57.6%	-0.37 [-0.79, 0.05]	•
Heterogeneity: Not app	olicable								
Test for overall effect: 2		(P = 0	08)						
			,						
Total (95% CI)			80			77	100.0%	-0.39 [-0.71, -0.08]	•
Heterogeneity: Tau <sup>2</sup> = 1	0.00: Ch	i <sup>z</sup> = 0.2	3. df=	2 (P = 0	.89); P	<sup>2</sup> =0%			
Test for overall effect: 2									-10 -5 0 5 10
Test for subgroup diffe		•	· ·	If = 1 (P	- 0.87	n ⊫= n	96		Favours self-help + AD Favours AD
AD: antidepressar			0.00, 0	0 - 1 Q	- 0.07	/= U			
AD. antidepressar	п								

#### Figure 71: Depression symptomatology at 1-month follow-up

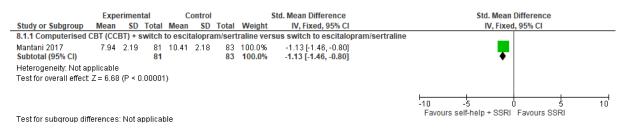


#### Figure 72: Discontinuation due to any reason



#### Comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only

#### Figure 73: Depression symptomatology endpoint



#### Figure 74: Depression symptomatology change score

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.2.1 Computerised (	CBT (CCE	3T) + s	witch	to escit	alopra	m/sert	traline ver	sus switch to escitalopram/ser	raline
Mantani 2017 Subtotal (95% CI)	-5.56	4.12	81 <mark>81</mark>	-2.49	3.94	83 <mark>83</mark>	100.0% <b>100.0%</b>	-0.76 [-1.08, -0.44] - <b>0.76 [-1.08, -0.44]</b>	<b>↓</b>
Heterogeneity: Not ap Test for overall effect:			1.00001	)					
Test for subgroup diff	erences:	: Not a	pplicab	ole					Favours self-help + SSRI Favours SSRI

#### Figure 75: Remission (ITT)

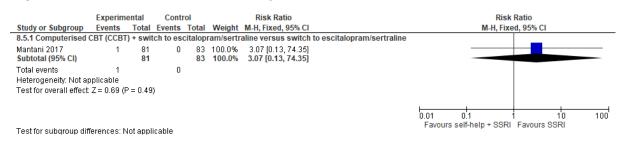


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#### Figure 76: Response (ITT)

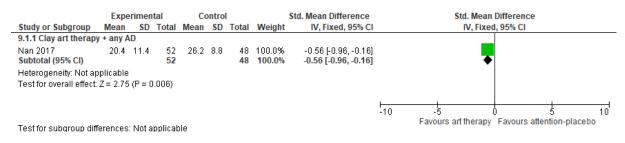
	Experime	ental	Contro	d		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	ed, 95% CI		
8.4.1 Computerised	CBT (CCBT	) + swit	ch to esci	talopi	ram/sertr	aline versus switch	to escitalopram/sertraline					
Mantani 2017 Subtotal (95% CI)	34	81 <b>81</b>	18	83 <mark>83</mark>	100.0% <b>100.0%</b>	1.94 [1.19, 3.14] 1.94 [1.19, 3.14]				-		
Total events Heterogeneity: Not ap Test for overall effect:		P = 0.00	18 7)					L				
Test for subgroup dif	ferences: N	lot appl	icable					0.01	0.1 Favours SSRI	Favours s	self-help +	100 SSRI

#### Figure 77: Discontinuation due to any reason

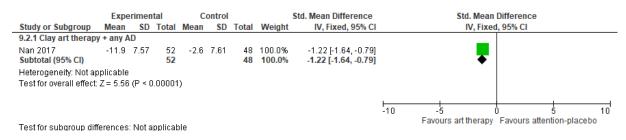


#### Comparison 9. Augmenting with art therapy versus attention-placebo

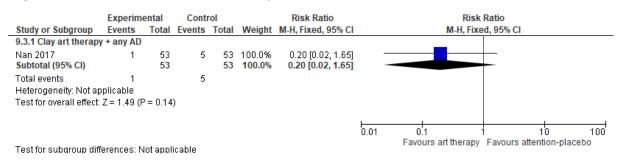
#### Figure 78: Depression symptomatology endpoint



#### Figure 79: Depression symptomatology change score

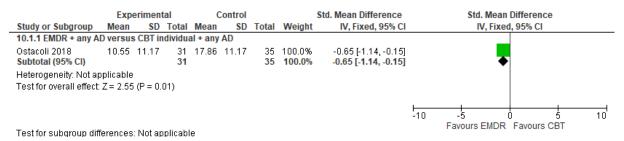


#### Figure 80: Discontinuation due to any reason

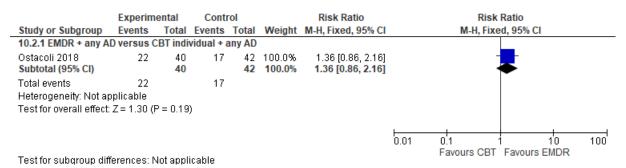


# Comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

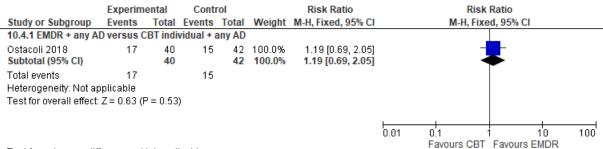
#### Figure 81: Depression symptomatology endpoint



#### Figure 82: Remission (ITT)

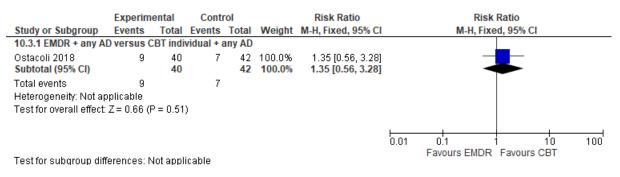


#### Figure 83: Remission (ITT) at 6-month follow-up



Test for subgroup differences: Not applicable

#### Figure 84: Discontinuation due to any reason

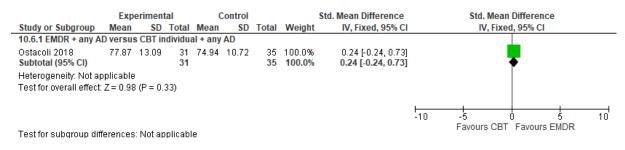


#### Figure 85: Global functioning at endpoint

	Expe	eriment	tal	0	Control			Std. Mean Difference		Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
10.5.1 EMDR + any AD	) versus	CBT in	ndividua	al + any	AD							
Ostacoli 2018 <b>Subtotal (95% CI)</b>	77.9	10.97	31 <b>31</b>	74.6	17.84	35 <b>35</b>		0.22 [-0.27, 0.70] 0.22 [-0.27, 0.70]			•	
Heterogeneity: Not ap Test for overall effect: .			38)									
									⊢ -10	-5 0	) 5 Favours EMDR	10

rest for subgroup unierences. Not applicable

#### Figure 86: Global functioning at 6-month follow-up

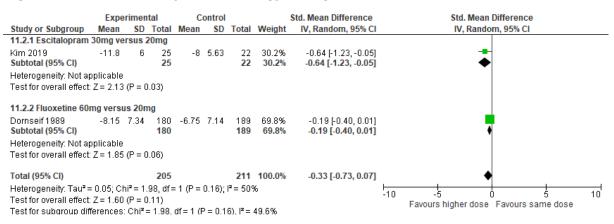


#### Comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose

#### Figure 87: Depression symptomatology endpoint

	Expe	erimen	tal	C	ontrol			Std. Mean Difference			Std. Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI			IV, Fixed	l, 95% Cl		
11.1.1 Paroxetine 30	-50mg v	ersus	20mg											
Ruhe 2009 Subtotal (95% CI)	16.1	1.22	30 <b>30</b>	15.3	1.28	27 <b>27</b>	100.0% <b>100.0%</b>	0.63 [0.10, 1.17] <b>0.63 [0.10, 1.17]</b>				◆		
Heterogeneity: Not ap Test for overall effect:	•		).02)											
									-10	-5	(	)	5	10
Test for subgroup dif	ferences	: Not a	pplicat	ole						Favours h	higher dose	Favours s	ame dos	е

#### Figure 88: Depression symptomatology change score



#### Figure 89: Remission (ITT)

	Experime		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events			Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
11.3.1 Escitalopram					17.00		_
Kim 2019 Subtotal (95% Cl)	15	25 <b>25</b>	10	25 <b>25</b>	17.2% <b>17.2%</b>	1.50 [0.84, 2.67] <b>1.50 [0.84, 2.67]</b>	•
Total events	15		10				
Heterogeneity: Not a							
Test for overall effect	: Z = 1.38 (F	r = 0.17)					
11.3.2 Fluoxetine 60	mg versus	20mg					
Dornseif 1989	51	181	51	190	34.7%	1.05 [0.75, 1.46]	<u>+</u>
Subtotal (95% CI)		181		190	34.7%	1.05 [0.75, 1.46]	<b>—</b>
Total events	51		51				
Heterogeneity: Not a Test for overall effect		) - 0 77)					
Testion overall effect	. 2 - 0.23 (i	- 0.77)					
11.3.3 Paroxetine 30	)-50mg ver		•				
Ruhe 2009 Subtotal (95% CI)	4	30 30	2	30 30	2.8% <b>2.8%</b>	2.00 [0.40, 10.11] 2.00 [0.40, 10.11]	
Total events	4	30	2	50	2.070	2.00 [0.40, 10.11]	
Heterogeneity: Not a			2				
Test for overall effect		P = 0.40					
	· _ · · · · · ·	,					
11.3.4 Sertraline 150	Omg versus	s 50mg					
Schweizer 2001	18	38	12	37	17.4%	1.46 [0.82, 2.59]	
Subtotal (95% CI)		38		37	17.4%	1.46 [0.82, 2.59]	-
Total events	18 Innliaehle		12				
Heterogeneity: Not a Test for overall effect		2 - 0 201					
restion overall effect	. 2 - 1.50 (i	- 0.20)					
11.3.5 Sertraline 200	Omg versus	s 100mg	1				
Licht 2002	28	98	37	99	27.9%	0.76 [0.51, 1.14]	
Subtotal (95% CI)		98		99	27.9%	0.76 [0.51, 1.14]	◆
Total events	28		37				
Heterogeneity: Not a							
Test for overall effect	: Z = 1.30 (F	' = 0.19)					
Total (95% CI)		372		381	100.0%	1.10 [0.84, 1.45]	<b>•</b>
Total events	116		112				
Heterogeneity: Tau² =	•	•		= 0.22)	); I² = 30%	5	0.01 0.1 1 10 100
Test for overall effect				<i>(</i> <b>D</b> -			Favours same dose Favours higher dose
Test for subgroup dif	terences: C	ni*= 5.7	'U, df = 4	(P = 0	.22), F= 2	(9.8%	

# Figure 90: Response (ITT)

	Experime		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events			Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
11.4.1 Escitalopram		-		25	44.000	4 67 14 06 0 601	
Kim 2019 Subtotal (95% CI)	20	25 25	12	25 25	14.3% 14.3%	1.67 [1.06, 2.62] 1.67 [1.06, 2.62]	▲
Total events	20	20	12	20	14.570	1.07 [1.00, 2.02]	-
Heterogeneity: Not a			12				
Test for overall effect	•	= 0.03)					
11.4.2 Fluoxetine 60	mg versus i	20mg					
Dornseif 1989	63	181	62	190	20.6%	1.07 [0.80, 1.42]	_ <b>_</b>
Schweizer 1990	18	36	21	41	14.7%	0.98 [0.63, 1.52]	_ <b>_</b>
Subtotal (95% CI)		217		231	35.3%	1.04 [0.82, 1.32]	<b>•</b>
Total events	81		83				
Heterogeneity: Tau <sup>2</sup> =	•		f=1 (P	= 0.74)	); I² = 0%		
Test for overall effect	: Z = 0.31 (P	= 0.75)					
11.4.3 Paroxetine 30	)-50mg vers	sus 20m	g				
Ruhe 2009	10	30	10	30	8.2%	1.00 [0.49, 2.05]	
Subtotal (95% CI)		30		30	8.2%	1.00 [0.49, 2.05]	-
Total events	10		10				
Heterogeneity: Not a		4.000					
Test for overall effect	: Z = 0.00 (P	= 1.00)					
11.4.4 Sertraline 150	)mg versus	50mg					
Schweizer 2001	30	38	21	37	19.0%	1.39 [1.00, 1.93]	<b>±</b>
Subtotal (95% CI)		38		37	19.0%	1.39 [1.00, 1.93]	◆
Total events	30		21				
Heterogeneity: Not a	•						
Test for overall effect	: Z = 1.99 (P	= 0.05)					
11.4.5 Sertraline 200	-	-					
Licht 2002	54	98	69	99	23.3%	0.79 [0.63, 0.99]	<b>T</b>
Subtotal (95% CI)		98		99	23.3%	0.79 [0.63, 0.99]	•
Total events	54		69				
Heterogeneity: Not ap	•	- 0.040					
Test for overall effect	: Z = 2.08 (P	= 0.04)					
Total (95% CI)		408		422	100.0%	1.10 [0.86, 1.39]	<b>+</b>
Total events	195		195				
Heterogeneity: Tau <sup>2</sup> =			df = 5 (i	P = 0.01	2); I² = 62	%	
Test for overall effect							Favours same dose Favours higher dose
est for subgroup dif	ferences: C	hi <b>²</b> = 13.1	13. df=	4 (P = I	0.01), I <b>²</b> =	69.5%	

# Figure 91: Discontinuation due to any reason

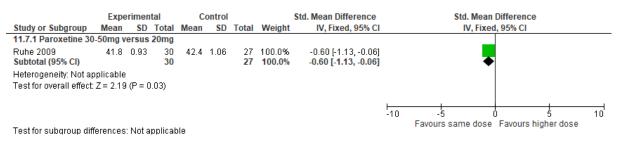
	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events			Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
11.5.1 Escitalopram							
Kim 2019 Subtotal (95% CI)	1	25 <b>25</b>	6	25 <b>25</b>	8.2% <mark>8.2%</mark>	0.17 [0.02, 1.29] 0.17 [0.02, 1.29]	
Total events	1		6				
Heterogeneity: Not a							
Test for overall effect	t: Z = 1.72 (F	P = 0.09)					
11.5.2 Fluoxetine 60	mg versus	20mg					
Dornseif 1989	45	181	48	190	38.8%	0.98 [0.69, 1.40]	- <u>+</u> -
Subtotal (95% CI)		181		190	38.8%	0.98 [0.69, 1.40]	<b>•</b>
Total events	45		48				
Heterogeneity: Not a							
Test for overall effect	t: Z = 0.09 (f	P = 0.93)					
11.5.3 Paroxetine 3	0-50mg ver	rsus 20n	ng				
Ruhe 2009	1	30	8	30	8.4%	0.13 [0.02, 0.94]	
Subtotal (95% CI)		30		30	8.4%	0.13 [0.02, 0.94]	
Total events	. 1		8				
Heterogeneity: Not a							
Test for overall effect	t: Z = 2.02 ()	P = 0.04)					
11.5.4 Sertraline 15	Omg versu	s 50mg					
Schweizer 2001	4	38	5	37	17.0%	0.78 [0.23, 2.68]	
Subtotal (95% CI)		38		37	17.0%	0.78 [0.23, 2.68]	
Total events	4		5				
Heterogeneity: Not a							
Test for overall effect	t: Z = 0.40 (F	P = 0.69)					
11.5.5 Sertraline 20	Omg versu	s 100mg					
Licht 2002	15	98	10	99	27.6%	1.52 [0.72, 3.21]	
Subtotal (95% CI)		98		99	27.6%	1.52 [0.72, 3.21]	-
Total events	15		10				
Heterogeneity: Not a							
Test for overall effect	t: Z = 1.09 (i	P = 0.28)					
Total (95% CI)		372		381	100.0%	0.77 [0.40, 1.48]	-
Total events	66		77				
Heterogeneity: Tau <sup>2</sup>		•		= 0.07)	); I² = 53%		0.01 0.1 1 10 1
Test for overall effect	t: Z = 0.77 (f	P = 0.44)					Favours higher dose Favours same dose
Test for subaroup di	fferences: (	Chi² = 8.3	30, df = 4	(P = 0)	.08), <b>i²</b> = 5	i1.8%	. El caro mignor dobo i raroaro camo dobo

# Figure 92: Discontinuation due to side effects

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
11.6.1 Escitalopram 3	Omg vers	us 20m	ng				
Kim 2019 Subtotal (95% CI)	0	25 <b>25</b>	0	25 <b>25</b>		Not estimable Not estimable	
Total events	0		0				
Heterogeneity: Not app	olicable						
Test for overall effect: N	Not applic	able					
11.6.2 Fluoxetine 60m	g versus	20mg					
Dornseif 1989	21	181	10	190	50.9%	2.20 [1.07, 4.55]	<b></b>
Schweizer 1990	6	36	2	41	33.3%	3.42 [0.74, 15.88]	
Subtotal (95% CI)		217		231	84.2%	2.39 [1.24, 4.60]	$\bullet$
Total events	27		12				
Heterogeneity: Tau <sup>2</sup> = I	0.00; Chi²	= 0.26,	df=1 (P	= 0.61)	; I² = 0%		
Test for overall effect: 2	Z = 2.60 (F	) = 0.00	9)				
11.6.3 Paroxetine 30-	50mg ver	sus 20r	ng				
Ruhe 2009	0	30	4	30	15.8%	0.11 [0.01, 1.98]	<
Subtotal (95% CI)		30		30	15.8%	0.11 [0.01, 1.98]	
Total events	0		4				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 1.50 (F	P = 0.13	)				
Total (95% CI)		272		286	100.0%	1.59 [0.42, 6.03]	
Total events	27		16				
Heterogeneity: Tau <sup>2</sup> = I	0.77; Chi <sup>z</sup>	= 4.62,	df = 2 (P	= 0.10)	; I <sup>z</sup> = 57%	b	
Test for overall effect: 2	Z = 0.69 (F	P = 0.49	)				Favours higher dose Favours same dose
Test for subgroup diffe	rences: C	hi <b>²</b> = 4.1	15, df = 1	(P = 0.	04), I <sup>2</sup> = 7	'5.9%	r aroaro nightir accorr avouro banno accor

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### Figure 93: Quality of life physical component score (PCS) endpoint

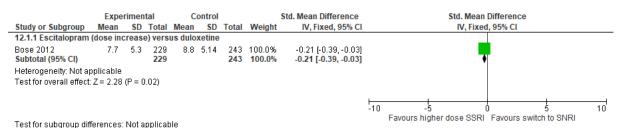


### Figure 94: Quality of life mental component score (MCS) endpoint

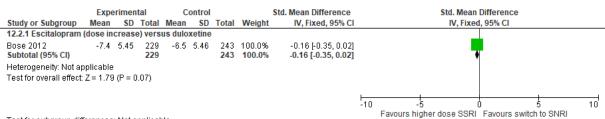
	Expe	rimen	tal	C	ontrol		Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
11.8.1 Paroxetine 30	-50mg v	ersus	20mg						
Ruhe 2009 Subtotal (95% CI)	29.6	1.37	30 <b>30</b>	27.3	1.57	27 <b>27</b>	100.0% <b>100.0%</b>	1.55 [0.95, 2.14] <b>1.55 [0.95, 2.14]</b>	
Heterogeneity: Not ap Test for overall effect:			).00001	)					
									10 -5 0 5 10
Test for subaroup diff	ferences	: Not a	nnlicat	ole					Favours same dose Favours higher dose

#### Comparison 12. Increasing the dose of SSRI versus switching to SNRI

#### Figure 95: Depression symptomatology endpoint

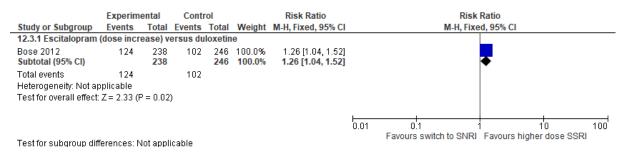


### Figure 96: Depression symptomatology change score



Test for subgroup differences: Not applicable

## Figure 97: Remission (ITT)



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# Figure 98: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
12.4.1 Escitalopram	(dose incr	ease) v	ersus du	loxetin	e		
Bose 2012 Subtotal (95% Cl)	167	238 <b>238</b>	170	246 <b>246</b>	100.0% <b>100.0%</b>	1.02 [0.90, 1.14] <b>1.02 [0.90, 1.14]</b>	
Total events Heterogeneity: Not aj Test for overall effect		P = 0.80	170 )				
Test for subgroup dif	fferences: N	Jot appl	icable				0.01 0.1 1 10 100 Favours switch to SNRI Favours higher dose SSRI

### Figure 99: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio		Risk Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 9	5% CI	
12.5.1 Escitalopram	(dose incr	ease) v	ersus du	loxetin	е					
Bose 2012 Subtotal (95% CI)	56	238 <b>238</b>	53	246 <b>246</b>	100.0% <b>100.0%</b>	1.09 [0.78, 1.52] 1.09 [0.78, 1.52]				
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.60	53							
							0.01	0.1 1 Favours higher dose SSRI Fa	10 vours switch to SNPI	100

Test for subgroup differences: Not applicable

#### Figure 100: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixed, 95% C	1	
12.6.1 Escitalopram	(dose incr	ease) v	ersus du	loxetin							
Bose 2012 Subtotal (95% Cl)	13	238 <b>238</b>	13	246 <b>246</b>	100.0% <b>100.0%</b>	1.03 [0.49, 2.18] <b>1.03 [0.49, 2.18]</b>			-		
Total events Heterogeneity: Not aj Test for overall effect		P = 0.93	13 ))								
Test for subaroun dif	foroncoc: b	lot oppi	icoblo				0.01 Fa	0.1 vours higher do	se SSRI Favours	10 s witch to SNRI	100

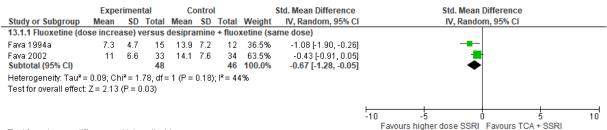
Test for subgroup differences: Not applicable

# Figure 101: Quality of life endpoint

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
12.7.1 Escitalopram	(dose in	creas	e) vers	us dulo:	xetine				
Bose 2012 Subtotal (95% CI)	47.2	10.9	229 <b>229</b>	46.1	9.98		100.0% <b>100.0%</b>		
Heterogeneity: Not a Test for overall effect			).25)						
									-10 -5 0 5 10 Favours switch to SNRI Favours higher dose SSRI
Test for subgroup dif	fferences	: Not a	opplicat	ble					

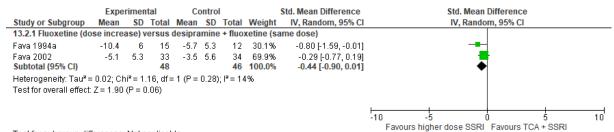
# Comparison 13. Increasing the dose of SSRI versus augmenting with TCA

#### Figure 102: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

### Figure 103: Depression symptomatology change score



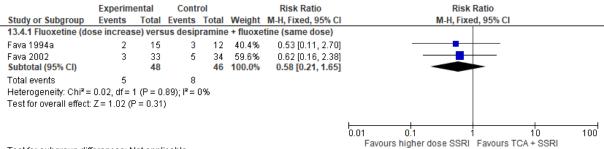
Test for subgroup differences: Not applicable

## Figure 104: Remission (ITT)

	Experim	ental	Contr	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
13.3.1 Fluoxetine (do	se increas	se) vers	us desip	ramin	e + fluoxe	tine (same dose)		
Fava 1994a	8	15	3	12	26.6%	2.13 [0.72, 6.33]		
Fava 2002 Subtotal (95% CI)	14	33 <b>48</b>	10	34 <b>46</b>	73.4% 100.0%	1.44 [0.75, 2.78] 1.60 [0.91, 2.81]		
Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	•		-	= 0.55	); I² = 0%			
T							L	0.1 1 10 100 Favours TCA + SSRI Favours higher dose SSRI

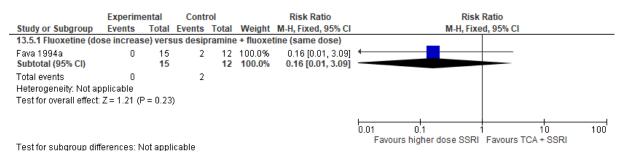
Test for subgroup differences: Not applicable

#### Figure 105: Discontinuation due to any reason



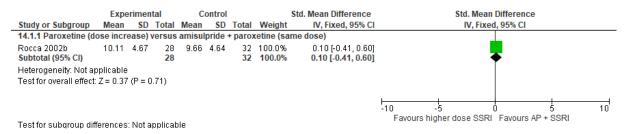
Test for subgroup differences: Not applicable

#### Figure 106: Discontinuation due to side effects

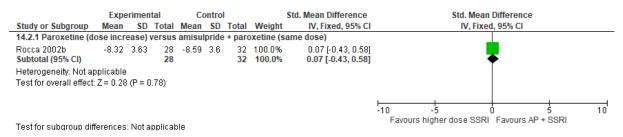


#### Comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

#### Figure 107: Depression symptomatology endpoint



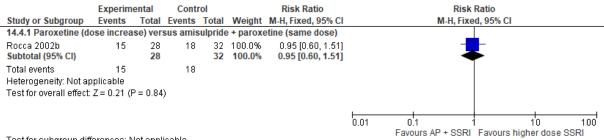
#### Figure 108: Depression symptomatology change score



# Figure 109: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	CI M-H, Fixed, 95% CI
14.3.1 Paroxetine (d	ose increa	se) ver	sus amis	ulpride	) + parox	etine (same dose)	
Rocca 2002b Subtotal (95% CI)	9	28 <b>28</b>	14	32 <b>32</b>	100.0% <b>100.0%</b>	0.73 [0.38, 1.43] <b>0.73 [0.38, 1.43]</b>	
Total events Heterogeneity: Not aj Test for overall effect		<sup>o</sup> = 0.36	14				
Test for subgroup dif	ferences: N	lot appl	icable				0.01 0.1 1 10 10 Favours AP + SSRI Favours higher dose SSRI

# Figure 110: Response (ITT)



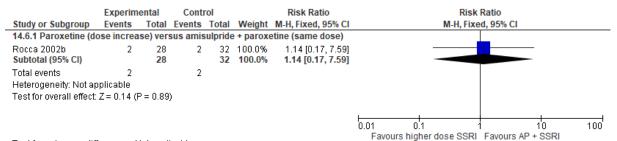
Test for subgroup differences: Not applicable

# Figure 111: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio		F	lisk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		М-Н,	Fixed, 95% CI	
14.5.1 Paroxetine (d	ose increa	se) ver	sus amis	ulpride	+ parox	etine (same dose)				
Rocca 2002b Subtotal (95% CI)	4	28 <b>28</b>	5	32 <b>32</b>	100.0% <b>100.0%</b>	0.91 [0.27, 3.08] <b>0.91 [0.27, 3.08]</b>				
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.88	5							
							L	0.1	1	 100

Test for subgroup differences: Not applicable

## Figure 112: Discontinuation due to side effects



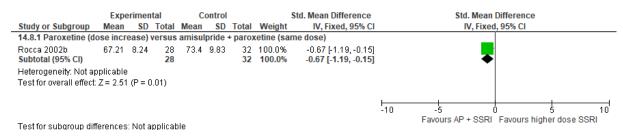
Test for subgroup differences: Not applicable

# Figure 113: Functional remission (GAF score ≥71)

	Experim	ental	Contr	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% CI	
14.7.1 Paroxetine (d	lose increa	se) ver	sus amis	sulpride	+ parox	etine (same dose)				
Rocca 2002b Subtotal (95% CI)	11	28 <b>28</b>	22	32 <b>32</b>	100.0% <b>100.0%</b>	0.57 [0.34, 0.96] <b>0.57 [0.34, 0.96]</b>		-	-	
Total events Heterogeneity: Not a Test for overall effect		<sup>o</sup> = 0.03	22							
							L0.01	0.1 Eavours AP + SSPI	1 10 Favours bigher dose	100

Test for subgroup differences: Not applicable

## Figure 114: Global functioning endpoint



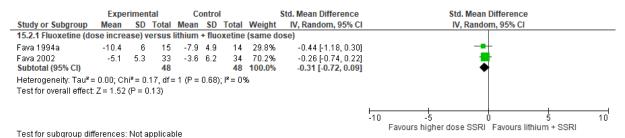
# Comparison 15. Increasing the dose of SSRI versus augmenting with lithium

# Figure 115: Depression symptomatology endpoint

	Expe	rimen	ntal	Co	ontro	1		Std. Mean Difference			Std. Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI			IV, Rando	m, 95% Cl		
15.1.1 Fluoxetine (d	ose increa	ase) v	/ersus	lithium	+ fluc	oxetine	(same do	ose)						
Fava 1994a	7.3	4.7	15	10.6	5.6	14	29.2%	-0.62 [-1.37, 0.13]				-		
Fava 2002 Subtotal (95% CI)	11	6.6	33 <b>48</b>	12.4	5.7	34 <b>48</b>	70.8% <b>100.0%</b>	-0.22 [-0.71, 0.26] - <b>0.34 [-0.75, 0.06]</b>			-	ŀ		
Heterogeneity: Tau <sup>2</sup> Test for overall effect	•		•	= 1 (P =	0.38)	; <b>I</b> ² = 0°	%							
									-10	-5	(	)	5	1(
										Favours highe	er dose SSRI	Favours lithiu	ım + SSRI	

Test for subgroup differences: Not applicable

# Figure 116: Depression symptomatology change score



# Figure 117: Remission (ITT)

#### Risk Ratio Control Risk Ratio Experimental Events Total Events Total Weight M-H, Random, 95% CI Study or Subgroup M-H, Random, 95% CI 15.3.1 Fluoxetine (dose increase) versus lithium + fluoxetine (same dose) 1.87 [0.72, 4.85] Fava 1994a 15 4 14 366% 8 1.80 [0.87, 3.72] 1.83 [1.03, 3.25] Fava 2002 14 33 8 34 63.4% Subtotal (95% CI) 100.0% 48 48 Total events 22 12 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.00, df = 1 (P = 0.95); I<sup>2</sup> = 0% Test for overall effect: Z = 2.05 (P = 0.04) 0.01 0.1 10 100

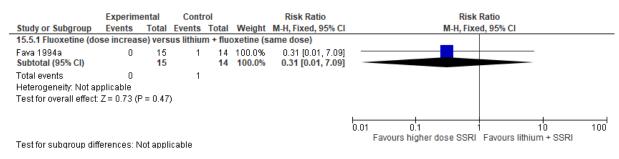
Favours lithium + SSRI Favours higher dose SSRI

Test for subgroup differences: Not applicable

# Figure 118: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	I M-H, Random, 95% CI
15.4.1 Fluoxetine (do	ose increas	se) vers	us lithiur	n + fluo	oxetine (s	same dose)	
Fava 1994a	2	15	2	14	35.5%	0.93 [0.15, 5.76]	<b>_</b>
Fava 2002 Subtotal (95% CI)	3	33 <b>48</b>	5	34 <b>48</b>	64.5% <b>100.0%</b>	0.62 [0.16, 2.38] 0.72 [0.24, 2.11]	
Total events Heterogeneity: Tau <sup>2</sup> : Test for overall effect				= 0.72)	); I² = 0%		
T	~ .						0.01 0.1 1 10 11 Favours higher dose SSRI Favours lithium + SSRI

# Figure 119: Discontinuation due to side effects



# Comparison 16. Switching to SSRI versus continuing with antidepressant

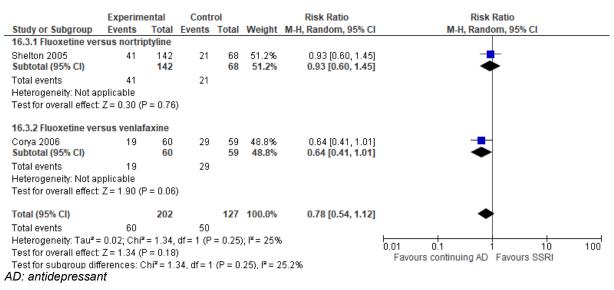
# Figure 120: Depression symptomatology change score

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
16.1.1 Fluoxetine ver	sus nort	riptyli	ne						
Shelton 2005 Subtotal (95% CI)	-8.51	8.34	142 <b>142</b>	-7.46	8.08	68 <mark>68</mark>	55.4% <b>55.4%</b>	-0.13 [-0.42, 0.16] -0.13 [-0.42, 0.16]	7
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z = 0.86	(P = 0	1.39)						
16.1.2 Fluoxetine ver	sus veni	afaxin	ie						
Corya 2006 Subtotal (95% CI)	-11.7	8.83	56 <b>56</b>	-13.73	8.91	58 58	44.6% <b>44.6%</b>	0.23 [-0.14, 0.60] 0.23 [-0.14, 0.60]	<b>.</b>
Heterogeneity: Not ap Test for overall effect:			1.23)						
Total (95% CI)			198			126	100.0%	0.03 [-0.31, 0.38]	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff AD: antidepresse	Z = 0.18 ferences:	(P = 0	1.86)						H H H H H -10 -5 0 5 10 Favours SSRI Favours continuing AD

# Figure 121: Remission (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
16.2.1 Fluoxetine ve	rsus nortrip	otyline					
Shelton 2005 Subtotal (95% CI)	19	142 <b>142</b>	12	68 <mark>68</mark>	55.6% <b>55.6%</b>	0.76 [0.39, 1.47] <b>0.76 [0.39, 1.47]</b>	
Total events	19		12				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.82 (F	P = 0.41)	)				
16.2.2 Fluoxetine ve	rsus venlaf	axine					
Corya 2006 Subtotal (95% CI)	10	60 <mark>60</mark>	13	59 <b>59</b>	44.4% <b>44.4%</b>	0.76 [0.36, 1.59] 0.76 [0.36, 1.59]	
Total events	10		13				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.74 (F	P = 0.46	)				
Total (95% CI)		202		127	100.0%	0.76 [0.46, 1.24]	•
Total events	29		25				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>z</sup>	= 0.00,	df = 1 (P	= 1.00)	; I² = 0%		0.01 0.1 1 10 100
Test for overall effect	: Z = 1.10 (F	P = 0.27	)				Favours continuing AD Favours SSRI
Test for subgroup dif		hi² = 0.1	00, df = 1	(P = 1.	00), I <sup>z</sup> = 0	%	rateare continuing to Tarears contr
AD: antidepressa	nt						

# Figure 122: Response (ITT)



# Figure 123: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
16.4.1 Fluoxetine ver	rsus nortri	ptyline						
Shelton 2005 Subtotal (95% CI)	28	142 142	8	68 68	48.1% <b>48.1%</b>	1.68 [0.81, 3.48] <b>1.68 [0.81, 3.48]</b>		
Total events	28		8					-
Heterogeneity: Not a	oplicable							
Test for overall effect	: Z = 1.39 (F	P = 0.17	)					
16.4.2 Fluoxetine ver	rsus venlat	faxine						
Corya 2006 Subtotal (95% Cl)	12	60 60	15	59 <b>59</b>	51.9% <b>51.9%</b>	0.79 [0.40, 1.54] <b>0.79 [0.40, 1.54]</b>		
Total events	12		15					
Heterogeneity: Not a	oplicable							
Test for overall effect	Z = 0.70 (F	P = 0.48	)					
Total (95% CI)		202		127	100.0%	1.13 [0.54, 2.38]		•
Total events	40		23					
Heterogeneity: Tau <sup>2</sup> =	= 0.16; Chi <sup>=</sup>	<sup>2</sup> = 2.27,	df = 1 (P	= 0.13)	); <b>I</b> ² = 56%	6		
Test for overall effect	•						0.01	0.1 1 10 100 Equation SSBL Equation continuing AD
Test for subgroup dif		⊃hi <b>²</b> = 2.	24. df = 1	(P = 0.	13), <b>i²</b> = 5	55.4%		Favours SSRI Favours continuing AD

# Figure 124: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
16.5.1 Fluoxetine ver	rsus nortri	ptyline					
Shelton 2005 Subtotal (95% CI)	4	142 <b>142</b>	2	68 <mark>68</mark>	64.1% <b>64.1%</b>	0.96 [0.18, 5.10] 0.96 [0.18, 5.10]	
Total events	4		2				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z=0.05 (F	P = 0.96	)				
16.5.2 Fluoxetine ver	sus venlat	faxine					
Corya 2006 Subtotal (95% CI)	3	60 60	1	59 <mark>59</mark>	35.9% <b>35.9%</b>	2.95 [0.32, 27.56] 2.95 [0.32, 27.56]	
Total events	3		1				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 0.95 (F	P = 0.34	)				
Total (95% CI)		202		127	100.0%	1.43 [0.38, 5.47]	
Total events	7		3				
Heterogeneity: Tau² =	= 0.00; Chi <sup>2</sup>	<sup>2</sup> = 0.63,	df = 1 (P	= 0.43)	); I² = 0%		0.01 0.1 1 10 100
Test for overall effect:	Z = 0.53 (F	° = 0.60	)				Favours SSRI Favours continuing AD
Test for subgroup diff	ferences: C	¢hi² = 0.	62, df = 1	(P = 0	43), I <sup>z</sup> = 0	1%	r avoirs contra r avoirs continuing Ab
AD: antidepressar	nt						

# Comparison 17. Switching to a different SSRI versus continuing same SSRI

# Figure 125: Remission (ITT)

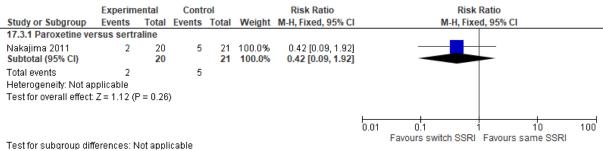
	Experim	ental	Cont	ol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
17.1.1 Paroxetine ve	ersus sertr	aline							
Nakajima 2011 Subtotal (95% CI)	12	20 <b>20</b>	3	21 <b>21</b>	100.0% <b>100.0%</b>	4.20 [1.39, 12.71] <b>4.20 [1.39, 12.71]</b>			
Total events Heterogeneity: Not a Test for overall effect	••	<sup>o</sup> = 0.01	3						
							L 0.01	0.1 1 10 Favours same SSRI Favours switch SS	100 RI

Test for subgroup differences: Not applicable

# Figure 126: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
17.2.1 Paroxetine ve	ersus sertr	aline						
Nakajima 2011 Subtotal (95% CI)	15	20 <b>20</b>	4	21 <b>21</b>	100.0% <b>100.0%</b>	3.94 [1.57, 9.85] <b>3.94 [1.57, 9.85]</b>		
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	4 3)					
Toot for subgroup di	~	1-41					0.01	0.1 1 10 100 Favours same SSRI Favours switch SSRI

# Figure 127: Discontinuation due to any reason

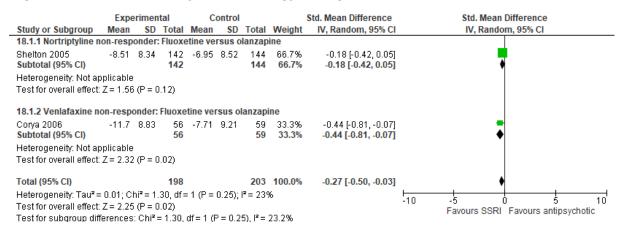


# Figure 128: Discontinuation due to side effects

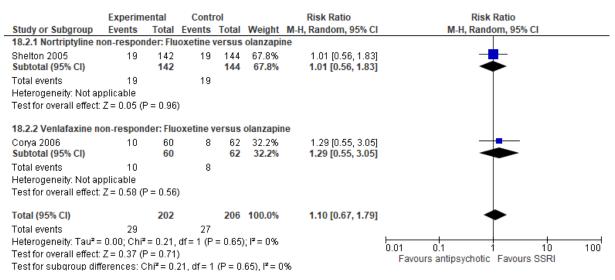
	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
17.4.1 Paroxetine ve	ersus sertr	aline					
Nakajima 2011 Subtotal (95% CI)	0	20 <b>20</b>	0	21 <b>21</b>		Not estimable Not estimable	
Total events Heterogeneity: Not a Test for overall effect		able	0				
Test for subgroup dif	forance: N	Jot anni	icable				0.01 0.1 1 10 100 Favours switch SSRI Favours same SSRI

# Comparison 18. Switching to SSRI versus antipsychotic

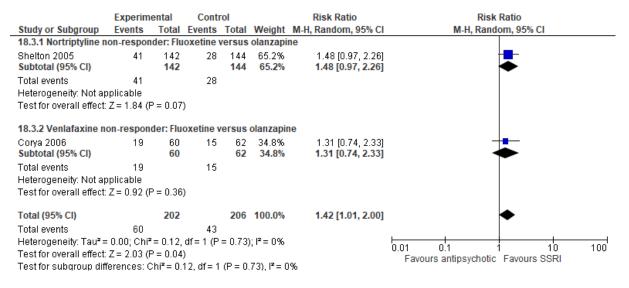
## Figure 129: Depression symptomatology change score



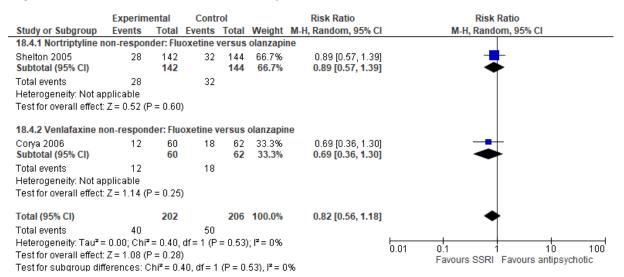
# Figure 130: Remission (ITT)



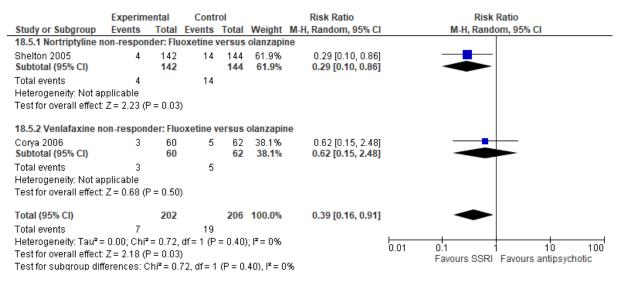
# Figure 131: Response (ITT)



#### Figure 132: Discontinuation due to any reason

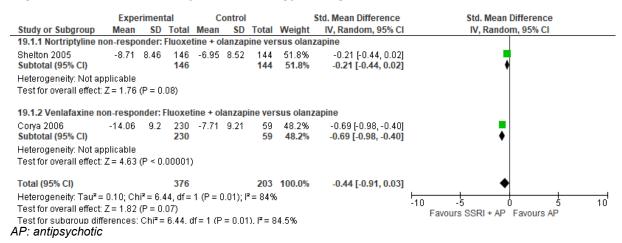


# Figure 133: Discontinuation due to side effects



# Comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychotic-only

#### Figure 134: Depression symptomatology change score



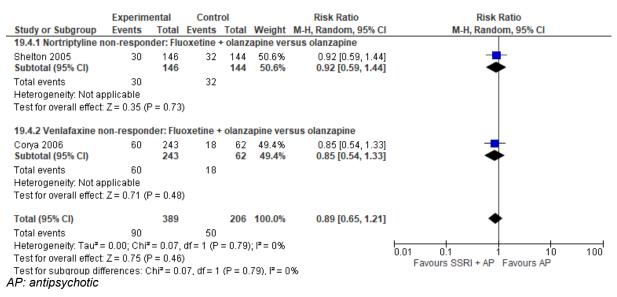
# Figure 135: Remission (ITT)

Experimental	Control		Risk Ratio	Risk Ratio
Events Tota	I Events Tota	l Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
on-responder: F	luoxetine + olan	zapine vei	rsus olanzapine	
25	19			
plicable				
Z = 0.93 (P = 0.3	85)			
on-responder: F	uoxetine + olan	zapine ver	sus olanzapine	
			2.20 [1.12, 4.33] <b>2.20 [1.12, 4.33]</b>	•
69	8			
plicable				
Z = 2.28 (P = 0.0	12)			
38	9 206	5 100.0%	1.63 [0.97, 2.73]	◆
94	27			
Z = 1.85 (P = 0.0	16)			0.01 0.1 1 10 100 Favours AP Favours SSRI + AP
	Events         Tota           on-responder: F         25         14i           25         14i         14i           25         plicable         2           Z = 0.93 (P = 0.3)         0n-responder: FI         69           69         24:         24:           69         24:         24:           69         24:         24:           69         24:         38:           91         0.04         (P = 0.0)           38:         94         0.04; Chi <sup>2</sup> = 1.4:           Z = 1.85 (P = 0.0)         1.4:         Z	Events         Total         Events         Total           on-responder: Fluoxetine + olan         25         146         19         144           25         146         19         144           25         19         146         144           25         19         19         146         144           25         19         19         146         144           25         19         19         144         146         144           25         19         146         144         146         144           25         19         146         144         146         144           25         19         144         146         144 <td>Events         Total         Events         Total         Weight           on-responder:         Fluoxetine + olanzapine velocitie         25         146         19         144         57.1%           25         146         19         144         57.1%         146         144         57.1%           25         19         146         144         57.1%         25         19           plicable         Z         0.93 (P = 0.35)         0</td> <td>Events         Total         Events         Total         Weight         M-H, Random, 95% CI           on-responder:         Fluoxetine + olanzapine         versus olanzapine           25         146         19         144         57.1%         1.30 [0.75, 2.25]           25         19         144         57.1%         1.30 [0.75, 2.25]         25           25         19         144         57.1%         1.30 [0.75, 2.25]         25           25         19         144         57.1%         1.30 [0.75, 2.25]         25           25         19         146         144         57.1%         1.30 [0.75, 2.25]           25         19         9         0.075, 2.25]         25         19           plicable         Z         20.3(P = 0.35)         0         0         0         0         1.33 [0.75, 2.25]         2.20 [1.12, 4.33]         243         62         42.9%         2.20 [1.12, 4.33]         69         8         8         8         1.63 [0.97, 2.73]         9         8         9         1.63 [0.97, 2.73]         94         27         0.04; Chi<sup>2</sup> = 1.43, df = 1 (P = 0.23); I<sup>2</sup> = 30%         1.63 [0.97, 2.73]         1.63 [0.97, 2.73]         1.63 [0.97, 2.73]         1.63 [0.97, 2.73]         1.63 [0.</td>	Events         Total         Events         Total         Weight           on-responder:         Fluoxetine + olanzapine velocitie         25         146         19         144         57.1%           25         146         19         144         57.1%         146         144         57.1%           25         19         146         144         57.1%         25         19           plicable         Z         0.93 (P = 0.35)         0	Events         Total         Events         Total         Weight         M-H, Random, 95% CI           on-responder:         Fluoxetine + olanzapine         versus olanzapine           25         146         19         144         57.1%         1.30 [0.75, 2.25]           25         19         144         57.1%         1.30 [0.75, 2.25]         25           25         19         144         57.1%         1.30 [0.75, 2.25]         25           25         19         144         57.1%         1.30 [0.75, 2.25]         25           25         19         146         144         57.1%         1.30 [0.75, 2.25]           25         19         9         0.075, 2.25]         25         19           plicable         Z         20.3(P = 0.35)         0         0         0         0         1.33 [0.75, 2.25]         2.20 [1.12, 4.33]         243         62         42.9%         2.20 [1.12, 4.33]         69         8         8         8         1.63 [0.97, 2.73]         9         8         9         1.63 [0.97, 2.73]         94         27         0.04; Chi <sup>2</sup> = 1.43, df = 1 (P = 0.23); I <sup>2</sup> = 30%         1.63 [0.97, 2.73]         1.63 [0.97, 2.73]         1.63 [0.97, 2.73]         1.63 [0.97, 2.73]         1.63 [0.

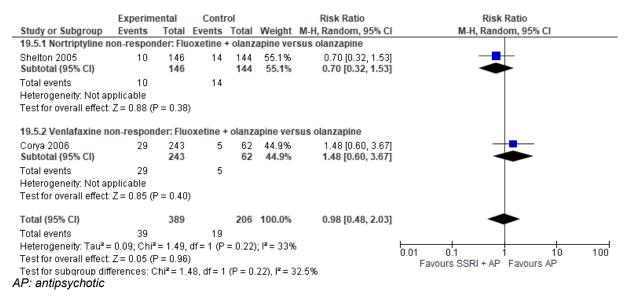
# Figure 136: Response (ITT)

	Experime	ntal	Contro	bl		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
19.3.1 Nortriptyline n	on-respond	er: Flu	oxetine +	olanz	apine vei	rsus olanzapine	
Shelton 2005 Subtotal (95% CI)	40	146 <b>146</b>	28	144 <b>144</b>	54.6% <b>54.6%</b>	1.41 [0.92, 2.15] <b>1.41 [0.92, 2.15]</b>	
Total events	40		28				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.58 (P	= 0.11)					
19.3.2 Venlafaxine no	on-respond	er: Fluc	xetine +	olanza	apine ver	sus olanzapine	
Corya 2006 Subtotal (95% CI)	100	243 <b>243</b>	15	62 62	45.4% <b>45.4%</b>	1.70 [1.07, 2.71] <b>1.70 [1.07, 2.71]</b>	
Total events	100		15				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 2.24 (P	= 0.03)					
Total (95% CI)		389		206	100.0%	1.53 [1.12, 2.10]	◆
Total events	140		43				
Heterogeneity: Tau² =	0.00; Chi <sup>2</sup> =	0.34,	df = 1 (P =	= 0.56)	; I² = 0%		
Test for overall effect:	Z = 2.68 (P	= 0.007	7)				Favours AP Favours SSRI + AP
Test for subgroup diff	erences: Ch	ni <b>r</b> = 0.3	34. df = 1	(P = 0.	56), I <sup>2</sup> = 0	1%	
AP: antipsychotic							

# Figure 137: Discontinuation due to any reason



#### Figure 138: Discontinuation due to side effects



#### Comparison 20. Augmenting with SSRI versus augmenting with lithium

#### Figure 139: Depression symptomatology change score Std. Mean Difference Experimental Control Std. Mean Difference IV, Fixed, 95% CI SD Total Weight IV, Fixed, 95% CI Study or Subgroup Mean SD Total Mean 20.1.1 Citalopram + imipramine Navarro 2019b -16.6 6.77 -12.25 8.65 100.0% -0.56 [-0.95, -0.16] 52 52 Subtotal (95% CI) 52 52 100.0% -0.56 [-0.95, -0.16] Heterogeneity: Not applicable Test for overall effect: Z = 2.78 (P = 0.005) -10 -5 10 ń Ġ Favours SSRI Favours lithium Test for subgroup differences: Not applicable

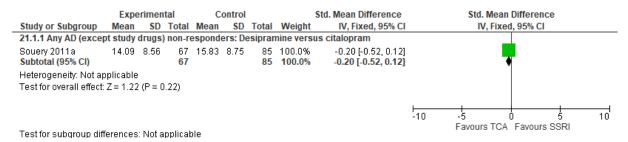
Depression in adults: Evidence review D FINAL (June 2022)

# Figure 140: Remission (ITT)

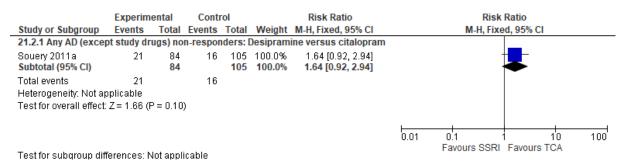
	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
20.2.1 Citalopram +	imipramine	9					
Navarro 2019b Subtotal (95% CI)	21	52 <b>52</b>	11	52 52	100.0% <b>100.0%</b>	1.91 [1.03, 3.55] <b>1.91 [1.03, 3.55]</b>	
Total events Heterogeneity: Not a Test for overall effect		° = 0.04	11 )				
Test for subgroup dif	fferences: N	lot appl	icable				0.01 0.1 1 10 100 Favours lithium Favours SSRI

# Comparison 21. Switching to TCA versus SSRI

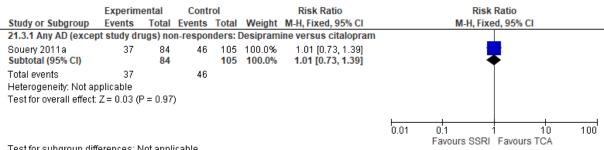
# Figure 141: Depression symptomatology endpoint



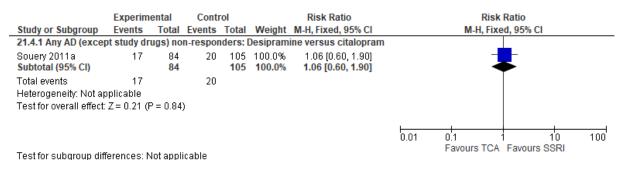
# Figure 142: Remission (ITT)



# Figure 143: Response (ITT)

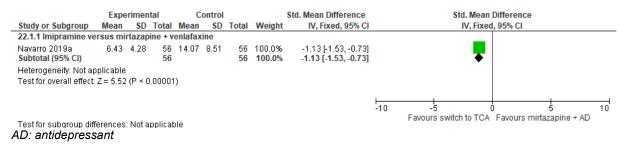


# Figure 144: Discontinuation due to any reason

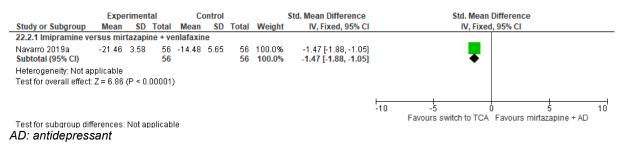


# Comparison 22. Switching to TCA versus augmenting with mirtazapine

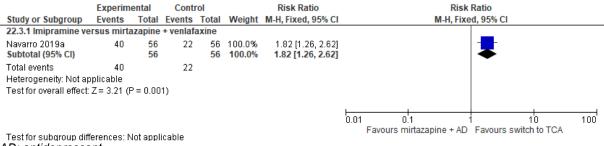
#### Figure 145: Depression symptomatology endpoint



## Figure 146: Depression symptomatology change score



## Figure 147: Remission (ITT)

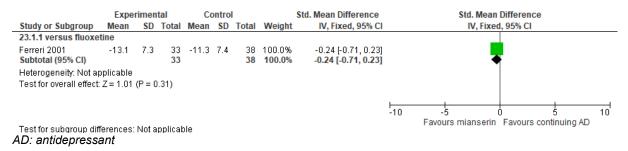


# Figure 148: Discontinuation due to any reason

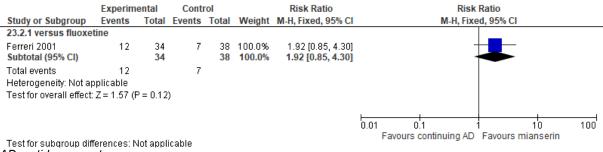
	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
22.4.1 Imipramine ve	ersus mirta	azapine	+ venlafa	axine			
Navarro 2019a Subtotal (95% CI)	5	56 <mark>56</mark>	2	56 <mark>56</mark>	100.0% <b>100.0%</b>	2.50 [0.51, 12.35] <b>2.50 [0.51, 12.35]</b>	
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.26	2				
Test for subgroup dift AD: antidepressa		lot appli	icable				0.01 0,1 1 10 100 Favours switch to TCA Favours mirtazapine + AD

# Comparison 23. Switching to mianserin versus continuing with antidepressant

#### Figure 149: Depression symptomatology change score

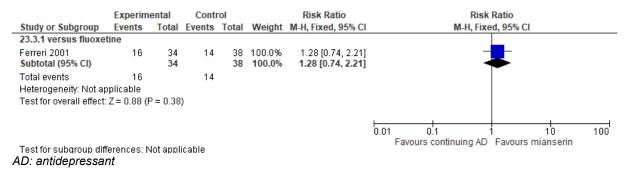


#### Figure 150: Remission (ITT)

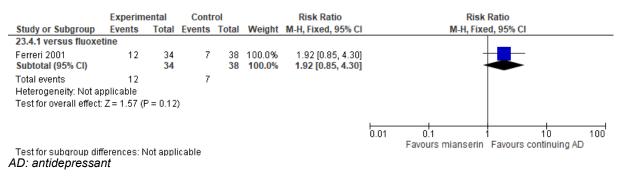


AD: antidepressant

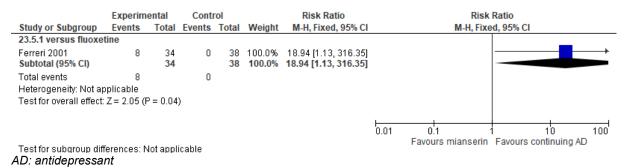
#### Figure 151: Response (ITT)



# Figure 152: Discontinuation due to any reason



# Figure 153: Discontinuation due to side effects



# Comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/placebo)

#### Figure 154: Depression symptomatology change score

	Exper	rimen	tal	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
24.1.1 Mianserin + f	uoxetine	versu	is fluo)	cetine					
Ferreri 2001 Subtotal (95% CI)	-16.1	7	32 <b>32</b>	-11.3	7.4	38 <b>38</b>	100.0% <b>100.0%</b>	-0.66 [-1.14, -0.17] - <b>0.66 [-1.14, -0.17]</b>	
Heterogeneity: Not a	pplicable								
Test for overall effect	: Z = 2.67	(P = 0	).008)						
									-10 -5 0 5
Test for subgroup dif	fferences:	Not a	pplicat	ole					Favours mianserin + AD Favours AD

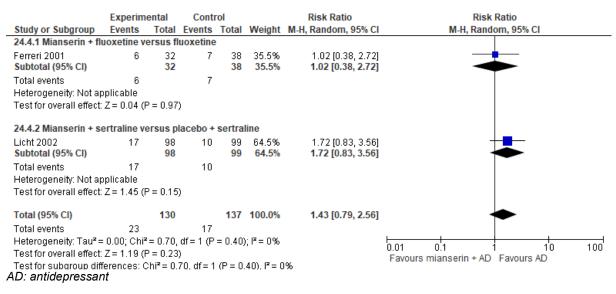
# Figure 155: Remission (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
24.2.1 Mianserin + fl	uoxetine ve	ersus fl	uoxetine				
Ferreri 2001	14	32	7	38	37.4%	2.38 [1.09, 5.16]	
Subtotal (95% CI)		32		38	37.4%	2.38 [1.09, 5.16]	$\bullet$
Total events	14		7				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 2.19 (P	= 0.03	)				
24.2.2 Mianserin + s	ertraline ve	rsus pl	lacebo +	sertra	line		
Licht 2002	43	98	37	99	62.6%	1.17 [0.84, 1.65]	
Subtotal (95% CI)		98		99	62.6%	1.17 [0.84, 1.65]	◆
Total events	43		37				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.93 (P	= 0.35	)				
Total (95% CI)		130		137	100.0%	1.53 [0.78, 2.99]	-
Total events	57		44				
Heterogeneity: Tau <sup>2</sup> =	= 0.16; Chi <sup>2</sup> :	= 2.69,	df = 1 (P	= 0.10)	); I <sup>2</sup> = 63%	)	0.01 0.1 1 10 100
Test for overall effect	: Z = 1.24 (P	= 0.22	)				Favours AD Favours mianserin + AD
Test for subaroup dif	ferences: C	hi <b>=</b> 2.0	66. df = 1	(P = 0.	10), <b>i²</b> = 6	i2.4%	
D: antidepressa	nt						

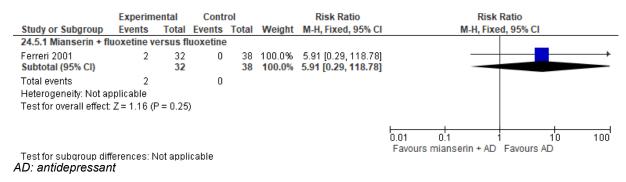
# Figure 156: Response (ITT)

	Experime	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	CI M-H, Random, 95% CI
24.3.1 Mianserin + fl	luoxetine ve	ersus fl	uoxetine	)			
Ferreri 2001 Subtotal (95% CI)	20	32 <b>32</b>	14	38 <b>38</b>	41.8% <b>41.8%</b>	1.70 [1.03, 2.78] 1.70 [1.03, 2.78]	
Total events	20		14				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 2.09 (F	P = 0.04)	)				
24.3.2 Mianserin + s	ertraline ve	ersus pl	acebo +	sertra	line		
Licht 2002 Subtotal (95% CI)	66	98 <mark>98</mark>	69	99 <b>99</b>	58.2% <b>58.2%</b>	0.97 [0.80, 1.17] 0.97 [0.80, 1.17]	
Total events	66		69				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.35 (F	P = 0.72)	)				
Total (95% CI)		130		137	100.0%	1.22 [0.70, 2.13]	8]
Total events	86		83				
Heterogeneity: Tau <sup>2</sup> :	= 0.13; Chi <sup>2</sup>	= 4.53,	df = 1 (P	= 0.03	); <b>I</b> ² = 78%	6	
Test for overall effect	: Z = 0.71 (F	e = 0.48	) .				0.01 0.1 1 10 100 Favours AD Favours mianserin + AD
Test for subgroup dit		:hi² = 4.3	33. df = 1	(P = 0	.04), I <sup>2</sup> = 7	6.9%	

# Figure 157: Discontinuation due to any reason

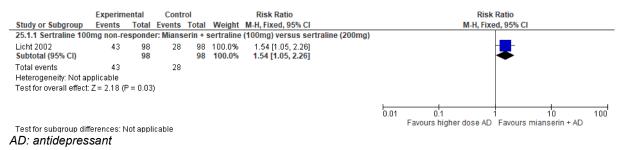


## Figure 158: Discontinuation due to side effects

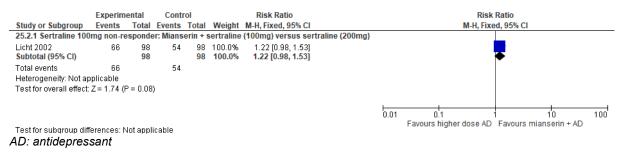


## Comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

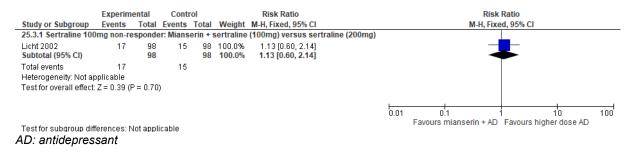
# Figure 159: Remission (ITT)



# Figure 160: Response (ITT)

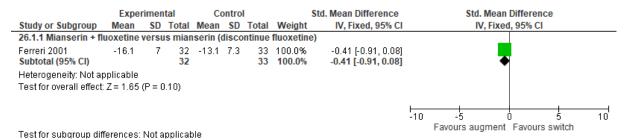


#### Figure 161: Discontinuation due to any reason

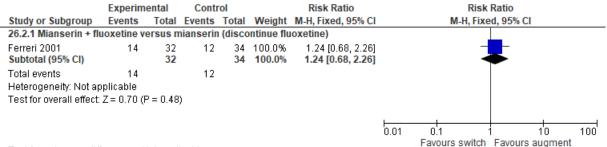


#### Comparison 26. Augmenting with mianserin versus switch to mianserin

#### Figure 162: Depression symptomatology change score



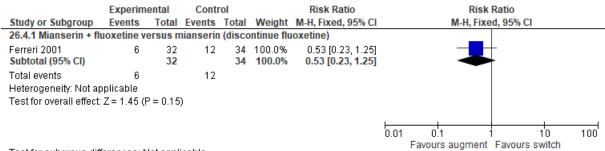
#### Figure 163: Remission (ITT)



# Figure 164: Response (ITT)

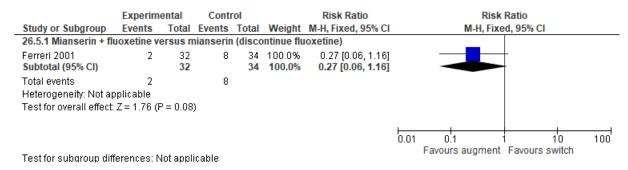
	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	CI M-H, Fixed, 95% CI	
26.3.1 Mianserin + f	luoxetine v	ersus n	nianserin	(disco	ontinue flu	ioxetine)		
Ferreri 2001 Subtotal (95% CI)	20	32 <b>32</b>	16	34 <b>34</b>	100.0% <b>100.0%</b>	1.33 [0.85, 2.08] <b>1.33 [0.85, 2.08]</b>	· ·	
Total events Heterogeneity: Not a Test for overall effect		P = 0.21	16 )					
Test for subaroup di	foroncoc: h	lot oppli	icabla				0.01 0.1 1 10 Favours switch Favours augment	100

## Figure 165: Discontinuation due to any reason



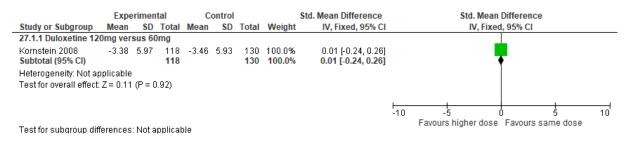
Test for subgroup differences: Not applicable

#### Figure 166: Discontinuation due to side effects

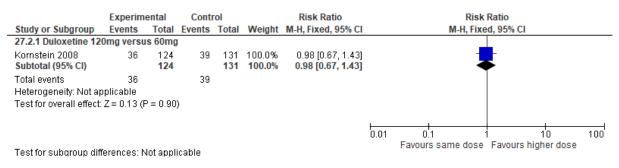


## Comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose

#### Figure 167: Depression symptomatology change score



# Figure 168: Remission (ITT)

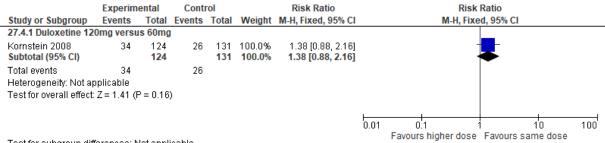


# Figure 169: Response (ITT)

	Experim	ental	Cont	rol		Risk Ratio		R	isk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, I	Fixed, 95% Cl	I	
27.3.1 Duloxetine 12	Omg versu	is 60mg	1								
Kornstein 2008 Subtotal (95% CI)	48	124 <b>124</b>	58	131 <b>131</b>	100.0% <b>100.0%</b>	0.87 [0.65, 1.17] 0.87 [0.65, 1.17]			•		
Total events Heterogeneity: Not a Test for overall effect		P = 0.37	58								
							⊢ 0.01	0.1 Favours same do		10 bigher dose	100

Test for subgroup differences: Not applicable

# Figure 170: Discontinuation due to any reason



Test for subgroup differences: Not applicable

# Figure 171: Discontinuation due to side effects

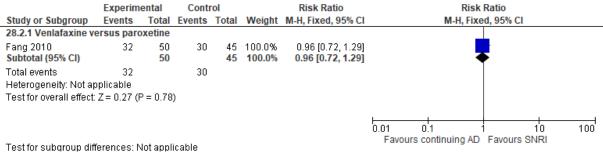
	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
27.5.1 Duloxetine 12	20mg versu	is 60mg	1					
Kornstein 2008 Subtotal (95% CI)	7	124 <b>124</b>	6	131 <b>131</b>	100.0% <b>100.0%</b>	1.23 [0.43, 3.57] <b>1.23 [0.43, 3.57]</b>		
Total events Heterogeneity: Not a	7 pplicable		6					
Test for overall effect	••	P = 0.70	)					
							L 0.01	0.1 1 10 100 Favours higher dose
Test for subaroun di	fferences: N	Jot anni	icahle					ravours nigher uose i ravours same dose

# Comparison 28. Switching to SNRI versus continuing with antidepressant

# Figure 172: Remission (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	
28.1.1 Venlafaxine ve	ersus paro	xetine						
Fang 2010 Subtotal (95% CI)	21	50 <mark>50</mark>	21	45 <b>45</b>	100.0% <b>100.0%</b>	0.90 [0.57, 1.41] 0.90 [0.57, 1.41]	<b>•</b>	
Total events Heterogeneity: Not ar Test for overall effect:	•	° = 0.65	21					
Test for subgroup diff AD: antidepressan		lot appli	cable				0.01 0.1 1 1 Favours continuing AD Favours SN	0 100 RI

# Figure 173: Response (ITT)



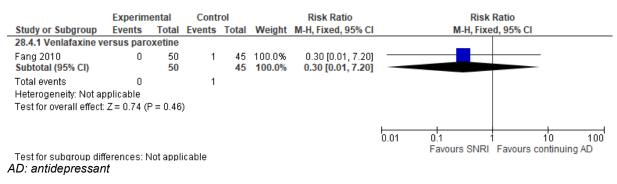
Test for subgroup differences: Not applicable AD: antidepressant

# Figure 174: Discontinuation due to any reason

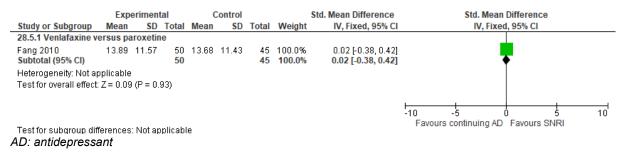
	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI	
28.3.1 Venlafaxine v	ersus paro	oxetine							
Fang 2010 Subtotal (95% CI)	9	50 <b>50</b>	8	45 <b>45</b>	100.0% <b>100.0%</b>	1.01 [0.43, 2.40] 1.01 [0.43, 2.40]		-	
Total events Heterogeneity: Not a Test for overall effect	• •	P = 0.98	8						
Test for subgroup di	fferences: N	lot appl	icable				L	0.1 1 Favours SNRI Favours	10 100 continuing AD

Test for subgroup differences: Not applicable AD: antidepressant

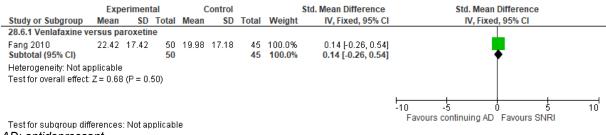
# Figure 175: Discontinuation due to side effects



# Figure 176: Quality of life physical component score (PCS) change score

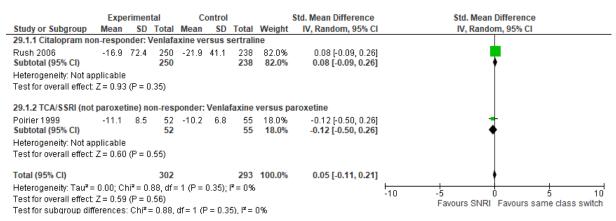


#### Figure 177: Quality of life mental component score (MCS) change score



# Comparison 29. Switching to SNRI versus switching to another antidepressant from same class

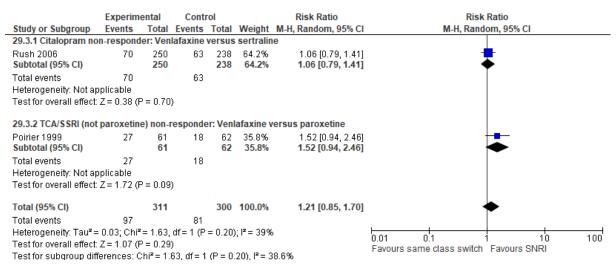
#### Figure 178: Depression symptomatology change score



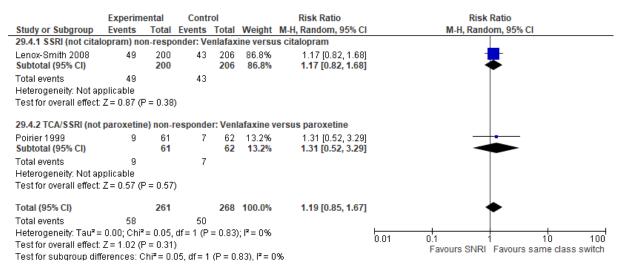
# Figure 179: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
29.2.1 Citalopram no	n-respond	er: Ven	lafaxine	versus	sertralin	le	
Rush 2006 Subtotal (95% CI)	62	250 <b>250</b>	63	238 <b>238</b>	37.6% <b>37.6%</b>	0.94 [0.69, 1.27] <b>0.94 [0.69, 1.27]</b>	*
Total events	62		63				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.42 (F	P = 0.67)	)				
29.2.2 SSRI (not cital	opram) no	n-respo	onder: Ve	enlafax	ine versu	is citalopram	
Lenox-Smith 2008 Subtotal (95% CI)	61	200 200	33	206 <b>206</b>	35.3% <b>35.3%</b>	1.90 [1.31, 2.77] 1.90 [1.31, 2.77]	
Total events	61		33				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 3.35 (F	P = 0.00	08)				
29.2.3 TCA/SSRI (not	paroxetin	e) non-r	esponde	er: Venl	afaxine v	ersus paroxetine	
Poirier 1999 Subtotal (95% CI)	22	61 61	11	62 62		2.03 [1.08, 3.82] <b>2.03 [1.08, 3.82]</b>	<b>—</b>
Total events	22	01	11	υz	27.170	2.03 [1.00, 5.02]	$\bullet$
Heterogeneity: Not ap							
Test for overall effect:		P = 0.03	)				
		0.00	, ,				
Total (95% CI)		511		506	100.0%	1.48 [0.86, 2.56]	◆
Total events	145		107				
Heterogeneity: Tau² =	0.18; Chi²	= 10.40	), df = 2 (ł	P = 0.0	06); I <b>²</b> = 8	1%	0.01 0.1 1 10 100
Test for overall effect:	Z = 1.42 (F	P = 0.16	)				Favours same class switch Favours SNRI
Test for subgroup diff	'erences: C	:hi² = 10	).37, df=	2 (P = )	0.006), <b>i</b> ²:	= 80.7%	

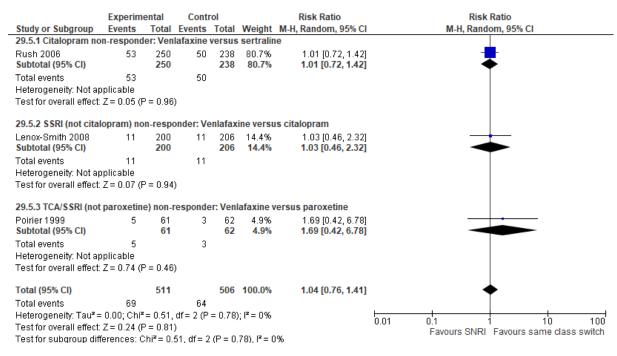
# Figure 180: Response (ITT)



# Figure 181: Discontinuation due to any reason

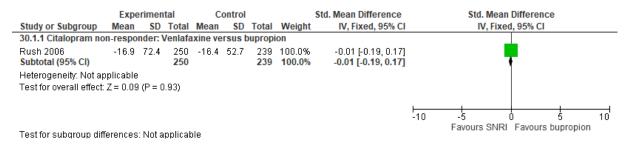


# Figure 182: Discontinuation due to side effects

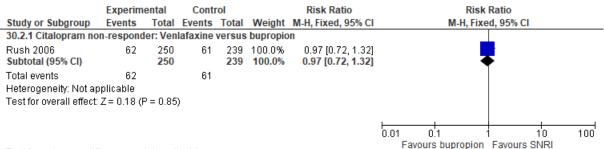


# Comparison 30. Switching to SNRI versus switching to bupropion

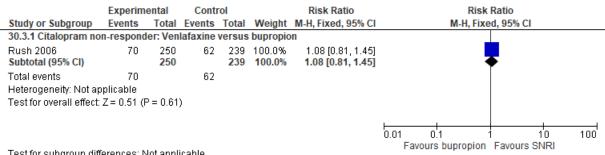
# Figure 183: Depression symptomatology change score



## Figure 184: Remission (ITT)

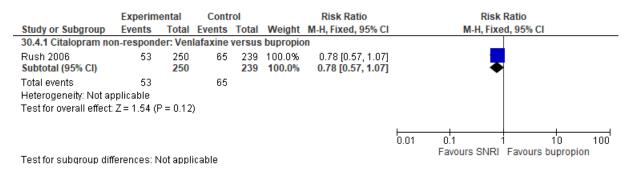


# Figure 185: Response (ITT)



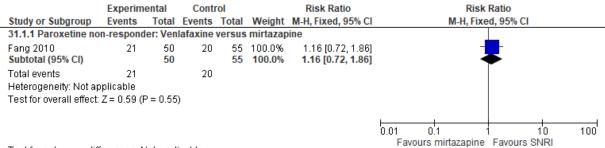
Test for subgroup differences: Not applicable

# Figure 186: Discontinuation due to side effects



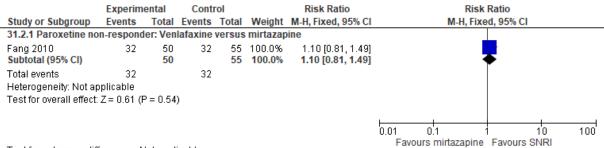
## Comparison 31. Switching to SNRI versus switching to mirtazapine

# Figure 187: Remission (ITT)

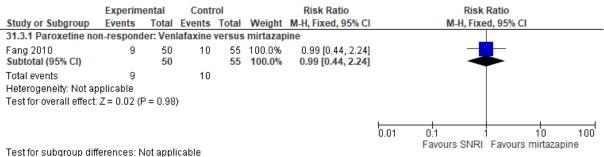


Test for subgroup differences: Not applicable

# Figure 188: Response (ITT)



# Figure 189: Discontinuation due to any reason

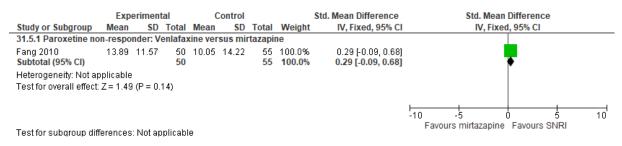


# Figure 190: Discontinuation due to side effects

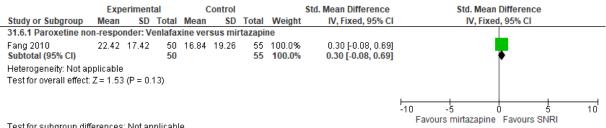
	Experim	ental	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% Cl	
31.4.1 Paroxetine no	on-respond	ler: Ven	lafaxine	versus	mirtaza	pine				
Fang 2010 Subtotal (95% CI)	0	50 <b>50</b>	0	55 <b>55</b>		Not estimable Not estimable				
Total events Heterogeneity: Not a Test for overall effect		able	0							
Test for subgroup dif	~ k	1-1					H 0.01	0.1 Favours SNRI	1 10 Favours mirtazapine	100 9

Test for subgroup differences: Not applicable

# Figure 191: Quality of life physical component score (PCS) change score

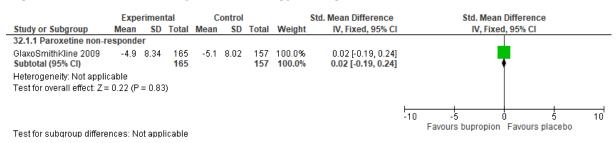


# Figure 192: Quality of life mental component score (MCS) change score

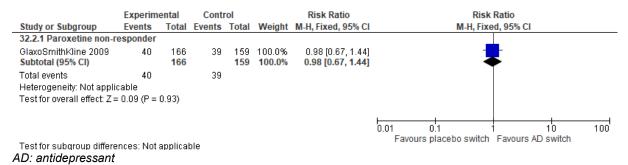


# Comparison 32. Switching to bupropion versus placebo

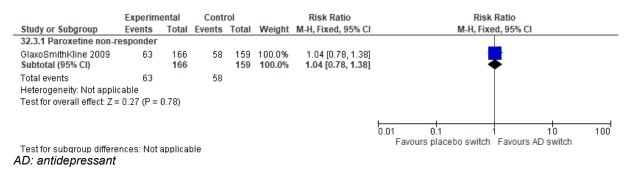
#### Figure 193: Depression symptomatology change score



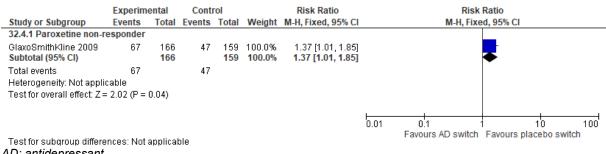
# Figure 194: Remission (ITT)



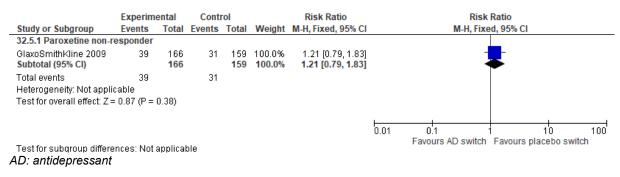
# Figure 195: Response (ITT)



#### Figure 196: Discontinuation due to any reason

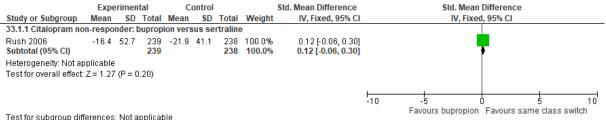


# Figure 197: Discontinuation due to side effects

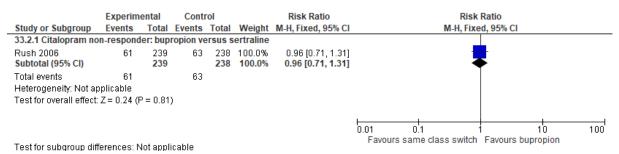


#### Comparison 33. Switching to bupropion versus switching to another antidepressant from same class

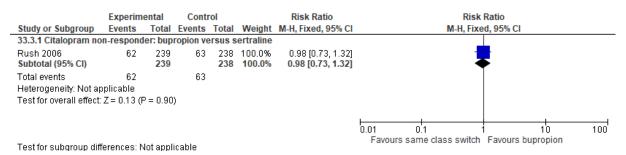
### Figure 198: Depression symptomatology change score



# Figure 199: Remission (ITT)



# Figure 200: Response (ITT)



# Figure 201: Discontinuation due to side effects

	Experime	ental	Contr	ol		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl		
33.4.1 Citalopram no	on-respond	e <mark>r: bup</mark> i	ropion ve	ersus s	ertraline						
Rush 2006 Subtotal (95% CI)	65	239 <b>239</b>	50	238 <b>238</b>	100.0% <b>100.0%</b>	1.29 [0.94, 1.79] <b>1.29 [0.94, 1.79]</b>			•		
Total events Heterogeneity: Not ap Test for overall effect:	•	9 = 0.12)	50 )								
Test for subgroup dif	ferences: N	ot appli	icable				L 0.01	0.1 Favours bupropion	Favours sar	10 me class	100 switch

# Comparison 34. Augmenting with bupropion versus placebo

# Figure 202: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
34.1.1 Augmenting	SSRI							
Gulrez 2012 Subtotal (95% CI)	18	30 <b>30</b>	7	30 <b>30</b>	100.0% <b>100.0%</b>	2.57 [1.26, 5.24] 2.57 [1.26, 5.24]		
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	9)					
Test for subgroup di	fferences: N	Vot appl	icable				L	0.1 1 10 100 Favours placebo Favours bupropion

# Comparison 35. Augmenting with bupropion versus switching to bupropion

# Figure 203: Remission (ITT)

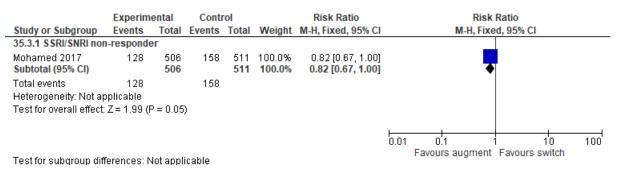
	Experim	ental	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% CI	
35.1.1 SSRI/SNRI no	n-responde	er								
Mohamed 2017 Subtotal (95% CI)	136	506 <mark>506</mark>	114	511 <b>511</b>	100.0% <b>100.0%</b>	1.20 [0.97, 1.50] <b>1.20 [0.97, 1.50]</b>			•	
Total events Heterogeneity: Not a Test for overall effec		° = 0.09	114 )							
Test for subgroup di	fferences: N	lot appl	icable				L 0.01	0.1 1 Favours switch	10 Favours aug	

# Figure 204: Response (ITT)

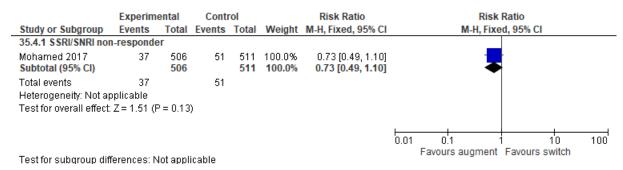
	Experim	ental	Contr	rol		Risk Ratio		Ri	sk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, F	ixed, 95% (	CI	
35.2.1 SSRI/SNRI nor	-responde	er									
Mohamed 2017 Subtotal (95% CI)	332	506 <b>506</b>	319	511 <b>511</b>	100.0% <b>100.0%</b>	1.05 [0.96, 1.15] <b>1.05 [0.96, 1.15]</b>			•		
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.29	319 )								
							L	0.1 Favours swit	1	10	100

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# Figure 205: Discontinuation due to any reason

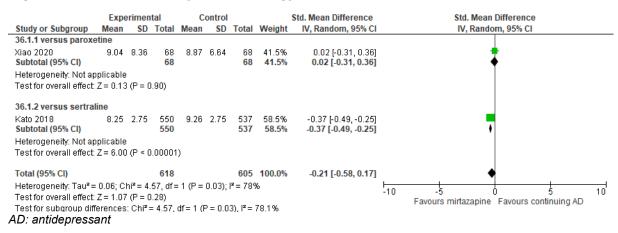


## Figure 206: Discontinuation due to side effects



#### Comparison 36. Switching to mirtazapine versus continuing with antidepressant

#### Figure 207: Depression symptomatology endpoint

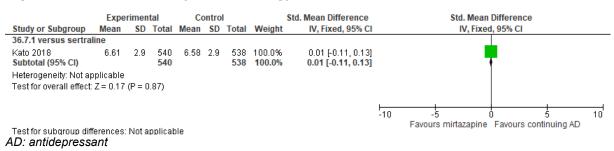


#### Figure 208: Depression symptomatology change score

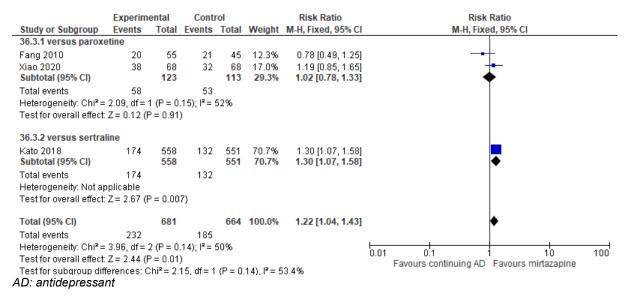
	Exper	riment	al	Co	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
36.2.1 versus parox	etine								
Xiao 2020 Subtotal (95% CI)	-13.65	7.5	68 68	-12.24	7.32	68 68	100.0% <b>100.0%</b>	-0.19 [-0.53, 0.15] - <b>0.19 [-0.53, 0.15]</b>	<b>→</b>
Heterogeneity: Not a Test for overall effect	• •	(P = 0.1	27)						-10 -5 0 5 10
Test for subgroup dir AD: antidepress		Not ap	plicab	le					Favours mirtazapine Favours continuing AD

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# Figure 209: Depression symptomatology at 4-month follow-up



# Figure 210: Remission (ITT)

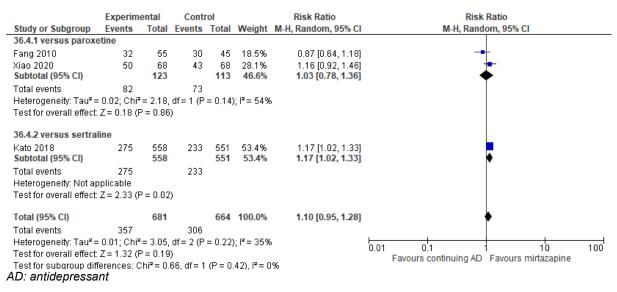


#### Figure 211: Remission (ITT) at 4-month follow-up

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
36.8.1 versus sertra	line						
Kato 2018 Subtotal (95% CI)	262	558 <b>558</b>	245	551 <b>551</b>	100.0% <b>100.0%</b>	1.06 [0.93, 1.20] <b>1.06 [0.93, 1.20]</b>	<b>•</b>
Total events Heterogeneity: Not a Test for overall effect	••	P = 0.41	245 )				
Test for subgroup di	fferences: N	Vot appl	icable				0.01 0.1 1 10 100 Favours continuing AD Favours mirtazapine

Test for subgroup differences: Not applicable AD: antidepressant

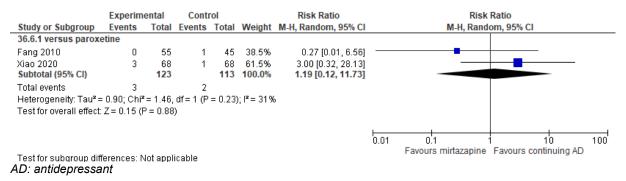
# Figure 212: Response (ITT)



#### Figure 213: Discontinuation due to any reason

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
36.5.1 versus paroxe		Total	Lionto	Total	Toight	in rightandoni joon or	in the trained of the second s
Fang 2010	10	55	8	45	30.3%	1.02 [0.44, 2.37]	<b>_</b>
Xiao 2020	12	68	12	68	40.7%	1.00 [0.48, 2.07]	<b>_</b>
Subtotal (95% CI)		123		113	71.0%	1.01 [0.58, 1.75]	<b>•</b>
Total events	22		20				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.00,	df = 1 (P :	= 0.97)	; I² = 0%		
Test for overall effect:	Z = 0.03 (F	P = 0.97	)				
36.5.2 versus sertral Kato 2018 Subtotal (95% CI)	8	558 <mark>558</mark>	14	551 551	29.0% <b>29.0%</b>	0.56 [0.24, 1.33] <b>0.56 [0.24, 1.33]</b>	-
Total events	8		14				
Heterogeneity: Not ap							
Test for overall effect:	Z=1.30 (F	° = 0.19	)				
Total (95% CI)		681		664	100.0%	0.85 [0.54, 1.36]	•
Total events	30		34				
Heterogeneity: Tau <sup>2</sup> =	•			= 0.53)	i; l* = 0%		0.01 0.1 1 10 100
Test for overall effect:				/D = 0	261 18 - 1	0.00	Favours mirtazapine Favours continuing AD
Test for subgroup diff AD: antidepressa		-m = 1.	20, ul = 1	(F = 0.	20), I" = 1	9.070	
AB. anacpicssa							

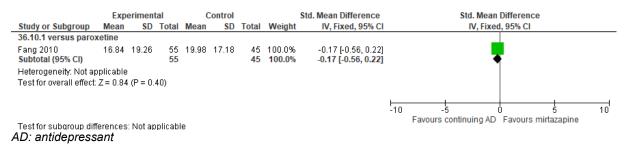
## Figure 214: Discontinuation due to side effects



#### Std. Mean Difference Experimental Control Std. Mean Difference IV, Fixed, 95% CI SD Total Weight Mean Study or Subgroup SD Total Mean IV. Fixed, 95% CI 36.9.1 versus paroxetine -0.28 [-0.67, 0.12] -0.28 [-0.67, 0.12] Fang 2010 Subtotal (95% CI) 10.05 14.22 55 13.68 11.43 45 100.0% 45 100.0% 55 Heterogeneity: Not applicable Test for overall effect: Z = 1.37 (P = 0.17) ⊢ -10 10 -6 ά ė Favours continuing AD Favours mirtazapine Test for subgroup differences: Not applicable AD: antidepressant

# Figure 215: Quality of life physical component score (PCS) change score

# Figure 216: Quality of life mental component score (MCS) change score

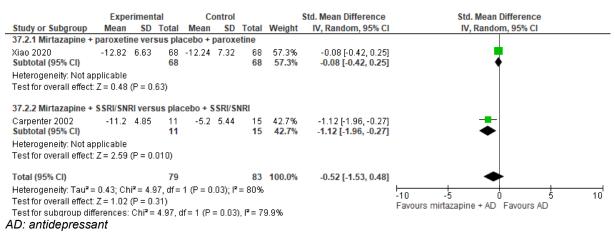


# Comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/placebo)

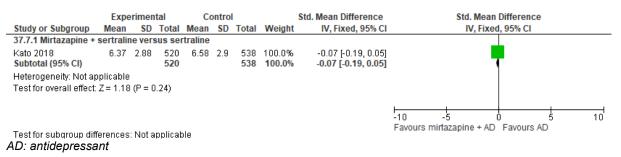
## Figure 217: Depression symptomatology endpoint

Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI           37.1.1         Mitazapine + paroxetine versus placebo + paroxetine         -         -0.14 [-0.48, 0.20]         -0.14 [-0.48, 0.20]           Subtotal (95% CI)         68         68         18.5%         -0.14 [-0.48, 0.20]         -0.14 [-0.48, 0.20]           37.1.2         Mitazapine + SSRI/SNRI versus placebo + SSRI/SNRI         -0.38 [-1.64, -0.01]         -0.14 [-0.33, 0.05]           Carpenter 2002         10.7         7         11         17.3         8.2         15         4.4%         -0.83 [-1.64, -0.01]           Kessler 2018a/2018b         18         12.3         214         19.7         2.4         217         33.7%         -0.14 [-0.33, 0.05]           Subtotal (95% CI)         225         232         38.1%         -0.36 [-1.00, 0.27]         -0.36 [-1.00, 0.27]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.48, -0.24]         -0.36 [-0.44, -0.09]         -10         -5         0         5         10           Test for overall effect Z = 5.82 (P < 0.0001) <th></th> <th>Expe</th> <th>erimen</th> <th>tal</th> <th>С</th> <th>ontrol</th> <th></th> <th></th> <th>Std. Mean Difference</th> <th>Std. Mean Difference</th>		Expe	erimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Xiao 2020 <b>7.97</b> 6.22 68 8.87 6.64 68 18.5% <b>9.014</b> [-0.48, 0.20] Heterogeneity: Not applicable Test for overall effect: $Z = 0.81$ (P = 0.42) <b>37.1.2 Mirtazapine + SSR/SNRI versus placebo + SSR/SNRI</b> Carpenter 2002 10.7 7 11 17.3 8.2 15 4.4% Carpenter 2002 10.7 7 11 17.3 8.2 15 4.4% <b>9.036</b> [-1.64, -0.01] Kessler 2018a/2018b 18 12.3 214 19.7 12.4 217 33.7% <b>9.014</b> [-0.33, 0.05] <b>9.036</b> [-1.00, 0.27] Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); I <sup>2</sup> = 62% Test for overall effect: $Z = 1.12$ (P = 0.26) <b>37.1.3 Mirtazapine + sertraline versus sertraline</b> Kato 2018 8.27 2.75 527 9.26 2.75 537 43.4% <b>9.036</b> [-0.48, -0.24] <b>9.036</b> [-0.44, -0.09] Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); I <sup>2</sup> = 52% Test for overall effect: $Z = 2.90$ (P = 0.004) Test for overall effect: $Z = 2.90$ (P = 0.004) Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), I <sup>2</sup> = 0%	Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Subtotal (95% CI)       68       68       18.5%       -0.14 [-0.48, 0.20]         Heterogeneity: Not applicable       Test for overall effect: $Z = 0.81$ ( $P = 0.42$ )       -0.38 [-1.64, -0.01]         37.1.2 Mirtazapine + SSRI/SNRI versus placebo + SSRI/SNRI       -0.83 [-1.64, -0.01]         Carpenter 2002       10.7       7       11       17.3       8.2       15       4.4%       -0.83 [-1.64, -0.01]         Kessler 2018a/2018b       18       12.3       214       19.7       12.4       217       33.7%       -0.14 [-0.33, 0.05]         Subtotal (95% CI)       225       232       38.1%       -0.36 [-1.00, 0.27]       -0.36 [-1.00, 0.27]         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); I <sup>2</sup> = 62%       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Subtotal (95% CI)       527       527       537       43.4%       -0.36 [-0.48, -0.24]         Subtotal (95% CI)       527       537       43.4%       -0.36 [-0.48, -0.24]       -0.36 [-0.44, -0.09]         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); I <sup>2</sup> = 52%       -0.26 [-0.44, -0.09]       -10       -5       0       5       10         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.48), I <sup>2</sup> = 0%       -0.26 [-0.44, -0.09]       -10       -5       0       5	37.1.1 Mirtazapine + pa	roxetine	e versu	is plac	ebo + p	aroxe	tine			
Heterogeneity: Not applicable Test for overall effect: $Z = 0.81$ (P = 0.42) <b>37.1.2 Mirtazapine + SSRI/SNRI versus placebo + SSRI/SNRI</b> Carpenter 2002 10.7 7 11 17.3 8.2 15 4.4% -0.83 [-1.64, -0.01] Kessler 2018a/2018b 18 12.3 214 19.7 12.4 217 33.7% -0.14 [-0.33, 0.05] Subtotal (95% Cl) 225 232 38.1% -0.36 [-1.00, 0.27] Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); l <sup>2</sup> = 62% Test for overall effect: $Z = 1.12$ (P = 0.26) <b>37.1.3 Mirtazapine + sertraline versus sertraline</b> Kato 2018 8.27 2.75 527 9.26 2.75 537 43.4% -0.36 [-0.48, -0.24] Subtotal (95% Cl) 527 537 43.4% -0.36 [-0.48, -0.24] Heterogeneity: Not applicable Test for overall effect: $Z = 5.82$ (P < 0.00001) <b>Total (95% Cl) 820 837 100.0%</b> -0.26 [-0.44, -0.09] Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); l <sup>2</sup> = 52% Test for overall effect: $Z = 2.90$ (P = 0.004) Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), l <sup>2</sup> = 0%	Xiao 2020	7.97	6.22		8.87	6.64		18.5%	-0.14 [-0.48, 0.20]	
Test for overall effect: $Z = 0.81 (P = 0.42)$ <b>37.1.2 Mirtazapine + SSRI/SNRI versus placebo + SSRI/SNRI</b> Carpenter 2002 10.7 7 11 17.3 8.2 15 4.4% -0.83 [1.64, -0.01] Kessler 2018a/2018b 18 12.3 214 19.7 12.4 217 33.7% -0.14 [-0.33, 0.05] Subtotal (95% CI) 225 232 38.1% -0.36 [-1.00, 0.27] Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); l <sup>2</sup> = 62% Test for overall effect: $Z = 1.12 (P = 0.26)$ <b>37.1.3 Mirtazapine + sertraline versus sertraline</b> Kato 2018 8.27 2.75 527 9.26 2.75 537 43.4% -0.36 [-0.48, -0.24] Heterogeneity: Not applicable Test for overall effect: $Z = 5.82 (P < 0.00001)$ <b>Total (95% CI)</b> 820 837 100.0% -0.26 [-0.44, -0.09] Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); l <sup>2</sup> = 52% Test for overall effect: $Z = 2.90 (P = 0.004)$ Test for overall effect: $Z = 2.90 (P = 0.004)$ Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), l <sup>2</sup> = 0%	Subtotal (95% CI)			68			68	18.5%	-0.14 [-0.48, 0.20]	•
37.1.2 Mirtazapine + SSRI/SNRI versus placebo + SSRI/SNRI         Carpenter 2002       10.7       7       11       17.3       8.2       15       4.4%       -0.83 [-1.64, -0.01]         Kessler 2018a/2018b       18       12.3       214       19.7       12.4       217       33.7%       -0.14 [-0.33, 0.05]         Subtoal (95% CI)       225       232       38.1%       -0.36 [-1.00, 0.27]         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); l <sup>2</sup> = 62%       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Test for overall effect: Z = 1.12 (P = 0.26)       527       537       43.4%       -0.36 [-0.48, -0.24]         Subtoal (95% CI)       527       537       43.4%       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Heterogeneity: Not applicable       527       537       43.4%       -0.36 [-0.44, -0.09]         Test for overall effect: Z = 5.82 (P < 0.00001)	Heterogeneity: Not appli	cable								
Carpenter 2002       10.7       7       11       17.3       8.2       15       4.4%       -0.83 [-1.64, -0.01]         Kessler 2018a/2018b       18       12.3       214       19.7       12.4       217       33.7%       -0.14 [-0.33, 0.05]         Subtotal (95% CI)       225       232       38.1%       -0.36 [-1.00, 0.27]       -0.36 [-1.00, 0.27]         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); I <sup>2</sup> = 62%       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Subtotal (95% CI)       527       537       43.4%       -0.36 [-0.48, -0.24]         Subtotal (95% CI)       527       537       43.4%       -0.36 [-0.48, -0.24]         Heterogeneity: Not applicable       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Heterogeneity: Not applicable       -0.36 [-0.44, -0.09]       -0.26 [-0.44, -0.09]         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); I <sup>2</sup> = 62%       -0.26 [-0.44, -0.09]       -10         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); I <sup>2</sup> = 52%       -0.26 [-0.44, -0.09]       -10         Test for overall effect: Z = 2.90 (P = 0.004)       -5       0       5       10         Favours AD       Favours AD       Favours AD       -10       -5       0	Test for overall effect: Z =	= 0.81 (F	P = 0.43	2)						
Kessler 2018a/2018b       18       12.3       214       19.7       12.4       217       33.7% $-0.14 [-0.33, 0.05]$ Subtotal (95% Cl)       225       232       38.1% $-0.36 [-1.00, 0.27]$ Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); P = 62% $-0.36 [-1.00, 0.27]$ Test for overall effect: Z = 1.12 (P = 0.26) $-0.36 [-0.48, -0.24]$ Subtotal (95% Cl)       527       537       43.4% $-0.36 [-0.48, -0.24]$ Subtotal (95% Cl)       527       537       43.4% $-0.36 [-0.48, -0.24]$ Heterogeneity: Not applicable       Test for overall effect: Z = 5.82 (P < 0.00001) $-0.26 [-0.44, -0.09]$ Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); P = 52% $-0.26 [-0.44, -0.09]$ $-10$ $-5$ $0$ $5$ $10$ Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); P = 52%       Test for overall effect: Z = 2.90 (P = 0.004)       Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), P = 0% $-0.26 [-0.44, -0.09]$ $-10$ $-5$ $0$ $5$ $10$ Favours AD       Favours AD       Favours AD       Favours AD       Favours AD	37.1.2 Mirtazapine + SS	RI/SNRI	versu	s place	bo + S	SRI/SN	RI			
Subtotal (95% Cl)       225       232       38.1%       -0.36 [-1.00, 0.27]         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); l <sup>2</sup> = 62%       -0.36 [-1.00, 0.27]         Test for overall effect: Z = 1.12 (P = 0.26)       -0.36 [-0.48, -0.24] <b>37.1.3 Mirtazapine + sertraline versus sertraline</b> Kato 2018       8.27       2.75       527       9.26       2.75       537       43.4%       -0.36 [-0.48, -0.24]         Subtotal (95% Cl)       527       537       43.4%       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Heterogeneity: Not applicable       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Test for overall effect: Z = 5.82 (P < 0.00001)	Carpenter 2002	10.7	7	11	17.3	8.2	15	4.4%	-0.83 [-1.64, -0.01]	
Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.61, df = 1 (P = 0.11); I <sup>2</sup> = 62% Test for overall effect: Z = 1.12 (P = 0.26) <b>37.1.3 Mirtazapine + sertraline versus sertraline</b> Kato 2018 8.27 2.75 527 9.26 2.75 537 43.4% -0.36 [-0.48, -0.24] Subtotal (95% Cl) 527 537 43.4% -0.36 [-0.48, -0.24] Heterogeneity: Not applicable Test for overall effect: Z = 5.82 (P < 0.00001) <b>Total (95% Cl) 820 837 100.%</b> -0.26 [-0.44, -0.09] Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); I <sup>2</sup> = 52% Test for overall effect: Z = 2.90 (P = 0.004) Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), I <sup>2</sup> = 0%		18	12.3	- · ·	19.7	12.4	- · ·			
Test for overall effect: $Z = 1.12$ (P = 0.26) <b>37.1.3 Mirtazapine + sertraline versus sertraline</b> Kato 2018       8.27       2.75       527       9.26       2.75       537       43.4%       -0.36 [-0.48, -0.24]         Subtotal (95% CI)       527       537       43.4%       -0.36 [-0.48, -0.24]       -0.36 [-0.48, -0.24]         Heterogeneity: Not applicable       527       537       43.4%       -0.36 [-0.44, -0.09]       -0.26 [-0.44, -0.09]         Total (95% CI)       820       837       100.0%       -0.26 [-0.44, -0.09]       -10         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); l <sup>2</sup> = 52%       -0.26 [-0.44, -0.09]       -10       -5         Test for overall effect: $Z = 2.90$ (P = 0.004)       Test for overall effect: $Z = 2.90$ (P = 0.004)       Favours mirtazapine + AD       Favours AD								38.1%	-0.36 [-1.00, 0.27]	•
37.1.3 Mirtazapine + sertraline versus sertraline         Kato 2018       8.27       2.75       527       9.26       2.75       537       43.4%       -0.36 [-0.48, -0.24]         Subtotal (95% CI)       527       537       43.4%       -0.36 [-0.48, -0.24]         Heterogeneity: Not applicable         Test for overall effect: Z = 5.82 (P < 0.00001)					(P = 0.1)	11); l² =	= 62%			
Kato 2018       8.27       2.75       527       9.26       2.75       537       43.4% $-0.36$ [-0.48, -0.24]         Subtotal (95% Cl)       527       537       43.4% $-0.36$ [-0.48, -0.24]         Heterogeneity: Not applicable       Test for overall effect: $Z = 5.82$ (P < 0.00001)       -0.26 [-0.44, -0.09]         Total (95% Cl)       820       837       100.0%       -0.26 [-0.44, -0.09]         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); l <sup>2</sup> = 52%       -0.26 [-0.44, -0.09]       -10       -5       0       5       10         Test for overall effect: $Z = 2.90$ (P = 0.004)       Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), l <sup>2</sup> = 0%       -70       -70       5       10	Test for overall effect: Z =	= 1.12 (F	P = 0.26	5)						
Subtotal (95% Cl)         527         537         43.4%         -0.36 [-0.48, -0.24]           Heterogeneity: Not applicable	37.1.3 Mirtazapine + se	rtraline	versus	s sertra	aline					
Heterogeneity: Not applicable         Test for overall effect: Z = 5.82 (P < 0.00001)		8.27	2.75		9.26	2.75				
Test for overall effect: Z = 5.82 (P < 0.00001)	Subtotal (95% CI)			527			537	43.4%	-0.36 [-0.48, -0.24]	•
Total (95% CI)       820       837       100.0%       -0.26 [-0.44, -0.09]         Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); l <sup>2</sup> = 52%       -10       -5       0       5       10         Test for overall effect: Z = 2.90 (P = 0.004)       Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), l <sup>2</sup> = 0%       Favours mirtazapine + AD       Favours AD										
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 6.22, df = 3 (P = 0.10); l <sup>2</sup> = 52%         Test for overall effect: Z = 2.90 (P = 0.004)         Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), l <sup>2</sup> = 0%	Test for overall effect: Z =	= 5.82 (F	° < 0.01	0001)						
Test for overall effect: Z = 2.90 (P = 0.004) Test for subgroup differences: Chi <sup>2</sup> = 1.47, df = 2 (P = 0.48), l <sup>2</sup> = 0% Favours mirtazapine + AD Favours AD	Total (95% CI)			820			837	100.0%	-0.26 [-0.44, -0.09]	•
Test for overall effect: Z = 2.90 (P = 0.004) Test for subgroup differences: Chi <sup>z</sup> = 1.47, df = 2 (P = 0.48), I <sup>z</sup> = 0% Favours mirtazapine + AD Favours AD	Heterogeneity: Tau <sup>2</sup> = 0.	02; Chi <sup>z</sup>	= 6.22	, df = 3	(P = 0.1)	10); l² =	= 52%			
Test for subgroup differences: Chi² = 1.47, df = 2 (P = 0.48), l² = 0%	Test for overall effect: Z =	= 2.90 (F	P = 0.00	04)						
AD: antidepressant			¢hi² = 1	.47, df:	= 2 (P =	0.48),	l <sup>z</sup> = 0%	5		avoirs mitacapine - Ab T avoirs Ab
nu. annucpressant	AD: antidepressan	t								

# Figure 218: Depression symptomatology change score



#### Figure 219: Depression symptomatology at 4-month follow-up



#### Figure 220: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
37.3.1 Mirtazapine + pa	roxetine v	ersus p	lacebo +	parox	etine		
Xiao 2020 Subtotal (95% CI)	34	68 <mark>68</mark>	32	68 <mark>68</mark>	24.9% <b>24.9%</b>	1.06 [0.75, 1.50] <b>1.06 [0.75, 1.50]</b>	<b>→</b>
Total events	34		32				
Heterogeneity: Not appli	icable						
Test for overall effect: Z =	= 0.34 (P =	0.73)					
37.3.2 Mirtazapine + SS	RI/SNRI ve	ersus pl	acebo +	SSRI/S	NRI		
Carpenter 2002	5	11	2	15	2.2%	3.41 [0.80, 14.44]	
Kessler 2018a/2018b Subtotal (95% Cl)	63	241 252	53	239 <b>254</b>	27.6% <b>29.8%</b>	1.18 [0.86, 1.62] 1.57 [0.62, 3.97]	
Total events	68		55				
Heterogeneity: Tau <sup>2</sup> = 0.	28; Chi <b>²</b> =	1.98, df	= 1 (P = I	0.16); P	'= 50%		
Test for overall effect: Z	= 0.96 (P =	0.34)					
37.3.3 Mirtazapine + se	rtraline ve	rsus se	ertraline				
Kato 2018 Subtotal (95% CI)	188	537 <b>537</b>	132	551 <b>551</b>	45.3% <b>45.3%</b>	1.46 [1.21, 1.76] <b>1.46 [1.21, 1.76]</b>	
Total events	188		132				
Heterogeneity: Not appli	icable						
Test for overall effect: Z	= 3.95 (P <	0.0001	)				
Total (95% CI)		857		873	100.0%	1.30 [1.04, 1.61]	•
Total events	290		219				
Heterogeneity: Tau <sup>2</sup> = 0.	02; Chi² =	4.79, df	= 3 (P = 1	0.19); P	'= 37%		
Test for overall effect: Z =							Favours AD Favours mirtazapine + AD
Test for subgroup differe		<sup>2</sup> = 2.60,	. df = 2 (F	? = 0.27	), <b>I<sup>z</sup> =</b> 23.3	2%	areare no in areare initiatelying into
AD <sup>.</sup> antidenressant							

#### Figure 221: Remission (ITT) at 4-month follow-up

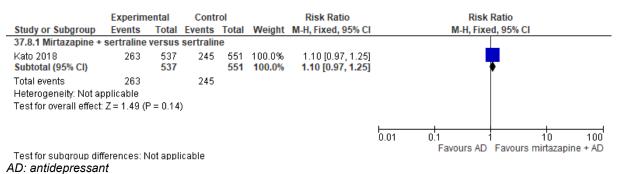
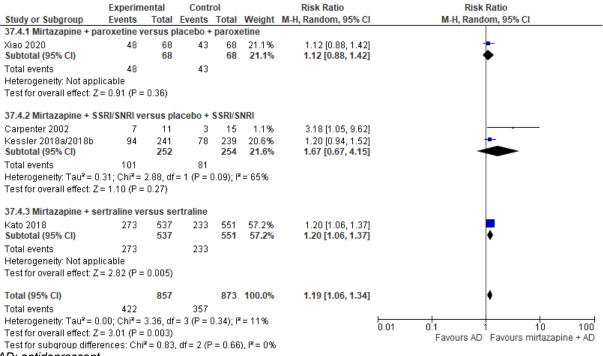
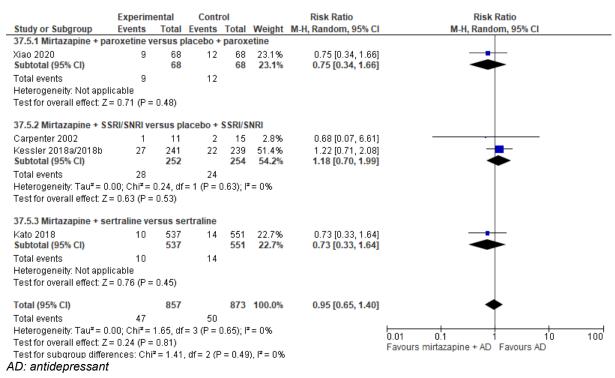


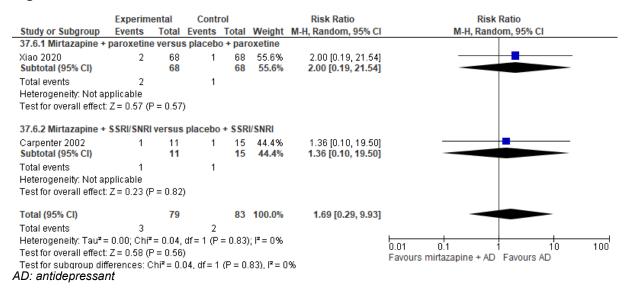
Figure 222: Response (ITT)



# Figure 223: Discontinuation due to any reason



#### Figure 224: Discontinuation due to side effects



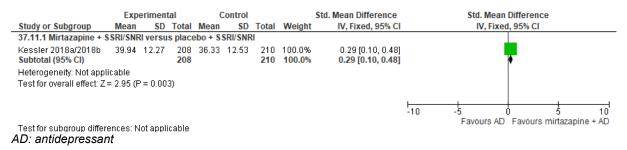
#### Figure 225: Quality of life endpoint

	Expe	erimen	tal	Co	ntrol			Std. Mean Difference		Std. Mean	Difference		
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI		
37.9.1 Mirtazapine + S	SRI/SNRI	versu	s place	ebo + SS	RI/SN	RI					_		
Kessler 2018a/2018b Subtotal (95% CI)	0.72	0.27	213 <b>213</b>	0.73	0.25	216 <b>216</b>	100.0% <b>100.0%</b>	-0.04 [-0.23, 0.15] - <b>0.04 [-0.23, 0.15]</b>			,		
Heterogeneity: Not appl Test for overall effect: Z		P = 0.6	9)										
									-10	-5 (	)	-	10
Test for subgroup differ AD: antidepressar		lot app	licable							Favours AD	Favours mi	nazapine + /	AD

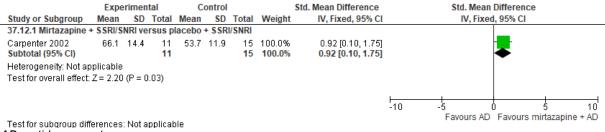
#### Figure 226: Quality of life physical component score (PCS) endpoint

	Exp	eriment	tal	0	Control			Std. Mean Difference		Std. Mea	n Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fix	ed, 95% Cl		
37.10.1 Mirtazapine + 9	SSRI/SNF	RI versu	s place	ebo + S	SRI/SNF	8							
Kessler 2018a/2018b Subtotal (95% CI)	44.09	12.87	208 <b>208</b>	45.85	12.54	210 <b>210</b>	100.0% <b>100.0%</b>	-0.14 [-0.33, 0.05] - <b>0.14 [-0.33, 0.05]</b>			•		
Heterogeneity: Not appl Test for overall effect: Z		P = 0.16	)						L	-1			
Test for subgroup differ AD: antidepressar		lot appli	icable						-10	-'5 Favours Al	Ó ) Favours n	5 nirtazap	10 vine + AD

#### Figure 227: Quality of life mental component score (MCS) endpoint

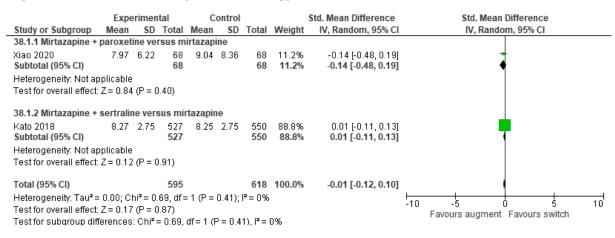


#### Figure 228: Global functioning endpoint

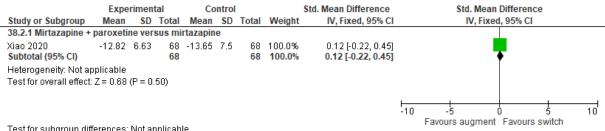


## Comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

#### Figure 229: Depression symptomatology endpoint

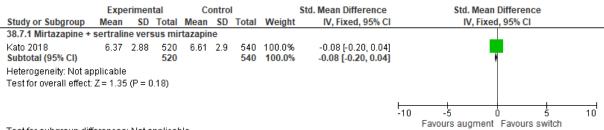


# Figure 230: Depression symptomatology change score



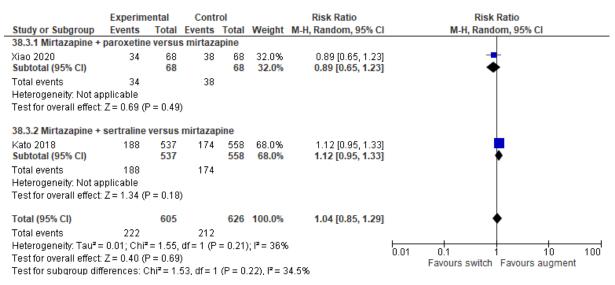
Test for subgroup differences: Not applicable

#### Figure 231: Depression symptomatology at 4-month follow-up

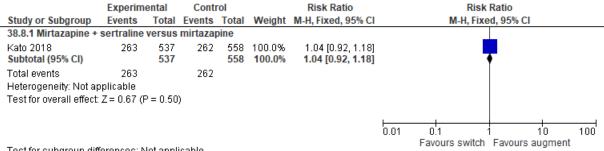


Test for subgroup differences: Not applicable

#### Figure 232: Remission (ITT)



#### Figure 233: Remission (ITT) at 4-month follow-up

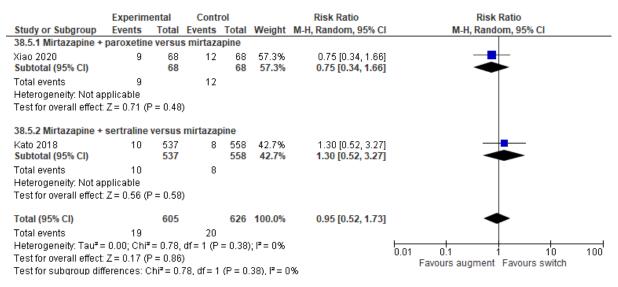


Test for subgroup differences: Not applicable

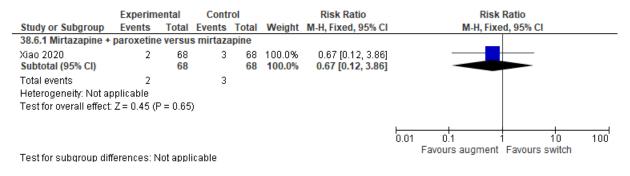
#### Figure 234: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
38.4.1 Mirtazapine +	paroxetine	e versu	s mirtaza	pine					
Xiao 2020 Subtotal (95% CI)	48	68 <mark>68</mark>	50	68 <mark>68</mark>	24.2% <b>24.2%</b>	0.96 [0.78, 1.18] 0.96 [0.78, 1.18]			
Total events	48		50						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=0.38 (F	P = 0.70	)						
38.4.2 Mirtazapine +	sertraline	versus	mirtazaj	oine					
Kato 2018 Subtotal (95% CI)	273	537 <b>537</b>	275	558 <b>558</b>	75.8% <b>75.8%</b>	1.03 [0.92, 1.16] <mark>1.03 [0.92, 1.16]</mark>			
Total events	273		275						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=0.51 (P	° = 0.61	)						
Total (95% CI)		605		626	100.0%	1.01 [0.91, 1.12]		+	
Total events	321		325						
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.36,	df = 1 (P	= 0.55)	); I² = 0%		0.01		00
Test for overall effect:	Z = 0.26 (F	P = 0.79	)				0.01	Favours switch Favours augment	00
Test for subgroup diff	erences: C	¢hi² = 0.	34. df = 1	(P = 0.	.56), I <sup>z</sup> = 0	1%		r avours sinter i avours augment	

#### Figure 235: Discontinuation due to any reason



#### Figure 236: Discontinuation due to side effects

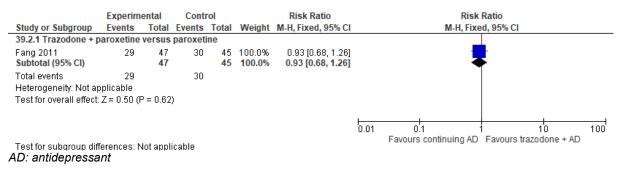


# Comparison 39. Augmenting with trazodone versus continuing with antidepressant

# Figure 237: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	
39.1.1 Trazodone +	paroxetine	versus	paroxeti	ne				
Fang 2011 Subtotal (95% CI)	20	47 <b>47</b>	21	45 <b>45</b>	100.0% <b>100.0%</b>	0.91 [0.58, 1.44] <b>0.91 [0.58, 1.44]</b>		
Total events Heterogeneity: Not a Test for overall effect		⊃ = 0.69	21					
Test for subgroup dit		lot appl	icable				0.01 0.1 1 10 Favours continuing AD Favours trazodone + AD	100

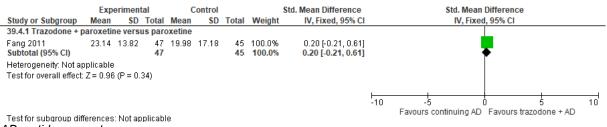
### Figure 238: Response (ITT)



#### Figure 239: Quality of life physical component score (PCS) change score

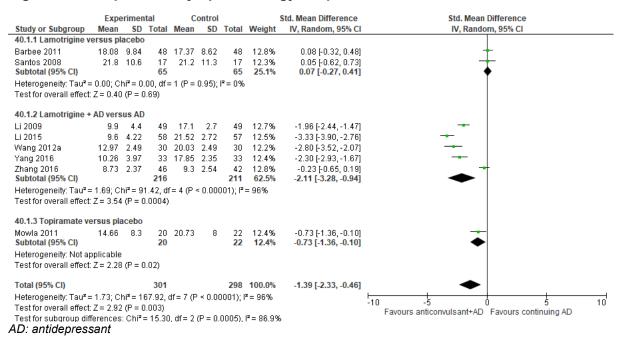
	Exp	eriment	tal	C	Control			Std. Mean Difference		Std. Mean Difference	
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% Cl	
39.3.1 Trazodone + p	paroxeti	ne versi	us paro	oxetine							
Fang 2011 Subtotal (95% Cl)	10.71	11.58	47 <b>47</b>	13.68	11.43	45 <b>45</b>	100.0% <b>100.0%</b>	-0.26 [-0.67, 0.15] - <b>0.26 [-0.67, 0.15]</b>			
Heterogeneity: Not ap Test for overall effect:	•		22)								
Test for subgroup dif AD: antidepress		:: Not ap	plicabl	e					-10	-5 0 5 Favours continuing AD Favours trazodone + AD	10

#### Figure 240: Quality of life mental component score (MCS) change score

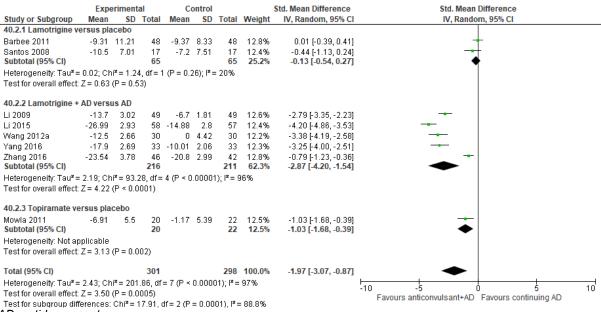


# Comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/- placebo)

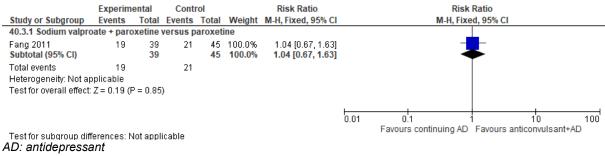
#### Figure 241: Depression symptomatology endpoint



#### Figure 242: Depression symptomatology change score



### Figure 243: Remission (ITT)



#### Figure 244: Response (ITT)

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
40.4.1 Lamotrigine v	ersus plac	ebo					
Barbee 2011	16	48	16	48	14.9%	1.00 [0.57, 1.76]	<b>_</b>
Santos 2008	5	17	6	17	9.9%	0.83 [0.31, 2.22]	
Subtotal (95% CI)		65		65	24.8%	0.96 [0.59, 1.56]	<b>•</b>
Total events	21		22				
Heterogeneity: Tau² =				= 0.75	); I² = 0%		
Test for overall effect:	Z=0.18 (F	P = 0.85	)				
40.4.2 Lamotrigine +	AD versus	s AD					
Li 2009	25	49	16	49	15.9%	1.56 [0.96, 2.54]	<b>⊢</b> ∎
Li 2015	35	58	9	57	14.0%	3.82 [2.03, 7.21]	<b>_</b> _
Wang 2012a	9	30	0	30	2.2%	19.00 [1.16, 312.42]	<b>_</b>
Yang 2016	9	33	3	33	7.8%	3.00 [0.89, 10.10]	+
Zhang 2016	26	46	25	42	17.5%	0.95 [0.67, 1.36]	-
Subtotal (95% CI)		216		211	57.3%	2.18 [1.03, 4.61]	$\bullet$
Total events	104		53				
Heterogeneity: Tau² =				P = 0.0	001); I² =	82%	
Test for overall effect:	Z = 2.03 (F	P = 0.04	)				
40.4.3 Sodium valpro	oate + AD v	ersus A	AD				
Fang 2011	24	39	30	45	17.8%	0.92 [0.67, 1.27]	
Subtotal (95% CI)		39		45	17.8%	0.92 [0.67, 1.27]	◆
Total events	24		30				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z=0.49 (F	P = 0.63	)				
Total (95% CI)		320		321	100.0%	1.44 [0.93, 2.24]	•
Total events	149		105				
Heterogeneity: Tau <sup>z</sup> =	= 0.25; Chi <sup>z</sup>	= 28.98	6, df = 7 (	P = 0.0	001); I <sup>z</sup> = 1	76%	0.01 0.1 1 10 100
Test for overall effect:	Z = 1.64 (F	<sup>o</sup> = 0.10)	)				Favours continuing AD Favours anticonvulsant+AD
Test for subgroup diff		Chi² = 4.3	36. df = 2	! (P = 0	.11), I <sup>z</sup> = 6	54.1%	r avoirs commany AB T avoirs anticonvirsant AB
AD: antidepressa	ant						

# Figure 245: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
40.5.1 Lamotrigine v	ersus plac	ebo					
Barbee 2011	14	48	17	48	66.9%	0.82 [0.46, 1.48]	— <b>—</b> —
Santos 2008	3	17	4	17	12.7%	0.75 [0.20, 2.86]	
Subtotal (95% CI)		65		65	79.6%	0.81 [0.48, 1.38]	
Total events	17		21				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>z</sup>	= 0.02,	df = 1 (P	= 0.90)	); I <sup>z</sup> = 0%		
Test for overall effect	: Z = 0.77 (F	° = 0.44	)				
40.5.2 Topiramate ve	ersus place	ebo					
Mowla 2011	6	26	5	27	20.4%	1.25 [0.43, 3.59]	e
Subtotal (95% CI)		26		27	20.4%	1.25 [0.43, 3.59]	
Total events	6		5				
Heterogeneity: Not ap	pplicable						
Test for overall effect	:Z=0.41 (F	P = 0.68	)				
Total (95% CI)		91		92	100.0%	0.89 [0.55, 1.43]	•
Total events	23		26				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>z</sup>	= 0.52.	df = 2 (P	= 0.77	); I <b>ž</b> = 0%		
Test for overall effect:							0.01 0.1 1 10 100
Test for subaroup dif			-	(P = 0)	.48), <b> </b> <sup>2</sup> = 0	1%	Favours anticonvulsant+AD Favours continuing AD
D: antidepress							

# Figure 246: Discontinuation due to side effects

	Experime	ental	Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
40.6.1 Lamotrigine v	ersus plac	ebo					
Barbee 2011	7	48	10	48	76.1%	0.70 [0.29, 1.69]	
Santos 2008 Subtotal (95% CI)	2	17 65	0	17 65	23.9% <b>100.0%</b>	5.00 [0.26, 97.00] 1.12 [0.21, 5.94]	
Total events Heterogeneity: Tau² = Test for overall effect:				= 0.21)	); I² = 38%		
Test for subaroup dif AD: antidepress		lot appl	icable				0.01 0.1 1 10 100 Favours anticonvulsant+AD Favours continuing AD

#### Figure 247: Quality of life physical component score (PCS) change score

	Expe	erimen	tal	0	Control			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
40.7.1 Sodium valpr	oate + pa	iroxeti	ine ver	sus par	oxetine	•				
Fang 2011 Subtotal (95% CI)	11.36	9.88	39 <b>39</b>	13.68	11.43	45 <b>45</b>	100.0% <b>100.0%</b>	-0.21 [-0.64, 0.22] -0.21 [-0.64, 0.22]		<mark>.</mark>
Heterogeneity: Not a Test for overall effect	• •		).33)							
									-10	-5 0 5 10
Test for subgroup dit AD: antidepres		: Not a	pplicat	ole						Favours continuing AD Favours anticonvulsant+AD

# Figure 248: Quality of life mental component score (MCS) change score

	Exp	eriment	tal	0	Control		5	Std. Mean Difference		Std. Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
40.8.1 Sodium valpro	oate + pa	aroxetin	ie vers	us paro	xetine								
Fang 2011 Subtotal (95% CI)	23.04	14.05	39 <b>39</b>	19.98	17.18	45 <b>45</b>	100.0% <b>100.0%</b>	0.19 [-0.24, 0.62] 0.19 [-0.24, 0.62]			•		
Heterogeneity: Not ap Test for overall effect:			38)										
									-10	-5	0	5	10
Test for subaroup dif	foroncoc	· Not an	nlicahl							Favours continuing AD	Favours ant	iconvulsant+AD	

Test for subgroup differences: Not applicable

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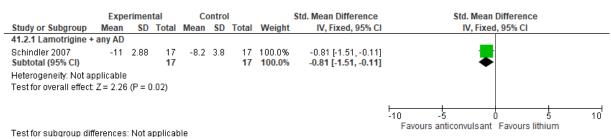
AD: antidepressant

#### Comparison 41. Augmenting with anticonvulsant versus lithium

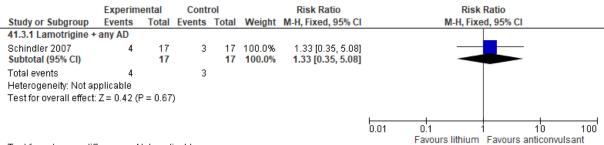
#### Figure 249: Depression symptomatology endpoint

	Expe	rimen	tal	Co	ontro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
41.1.1 Lamotrigine +	⊦ any AD								
Schindler 2007 Subtotal (95% CI)	11.7	4.2	17 <b>17</b>	13.3	5.7	17 <b>17</b>	100.0% <b>100.0%</b>	-0.31 [-0.99, 0.36] -0.31 [-0.99, 0.36]	
Heterogeneity: Not a Test for overall effect			).37)						
Test for subgroup dif	fferences:	Not a	pplical	ole					Favours anticonvulsant Favours lithium

#### Figure 250: Depression symptomatology change score

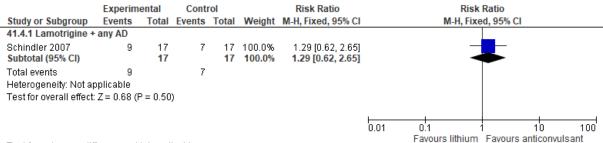


#### Figure 251: Remission (ITT)



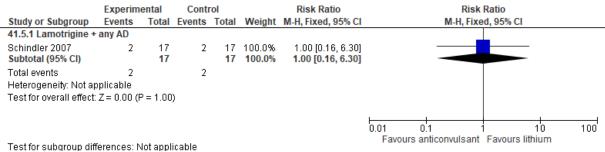
Test for subgroup differences: Not applicable

#### Figure 252: Response (ITT)



Test for subgroup differences: Not applicable

### Figure 253: Discontinuation due to any reason



#### Figure 254: Discontinuation due to side effects

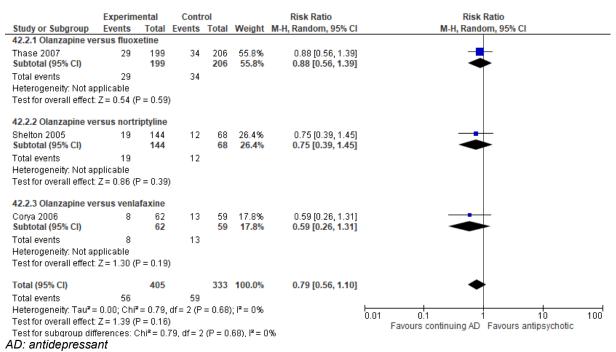
	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
41.6.1 Lamotrigine +	any AD						
Schindler 2007 Subtotal (95% CI)	0	17 <b>17</b>	0	17 <b>17</b>		Not estimable Not estimable	
Total events Heterogeneity: Not ap Test for overall effect:	•	able	0				
Test for subgroup dif	ferences: N	Vot appl	icable				0.01 0.1 1 10 100 Favours anticonvulsant Favours lithium

#### Comparison 42. Switching to antipsychotic versus continuing with antidepressant

#### Figure 255: Depression symptomatology change score

	Expe	eriment	tal	C	ontrol			Std. Mean Difference		Std. Mea	n Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Rand	om, 95% Cl		
42.1.1 Olanzapine ve	ersus flu	oxetine	e										
Thase 2007 Subtotal (95% CI)	-8.9	9	197 <b>197</b>	-9.2	9.7	203 203	38.1% <b>38.1%</b>	0.03 [-0.16, 0.23] 0.03 [-0.16, 0.23]			<b>†</b>		
Heterogeneity: Not a	pplicable												
Test for overall effect	: Z = 0.32	: (P = 0	.75)										
42.1.2 Olanzapine ve	ersus no	rtriptyli	ine										
Shelton 2005 Subtotal (95% Cl)	-6.95	8.52	144 <b>144</b>	-7.46	8.08	68 <mark>68</mark>	33.2% <b>33.2%</b>	0.06 [-0.23, 0.35] 0.06 [-0.23, 0.35]			‡		
Heterogeneity: Not a	pplicable												
Test for overall effect	: Z = 0.41	(P = 0	.68)										
42.1.3 Olanzapine ve	ersus vei	ılafaxi	ne										
Corya 2006	-7.71	9.21		-13.73	8.91	58	28.7%	0.66 [0.29, 1.03]			+		
Subtotal (95% CI)			59			58	28.7%	0.66 [0.29, 1.03]			•		
Heterogeneity: Not a													
Test for overall effect	: Z = 3.47	(P = 0	.0005)										
Total (95% CI)			400			329	100.0%	0.22 [-0.12, 0.56]			•		
Heterogeneity: Tau <sup>2</sup> :	= 0.07; Cl	hi² = 8.9	94, df=	= 2 (P = 0	0.01); I	<b>2</b> = 78%	6		-10		<u>.</u>	- L	10
Test for overall effect	: Z = 1.27	(P = 0	.20)							vours antipsychoti	Eavours	continuing AD	10
Test for subgroup dif		: Chi²=	= 8.94,	df = 2 (P	= 0.01	1), I² = 7	77.6%			incare anapoyonou		containing AD	
AD: antidepress	sant												

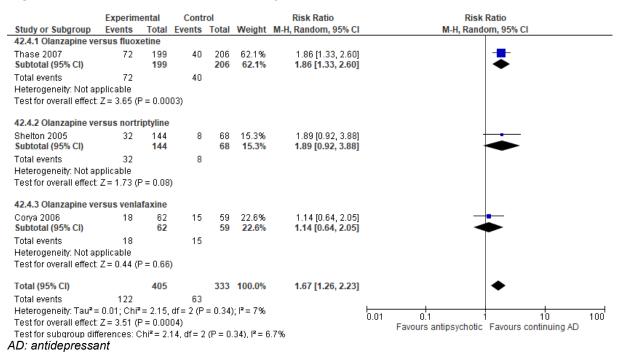
### Figure 256: Remission (ITT)



#### Figure 257: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
42.3.1 Olanzapine ve	rsus fluox	etine					
Thase 2007 Subtotal (95% CI)	51	199 <b>199</b>	60	206 <b>206</b>	43.2% <b>43.2%</b>	0.88 [0.64, 1.21] 0.88 [0.64, 1.21]	
Total events	51		60				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.79 (F	P = 0.43	)				
42.3.2 Olanzapine ve	rsus nortr	iptyline					
Shelton 2005 Subtotal (95% CI)	28	144 <b>144</b>	21	68 <mark>68</mark>	29.2% <b>29.2%</b>	0.63 [0.39, 1.02] 0.63 [0.39, 1.02]	-
Total events	28		21				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.86 (F	P = 0.06	)				
42.3.3 Olanzapine ve	rsus venla	faxine					
Corya 2006 Subtotal (95% CI)	15	62 62	29	59 <b>59</b>	27.6% <b>27.6%</b>	0.49 [0.30, 0.82] <mark>0.49 [0.30, 0.82]</mark>	<b></b>
Total events	15		29				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.72 (F	P = 0.00	7)				
Total (95% CI)		405		333	100.0%	0.68 [0.48, 0.96]	◆
Total events	94		110				
Heterogeneity: Tau <sup>2</sup> =	0.05; Chi <sup>z</sup>	= 3.94,	df = 2 (P	= 0.14)	; l² = 49%	, ,	
Test for overall effect:	Z = 2.16 (F	P = 0.03)	)				Favours continuing AD Favours antipsychotic
Test for subgroup diff		¦hi² = 3.9	94. df = 2	(P = 0.	14), I <sup>2</sup> = 4	9.2%	, areas containing, is in around anapoyonoud
D: antidepressa	nt						

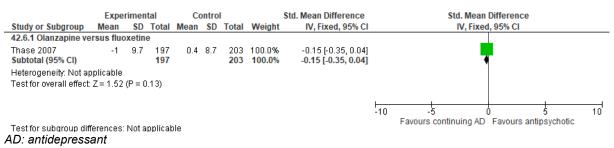
#### Figure 258: Discontinuation due to any reason



#### Figure 259: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
42.5.1 Olanzapine ve	rsus fluox	etine					
Thase 2007 Subtotal (95% CI)	32	199 <b>199</b>	5	206 <b>206</b>	62.8% 62.8%	6.63 [2.63, 16.66] 6.63 [2.63, 16.66]	
Total events Heterogeneity: Not ap	32 plicable		5				
Test for overall effect:		° < 0.00	01)				
42.5.2 Olanzapine ve	rsus nortr	iptyline					
Shelton 2005 Subtotal (95% Cl)	14	144 <b>144</b>	2	68 <mark>68</mark>	25.3% <b>25.3%</b>	3.31 [0.77, 14.14] 3.31 [0.77, 14.14]	
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.11)	2				
42.5.3 Olanzapine ve	rsus venla	faxine					
Corya 2006 <b>Subtotal (95% CI)</b>	5	62 62	1	59 <mark>59</mark>	11.9% <b>11.9%</b>	4.76 [0.57, 39.53] 4.76 [0.57, 39.53]	
Total events Heterogeneity: Not ap	5 nlicable		1				
Test for overall effect:	•	° = 0.15	)				
Total (95% CI)		405		333	100.0%	5.34 [2.57, 11.09]	•
Total events	51		8				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>z</sup>	= 0.64,	df = 2 (P	= 0.73)	; I² = 0%		
Test for overall effect:	Z=4.49 (F	° < 0.00	001)				Favours antipsychotic Favours continuing AD
Test for subgroup diff		;hi² = 0.1	64. df = 2	(P = 0	73), I² = 0	%	· arease anapoyeness if around continuing no
D: antidepressa	nt						

#### Figure 260: Quality of life physical component score (PCS) change score

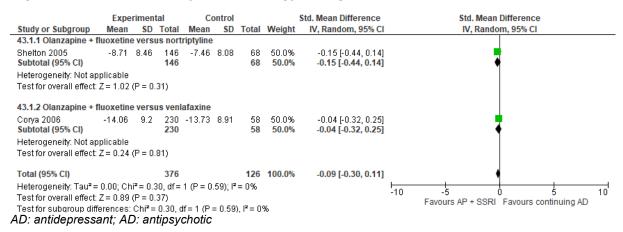


#### Figure 261: Quality of life mental component score (MCS) change score

	Expe	erimen	tal	С	ontrol			Std. Mean Difference		Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
42.7.1 Olanzapine ve	rsus flu	oxetin	е								
Thase 2007 Subtotal (95% CI)	6.7	11.2	197 <b>197</b>	7.3	12.3	203 <b>203</b>	100.0% <b>100.0%</b>	-0.05 [-0.25, 0.15] -0.05 [-0.25, 0.15]		<b>.</b>	
Heterogeneity: Not ap Test for overall effect:			).61)						<b></b>		4
Test for subgroup diff AD: antidepress		: Not a	pplicat	ble					-10	-5 0 5 Favours continuing AD Favours antipsychotic	10

#### Comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

#### Figure 262: Depression symptomatology change score



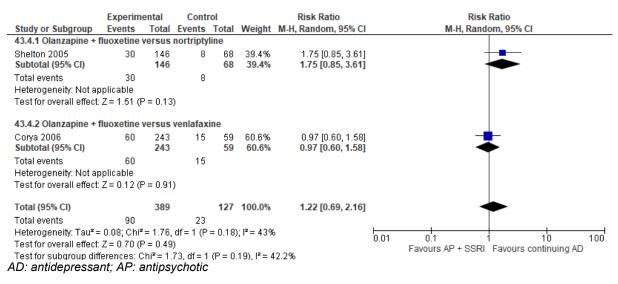
# Figure 263: Remission (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
43.2.1 Olanzapine + f	luoxetine v	ersus	nortriptyl	ine			
Shelton 2005	25	146	12	68	40.9%	0.97 [0.52, 1.81]	
Subtotal (95% CI)		146		68	40.9%	0.97 [0.52, 1.81]	-
Total events	25		12				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.09 (P	= 0.92)	)				
43.2.2 Olanzapine + f	luoxetine v	ersus	venlafaxi	ne			
Corya 2006	69	243	13	59	59.1%	1.29 [0.77, 2.17]	
Subtotal (95% CI)		243		59	59.1%	1.29 [0.77, 2.17]	★
Total events	69		13				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.96 (P	= 0.34)	)				
Total (95% CI)		389		127	100.0%	1.15 [0.77, 1.71]	+
Total events	94		25				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.47,	df = 1 (P :	= 0.49	); <b>I</b> ² = 0%		
Test for overall effect:	•						0.01 0.1 1 10 100
Test for subgroup diff	erences: C	hi² = 0.4	47. df = 1	(P = 0)	$49),  ^2 = 0$	1%	Favours continuing AD Favours AP + SSRI
D: antidepressal							
	,						

# Figure 264: Response (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
43.3.1 Olanzapine + 1	fluoxetine	ersus	nortripty	line			
Shelton 2005 Subtotal (95% CI)	40	146 <b>146</b>	21	68 <mark>68</mark>	31.4% <b>31.4%</b>	0.89 [0.57, 1.38] 0.89 [0.57, 1.38]	-
Total events	40		21				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 0.53 (F	P = 0.60	)				
43.3.2 Olanzapine + 1	fluoxetine	ersus	venlafax	ine			
Corya 2006	100	243	29	59	68.6%	0.84 [0.62, 1.13]	
Subtotal (95% CI)		243		59	68.6%	0.84 [0.62, 1.13]	•
Total events	100		29				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 1.16 (F	P = 0.25)	)				
Total (95% CI)		389		127	100.0%	0.85 [0.67, 1.09]	•
Total events	140		50				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff AD: antidepressa	Z = 1.26 (F ferences: C	? = 0.21) :hi² = 0.0	) 05. df = 1	(P = 0		%	0.01 0.1 1 10 100 Favours continuing AD Favours AP + SSRI

#### Figure 265: Discontinuation due to any reason

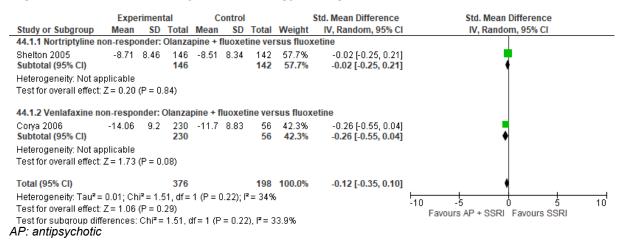


#### Figure 266: Discontinuation due to side effects

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
43.5.1 Olanzapine + f	luoxetine	/ersus	nortripty	ine			
Shelton 2005 Subtotal (95% CI)	10	146 <b>146</b>	2	68 <mark>68</mark>	63.7% <b>63.7%</b>	2.33 [0.52, 10.34] 2.33 [0.52, 10.34]	
Total events	10		2				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 1.11 (F	r = 0.27	)				
43.5.2 Olanzapine + f	luoxetine	/ersus	venlafaxi	ine			
Corya 2006 Subtotal (95% CI)	29	243 <b>243</b>	1	59 <b>59</b>	36.3% <b>36.3%</b>	7.04 [0.98, 50.65] 7.04 [0.98, 50.65]	
Total events	29		1				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 1.94 (F	' = 0.05	)				
Total (95% CI)		389		127	100.0%	3.48 [1.06, 11.44]	-
Total events	39		3				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.84,	df = 1 (P	= 0.36)	); I <sup>2</sup> = 0%		0.01 0.1 1 10 100
Test for overall effect:	Z = 2.06 (F	= 0.04	)				0.01 0.1 1 10 100 Favours AP + SSRI Favours continuing AD
Test for subaroup diff	erences: C	hi² = 0.1	77. df = 1	(P = 0)	.38), I <sup>z</sup> = 0	1%	Favours AF + SSRF Favours continuing AD
AD: antidepressa	nt; AP: a	ntipsy	chotic/				

#### Comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only

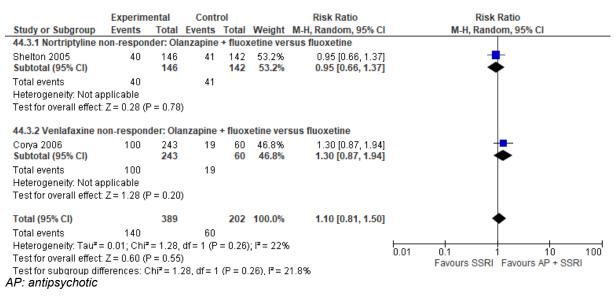
#### Figure 267: Depression symptomatology change score



#### Figure 268: Remission (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	I M-H, Random, 95% CI
44.2.1 Nortriptyline n	on-respon	der: Ola	anzapine	+ fluo)	cetine ve	rsus fluoxetine	
Shelton 2005 Subtotal (95% CI)	25	146 <b>146</b>	19	142 <b>142</b>		1.28 [0.74, 2.22] <b>1.28 [0.74, 2.22]</b>	
Total events	25		19				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.88 (P	= 0.38	)				
44.2.2 Venlafaxine no	on-respond	ler: Ola	nzapine	+ fluox	etine ver	sus fluoxetine	
Corya 2006 <b>Subtotal (95% CI)</b>	69	243 <b>243</b>	10	60 60		1.70 [0.94, 3.10] <b>1.70 [0.94, 3.10]</b>	
Total events Heterogeneity: Not ap	69 plicable		10				
Test for overall effect:	Z=1.74 (P	= 0.08	)				
Total (95% CI)		389		202	100.0%	1.46 [0.97, 2.19]	•
Total events	94		29				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chi <sup>z</sup>	= 0.48,	df = 1 (P	= 0.49)	); I² = 0%		
Test for overall effect:	Z = 1.82 (P	= 0.07	)				Favours SSRI Favours AP + SSRI
Test for subgroup diff	ferences: C	hi <b>²</b> = 0	47. df = 1	(P = 0.	49), <b>I<sup>2</sup> =</b> 0	1%	
AP: antipsychotic							

### Figure 269: Response (ITT)



#### Figure 270: Discontinuation due to any reason

	Experime	ntal	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
44.4.1 Nortriptyline no	on-respond	ler: Ola	anzapine	+ fluo)	cetine ver	rsus fluoxetine	
Shelton 2005 Subtotal (95% CI)	30	146 <b>146</b>	28	142 <b>142</b>	59.0% <b>59.0%</b>	1.04 [0.66, 1.65] <b>1.04 [0.66, 1.65]</b>	<b>‡</b>
Total events	30		28				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.18 (P	= 0.86	)				
44.4.2 Venlafaxine no	on-respond	er: Ola	nzapine	+ fluox	etine ver	sus fluoxetine	
Corya 2006 Subtotal (05%, CI)	60	243 <b>243</b>	12	60 60	41.0% <b>41.0%</b>	1.23 [0.71, 2.14] <b>1.23 [0.71, 2.14]</b>	<b>±</b>
Subtotal (95% CI)	00	<b>Z</b> 4J	40	00	41.0%	1.23 [0.71, 2.14]	
Total events	60 Bliachla		12				
Heterogeneity: Not ap		- 0.45					
Test for overall effect:	Z= 0.75 (P	= 0.49	)				
Total (95% CI)		389		202	100.0%	1.12 [0.78, 1.59]	<b>•</b>
Total events	90		40				
Heterogeneity: Tau² =	0.00; Chi <sup>2</sup> :	= 0.21,	df = 1 (P	= 0.64)	; I² = 0%		
Test for overall effect:	Z = 0.61 (P	= 0.54	)				Favours AP + SSRI Favours SSRI
Test for subgroup diff	erences: Cl	ni² = 0.1	21. df = 1	(P = 0.	64), I <sup>2</sup> = 0	1%	
AP: antipsychotic							

# Figure 271: Discontinuation due to side effects

	Experiment				Risk Ratio	Risk Ratio
Study or Subgroup				-	M-H, Random, 95% CI	M-H, Random, 95% Cl
44.5.1 Nortriptyline n	on-responde	r: Olanzapine	e + fluo	ketine ver	rsus fluoxetine	
Shelton 2005 Subtotal (95% CI)		146 4 <b>146</b>	142 <b>142</b>		2.43 [0.78, 7.57] <b>2.43 [0.78, 7.57]</b>	
Total events	10	4				
Heterogeneity: Not ap	plicable					
Test for overall effect:	Z=1.53 (P=	0.13)				
44.5.2 Venlafaxine no	on-responder	: Olanzapine	+ fluox	cetine ver	sus fluoxetine	
Corya 2006 Subtotal (95% CI)		243 3 <b>243</b>	60 60		2.39 [0.75, 7.57] <b>2.39 [0.75, 7.57]</b>	
Total events	29	3				
Heterogeneity: Not ap	•					
Test for overall effect:	Z=1.48 (P=	0.14)				
Total (95% CI)	:	389	202	100.0%	2.41 [1.07, 5.42]	-
Total events	39	7				
Heterogeneity: Tau² = Test for overall effect: Test for subgroup diff	Z = 2.13 (P =	0.03)			)%	0.01 0.1 1 10 100 Favours AP + SSRI Favours SSRI
AP: antipsychotic						

# Comparison 45. Augmenting with antipsychotic versus antidepressant-only or antidepressant + placebo

# Figure 272: Depression symptomatology endpoint

	Expe	rimen	ital	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
45.1.1 Aripiprazole versus pla	acebo								
Fava 2012/Mischoulon 2012 Subtotal (95% CI)	22.15	7.68	54 54	23.11	9.08	167 <b>167</b>	21.2% <b>21.2%</b>	-0.11 [-0.42, 0.20] - <b>0.11 [-0.42, 0.20]</b>	1
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.70	(P = 0.49	3)							
45.1.2 Quetiapine + AD versu	s AD								
Li 2013	10.08	2.6	49	14.24	4.14	46	19.3%	-1.20 [-1.64, -0.76]	+
Moica 2018	8.58	3.74	36	18.22	7.78	36	17.8%	-1.56 [-2.09, -1.03]	+
Subtotal (95% CI)			85			82	37.2%	-1.35 [-1.70, -1.00]	◆
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	ni² = 1.05	, df = 1	(P = 0	.31); I <sup>z</sup> =	: 5%				
Test for overall effect: Z = 7.62									
45.1.3 Risperidone versus pla	acebo								
Mahmoud 2007		5.56	106	16.2	5.61	112	21.7%	-0.50 [-0.77, -0.23]	-
Subtotal (95% CI)	10.1	0.00	106		0.01	112		-0.50 [-0.77, -0.23]	•
Heterogeneity: Not applicable									-
Test for overall effect: Z = 3.63		003)							
45.1.4 Risperidone + AD vers	us AD								
Song 2007	13.27	4 53	50	16.64	5 1 5	50	19.9%	-0.69 [-1.09, -0.29]	+
Subtotal (95% CI)	10.21		50	10.01	0.10	50	19.9%	-0.69 [-1.09, -0.29]	•
Heterogeneity: Not applicable									-
Test for overall effect: Z = 3.35		008)							
Total (95% CI)			295			411	100.0%	-0.78 [-1.24, -0.32]	•
Heterogeneity: Tau <sup>2</sup> = 0.23; Cł	ni² = 30 3	6 df=	4 (P <	0 0000 <sup>,</sup>	D: P=	87%			· · · ·
Test for overall effect: Z = 3.34				0.0000					-10 -5 0 5 10
Test for subgroup differences:			f = 3 (F)	⊳<000	001) F	<sup>2</sup> = 89 f	5%		Favours AP + AD Favours AD
D: antidepressant; Al				0.00	0077,1	55.0			
2. annaoprocoam, Ar		55,0							

# Figure 273: Depression symptomatology change score

•			•			0,			
Study or Subgroup 45.2.1 Aripiprazole versus plac	Mean	rimenta SD	l Total		ontrol SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl
Berman 2009	-10.12	9.76	174	-6.39	9.62	169	5.7%	-0.38 [-0.60, -0.17]	•
Fava 2012/Mischoulon 2012	-8.54	7.21	54	-8.09	8.13	167	4.6%	-0.06 [-0.36, 0.25]	+
Kamijima 2013	-10.05	8.39	391	-7.4	8.38	195	6.2%	-0.32 [-0.49, -0.14]	-
Kamijima 2018 Subtotal (95% CI)	-9.2	7.21	208 827	-7.2	7.12	203 734	6.0% 22.5%	-0.28 [-0.47, -0.08] -0.29 [-0.40, -0.19]	
Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 5.42 (F				l²= 2%		104	22.5 /	-6.25 [-0.46, -0.15]	,
45.2.2 Brexpiprazole versus pla	acebo								
Hobart 2018a	-10.4	8.29	191	-8.1	8.53	202	5.9%	-0.27 [-0.47, -0.07]	-
Otsuka Pharmaceutical 2015	-8.2	8.41	184	-7.02	8.34	181	5.8%	-0.14 [-0.35, 0.06]	•
Otsuka Pharmaceutical 2016 Thase 2015a	-7.19 -8.27	7.97	299 187	-6.09 -5.15	8.08 8.29	126 191	5.8%	-0.14 [-0.35, 0.07]	
Thase 2015b	-0.27	8.34 7.58	451	-6.45	7.53	218	5.9% 6.3%	-0.37 [-0.58, -0.17] -0.18 [-0.34, -0.02]	-
Subtotal (95% CI)	-1.02	1.50	1312	-0.45	1.00	918	29.7%	-0.22 [-0.30, -0.13]	4
Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 4.96 (F			0.42);	; I² = 0%					
15.2.3 Brexpiprazole/quetiapine	e versus p	lacebo							
Hobart 2018b	-5.62	5.7	290	-4.6	5.73	205	6.1%	-0.18 [-0.36, 0.00]	•
Subtotal (95% CI)			290			205	6.1%	-0.18 [-0.36, 0.00]	•
Heterogeneity: Not applicable Test for overall effect: Z = 1.95 (F	9 = 0.05)								
45.2.4 Cariprazine versus place	ebo								
Durgam 2016	-13.998	9.11	544	-12.5	8.12	264	6.5%	-0.17 [-0.32, -0.02]	•
Earley 2018 Eavo 2019	-7.2	5.81	211	-6.5	5.92	219	6.0% 5.0%	-0.12 [-0.31, 0.07]	1
Fava 2018 Subtotal (95% CI)	-8.63	9.54	149 904	-8	9	81 564	5.0% 17.6%	-0.07 [-0.34, 0.20] -0.14 [-0.24, -0.03]	T
Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 2.53 (F		= 2 (P =		² = 0%					
45.2.5 Olanzapine + AD versus	AD								
Thase 2007	-12.6	10.3	198	-9.2	9.7	203	5.9%	-0.34 [-0.54, -0.14]	-
Subtotal (95% CI)			198			203	5.9%	-0.34 [-0.54, -0.14]	•
Heterogeneity: Not applicable Test for overall effect: Z = 3.37 (F	P = 0.0007	)							
<mark>45.2.6 Pimavanserin versus pla</mark> Fava 2019	<b>icebo</b> -11.9	7.65	45	-7.1	6.2	127	4.2%	-0.72[1.07]-0.27]	+
Subtotal (95% Cl)	-11.9	7.00	40	-7.1	0.2	127	4.2%	-0.72 [-1.07, -0.37] - <b>0.72 [-1.07, -0.37]</b>	•
Heterogeneity: Not applicable Test for overall effect: Z = 4.07 (F	P < 0.0001	)						- / -	
45.2.7 Quetiapine + AD versus /	AD								
Li 2013	-15.88	2.96		-11.54	3.02	46	3.2%	-1.44 [-1.89, -0.99]	+
Moica 2018 Subtotal (95% Cl)	-13.59	2.51	36 85	-6.39	5.4	36 82	2.6% <b>5.7%</b>	-1.69 [-2.23, -1.15] - <b>1.54 [-1.89, -1.20]</b>	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> Fest for overall effect: Z = 8.70 (F				; I² = 0%		02	5.1%	-1.34 [-1.69, -1.20]	•
45.2.8 Risperidone versus plac	ebo								
Reeves 2008	-20.31	11.47	12	-13.2	11.48	11	1.3%	-0.60 [-1.44, 0.24]	7
Subtotal (95% CI)			12			11	1.3%	-0.60 [-1.44, 0.24]	-
Heterogeneity: Not applicable Fest for overall effect: Z = 1.39 (F	P = 0.16)								
45.2.9 Ziprasidone versus place									
Papakostas 2015 Subtotal (95% CI)	-6.4	6.4	71 71	-3.3	6.2	68 68	4.3% <b>4.3%</b>	-0.49 [-0.83, -0.15]	<b>▲</b>
Heterogeneity: Not applicable Test for overall effect: Z = 2.84 (F	9 = 0.005)		1			08	4.3%	-0.49 [-0.83, -0.15]	*
45.2.10 Ziprasidone + AD versu									
Dunner 2007	-7.07	8.96	40	-4.45	9.08	20	2.6%	-0.29 [-0.83, 0.25]	- <u>+</u> -
Subtotal (95% CI)			40			20	2.6%	-0.29 [-0.83, 0.25]	◆
Heterogeneity: Not applicable Test for overall effect: Z = 1.04 (F	P = 0.30)								
Total (95% CI)			3784			2932	100.0%	-0.33 [-0.44, -0.23]	
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup>	= 77.00, c	if = 19 (	P < 0.0	10001); P	= 75%				-10 -5 0 5
Fest for overall effect: Z = 6.12 (F Fest for subgroup differences: C D: antidepressant: AP	hi² = 69.0	6, df = 9		.00001),	l² = 87.	0%			Favours AP + AD Favours AD

AD: antidepressant; AP: antipsychotic

# Figure 274: Remission (ITT)

Study or Subgroup	Experim Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
45.3.1 Aripiprazole Berman 2007	47	184	28	178	3.8%	1.62 [1.07, 2.47]	
Berman 2009	64	177	32	172	4.5%	1.94 [1.34, 2.81]	
ava 2012/Mischoulon 2012	4	56	16	169	0.9%	0.75 [0.26, 2.16]	
Kamijima 2013	123	391	40	195	5.3%	1.53 [1.12, 2.10]	
Kamijima 2018	61	209	41	203	4.8%	1.45 [1.02, 2.04]	
_enze 2015 Marcus 2008	40 47	91 191	26 28	90 190	4.1% 3.8%	1.52 [1.02, 2.27] 1.67 [1.09, 2.55]	
Subtotal (95% CI)	47	1299	20	1197	27.1%	1.58 [1.36, 1.84]	♦
Total events	386		211				
Heterogeneity: Tau² = 0.00; Chi Fest for overall effect: Z = 5.98 (			: 0.74); I²	= 0%			
45.3.2 Brexpiprazole							
Bauer 2019	95	444	110	442	6.6%	0.86 [0.68, 1.09]	
Hobart 2018a Diseuka Pharmasoutisal 2015	56 48	192 185	52 27	202 187	5.2%	1.13 [0.82, 1.56]	Τ
Otsuka Pharmaceutical 2015 Otsuka Pharmaceutical 2016	40 60	303	17	126	3.8% 3.1%	1.80 [1.17, 2.75] 1.47 [0.89, 2.41]	<u> </u>
Thase 2015a	27	188	16	191	2.4%	1.71 [0.96, 3.08]	<u> </u>
Thase 2015b	64	456	25	221	3.7%	1.24 [0.80, 1.91]	- <u>+-</u> -
Subtotal (95% CI)		1768		1369	24.6%	1.26 [0.98, 1.63]	•
Fotal events Heterogeneity: Tau² = 0.06; Chi Fest for overall effect: Z = 1.79 (		df = 5 (P	247 = 0.03);	l² = 619	6		
15.3.3 Brexpiprazole/quetiapir	ie						
Hobart 2018b	15	297	9	205	1.4%	1.15 [0.51, 2.58]	<u> </u>
Subtotal (95% CI)		297		205	1.4%	1.15 [0.51, 2.58]	-
Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0.34 (	15 (P = 0.73)		9				
15.3.4 Cariprazine							
Durgam 2016	174	550	79	269	6.9%	1.08 [0.86, 1.35]	+
Earley 2018	65	269	49	258	5.0%	1.27 [0.92, 1.77]	
Fava 2018 Subtotal (95% CI)	37	150 969	16	81 608	2.9% <b>14.8%</b>	1.25 [0.74, 2.10] 1.15 [0.96, 1.36]	
Fotal events Heterogeneity: Tau² = 0.00; Chi			144 = 0.67); I <sup>2</sup>		141070	110 [0.00, 1.00]	ſ
Fest for overall effect: Z = 1.55 (	(P = 0.12)						
<b>15.3.5 Olanzapine</b> Thase 2007	54	200	34	206	4.3%	1.64 [1.12, 2.40]	
Subtotal (95% CI)		200		206	4.3%	1.64 [1.12, 2.40]	•
Fotal events Heterogeneity: Not applicable	54		34				
Fest for overall effect: Z = 2.52 (	(P = 0.01)						
45.3.6 Pimavanserin							
Fava 2019 Subtotol (05%, CI)	12	52	17	155	2.0%	2.10 [1.08, 4.11]	
Subtotal (95% CI)	40	52	47	155	2.0%	2.10 [1.08, 4.11]	-
Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 2.18 (	12 (P = 0.03)		17				
45.3.7 Quetiapine							
Bauer 2009	134	330	50	163	6.1%	1.32 [1.02, 1.73]	<u> </u>
El-Khalili 2010 Li 2013	137 19	298 49	47 12	148 46	6.1% 2.2%	1.45 [1.11, 1.89]	
.i 2013 AcIntyre 2007	19	49 29	12	46 29	2.3% 1.0%	1.49 [0.82, 2.71] 1.80 [0.69, 4.72]	
Subtotal (95% CI)	5	706	J	386	15.6%	1.40 [1.18, 1.68]	◆
Fotal events Heterogeneity: Tau² = 0.00; Chi			114 = 0.91); I <sup>2</sup>	= 0%			
Fest for overall effect: Z = 3.78 (	r = 0.0002	9					
15.3.8 Risperidone			~ .		0.5%	0.67.10.00.4.000	
Fang 2011 Keitner 2009	12 32	45 64	21 8	45 33	2.5% 2.0%	0.57 [0.32, 1.02] 2.06 [1.08, 3.95]	
Mahmoud 2007	32 26	141	12	133	2.0%	2.06 [1.08, 3.95]	
Subtotal (95% CI)		250		211	6.6%	1.33 [0.55, 3.17]	-
Fotal events Heterogeneity: Tau² = 0.49; Chi		lf = 2 (P	41 = 0.003)	; <b>I²</b> = 83	%		
Test for overall effect: Z = 0.63 (	(P = 0.53)						
<b>45.3.9 Ziprasidone</b> Dunner 2007	5	41	1	20	0.2%	2.44 [0.30, 19.51]	
Papakostas 2015	27	71	21	68	3.4%	1.23 [0.77, 1.96]	+
Subtotal (95% CI)		112		88	3.6%	1.27 [0.81, 2.00]	◆
Fotal events Heterogeneity: Tauª = 0.00; Chi Fest for overall effect: Z = 1.04 (		= 1 (P =	22 = 0.52); I	= 0%			
rest for overall effect: 2 = 1.04 ( Fotal (95% CI)	a – 0.30)	5653		4425	100.0%	1.37 [1.23, 1.52]	•
otal (55/0 Cl)		2033		4420	100.0%	1.57 [1.25, 1.52]	▼
Total events							
Fotal events Heterogeneity: Tau² = 0.03; Chi	1494 1 <sup>2</sup> = 44.79, 1	lf = 27 (	839 P = 0.02)	; <b> </b> ² = 40	%		

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# Figure 275: Response (ITT)

Study or Subgroup	Experime Events		Cont Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
45.4.1 Aripiprazole Berman 2007	61	104	40	170	4.000	1 //1 14 04 // 0.01	
Berman 2007 Berman 2009	81	184 177	42 45	178 172	4.0% 4.7%	1.41 [1.01, 1.96]	
Fava 2012/Mischoulon 2012	10	56	40	169	4.7%	1.75 [1.30, 2.36] 1.04 [0.54, 2.00]	
Kamijima 2013	159	391	29 55	195	5.6%	1.44 [1.12, 1.86]	-
Kamijima 2018	78	209	52	203	4.8%	1.46 [1.09, 1.95]	
Marcus 2008	60	191	32	190	3.4%	1.87 [1.28, 2.73]	-
Subtotal (95% CI)	00	1208	52	1107	23.8%	1.52 [1.33, 1.74]	•
Fotal events	449	1200	255		2010/0	102 [100, 114]	•
Heterogeneity: Tau² = 0.00; Chi		- 6 (P -		- 0%			
Fest for overall effect: Z = 6.20 (			- 0.53), 1	-0.0			
45.4.2 Brexpiprazole							
Hobart 2018a	72	192	66	202	5.3%	1.15 [0.88, 1.50]	+-
Otsuka Pharmaceutical 2015	55	185	36	187	3.5%	1.54 [1.07, 2.23]	
Otsuka Pharmaceutical 2016	111	303	25	126	3.3%	1.85 [1.26, 2.70]	
Thase 2015a	44	188	28	191	2.8%	1.60 [1.04, 2.45]	
Thase 2015b	102	456	33	221	3.7%	1.50 [1.05, 2.14]	
Subtotal (95% CI)		1324		927	18.6%	1.45 [1.22, 1.73]	◆
Fotal events Heterogeneity: Tau² = 0.01; Chi Fest for overall effect: Z = 4.24 (			188 = 0.30); I <sup>2</sup>	= 17%			
15.4.3 Brexpiprazole/quetiapir		,					
Hobart 2018b	28	297	14	205	1.5%	1.38 [0.75, 2.56]	<u> </u>
Subtotal (95% CI)	20	297 297	14	205 205	1.5%	1.38 [0.75, 2.56] 1.38 [0.75, 2.56]	L
	20	201	4.4	203	1.370	1.00 [0.10, 2.00]	
Fotal events Jotorogonoity: Not opplicable	28		14				
Heterogeneity: Not applicable Fest for overall effect: Z = 1.03 (	(P = 0.31)						
45.4.4 Cariprazine							
Durgam 2016	265	550	101	269	7.8%	1.28 [1.08, 1.53]	-
Earley 2018	75	269	71	258	5.1%	1.01 [0.77, 1.34]	+
ava 2018	51	150	21	81	2.8%	1.31 [0.85, 2.02]	† <u>-</u> -
Subtotal (95% CI)		969		608	15.7%	1.21 [1.04, 1.40]	•
Fotal events	391		193				
Heterogeneity: Tau² = 0.00; Chi Fest for overall effect: Z = 2.44 (		= 2 (P =	= 0.34); I <sup>2</sup>	= 7%			
15.4.5 Olanzapine							
Thase 2007	80	200	60	206	5.2%	1.37 [1.05, 1.80]	<b>T</b>
Subtotal (95% CI)		200		206	5.2%	1.37 [1.05, 1.80]	•
Total events	80		60				
Heterogeneity: Not applicable							
Fest for overall effect: Z = 2.28 (	(P = 0.02)						
45.4.6 Pimavanserin							
Fava 2019	27	52	38	155	3.4%	2.12 [1.45, 3.10]	
Subtotal (95% CI)	21	52		155	3.4%	2.12 [1.45, 3.10]	•
Total events	27	01	38	100	01170	2112 [1110, 0110]	•
Heterogeneity: Not applicable Test for overall effect: Z = 3.87 (		)	50				
45.4.7 Quetiapine							
Bauer 2009	185	330	74	163	7.3%	1.23 [1.02, 1.50]	<b>⊢</b>
El-Khalili 2010	160	298	66	148	6.9%	1.20 [0.98, 1.48]	<u> -</u>
Li 2013	24	49	20	46	2.7%	1.13 [0.73, 1.74]	<u> </u>
AcIntyre 2007	14	29	20	29	1.2%	1.75 [0.87, 3.52]	<u> </u>
Subtotal (95% CI)	14	706	0	386	18.1%	1.23 [1.08, 1.40]	
Fotal events	383		168	000	.0.1/0		ľ
Heterogeneity: Tau² = 0.00; Chi Test for overall effect: Z = 3.03 (		= 3 (P =	= 0.76); I <sup>z</sup>	= 0%			
15.4.8 Risperidone							
ang 2011	21	45	30	45	3.4%	0.70 [0.48, 1.02]	
<eitner 2009<="" td=""><td>34</td><td>64</td><td>11</td><td>33</td><td>2.0%</td><td>1.59 [0.93, 2.72]</td><td><u> </u></td></eitner>	34	64	11	33	2.0%	1.59 [0.93, 2.72]	<u> </u>
Mahmoud 2007	49	141	33	133	3.5%	1.40 [0.97, 2.03]	+
Reeves 2008		12	4	11	0.7%	1.38 [0.52, 3.61]	_ <del></del>
Bong 2007	25	60	15	60	2.0%	1.67 [0.98, 2.83]	<u> </u>
Subtotal (95% CI)		322		282	11.5%	1.25 [0.85, 1.83]	
Total events	135		93			- / -	-
Heterogeneity: Tau <sup>2</sup> = 0.12; Chi Fest for overall effect: Z = 1.15 (	i <sup>z</sup> = 11.56, d	lf = 4 (P		I <b>²</b> = 65%	6		
15.4.9 Ziprasidone	·						
Dunner 2007	10	41	2	20	0.3%	2.44 [0.59, 10.10]	
Papakostas 2015	25	71	14	68	1.8%	1.71 [0.97, 3.00]	<u> </u>
Subtotal (95% CI)	20	112	14	88	2.1%	1.79 [1.06, 3.03]	•
Total events	35	. 12	16	50	2.170		<b>~</b>
Heterogeneity: Tau² = 0.00; Chi Fest for overall effect: Z = 2.19 (	i² = 0.21, df	= 1 (P =		= 0%			
Fotal (95% CI)	,	5190		3964	100.0%	1.37 [1.27, 1.49]	
Fotal events	1912	0100	1025	0004		[121, 143]	'
Heterogeneity: Tau² = 0.01; Chi		if = 27 /		r   <sup>2</sup> = 33	96		<b>⊢ ⊢ ⊢</b>
			, = 0.00)	- i - 32			0.01 0.1 i 10 1
Test for overall effect: Z = 7.62 ( Test for subgroup differences:	(P < 0.0000	1)					0.01 0.1 1 10 Favours AD Favours AP + AI

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# Figure 276: Discontinuation due to any reason

Study or Subgroup	Experime Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
45.5.1 Aripiprazole Berman 2007	22	184	16	178	3.0%	1.33 [0.72, 2.45]	
Berman 2009	30	177	23	172	4.4%	1.27 [0.77, 2.09]	
ava 2012/Mischoulon 2012	8	56	17	169	1.9%	1.42 [0.65, 3.11]	
<amijima 2013<="" td=""><td>34</td><td>391</td><td>12</td><td>195</td><td>2.8%</td><td>1.41 [0.75, 2.67]</td><td></td></amijima>	34	391	12	195	2.8%	1.41 [0.75, 2.67]	
<amijima 2018<="" td=""><td>15</td><td>209</td><td>20</td><td>203</td><td>2.7%</td><td>0.73 [0.38, 1.38]</td><td></td></amijima>	15	209	20	203	2.7%	0.73 [0.38, 1.38]	
_enze 2015	4	91	7	90	0.8%	0.57 [0.17, 1.86]	
Marcus 2008 Subtotal (95% CI)	29	191 1299	28	190 <b>1197</b>	4.8% <b>20.4%</b>	1.03 [0.64, 1.66] 1.12 [0.89, 1.42]	
Total events	142	1200	123	1137	20.4/0	1.12 [0.00, 1.42]	Ť
Heterogeneity: Tau² = 0.00; Chi Test for overall effect: Z = 0.96 (	² = 4.52, df	= 6 (P =		= 0%			
45.5.2 Brexpiprazole							
Bauer 2019	95	444	62	442	11.3%	1.53 [1.14, 2.04]	
Hobart 2018a	15	192	6	202	1.3%	2.63 [1.04, 6.64]	
Otsuka Pharmaceutical 2015 Otsuka Pharmaceutical 2016	18 50	185 303	16 16	187 126	2.7% 4.0%	1.14 [0.60, 2.16]	
Thase 2015a	13	188	13	191	2.1%	1.30 [0.77, 2.19] 1.02 [0.48, 2.13]	
Thase 2015b	30	456	13	221	2.8%	1.12 [0.60, 2.10]	
Subtotal (95% CI)		1768		1369	24.4%	1.39 [1.13, 1.71]	•
Fotal events	221		126				
Heterogeneity: Tau² = 0.00; Chi Fest for overall effect: Z = 3.11 (		= 5 (P =	0.58); I²	= 0%			
45.5.3 Brexpiprazole/quetiapir							
Hobart 2018b Subtotal (95% CI)	40	297	20	206	4.3%	1.39 [0.84, 2.30]	<b>—</b>
Subtotal (95% CI) Fotal events	40	297	20	206	4.3%	1.39 [0.84, 2.30]	
Heterogeneity: Not applicable Fest for overall effect: Z = 1.27 (			20				
45.5.4 Cariprazine	, = 0.21)						
Durgam 2016	57	550	35	269	6.7%	0.80 [0.54, 1.18]	
Earley 2018	56	269	36	258	7.1%	1.49 [1.02, 2.19]	<b> </b>
Fava 2018	17	150	9	81	2.0%	1.02 [0.48, 2.18]	
Subtotal (95% CI)		969		608	15.9%	1.08 [0.69, 1.67]	◆
Total events Heterogeneity: Tau² = 0.09; Chi Test for overall effect: Z = 0.33 (		= 2 (P =	80 °1 ;(0.08	= 60%			
45.5.5 Olanzapine	( = 0.74)						
Thase 2007	52	200	40	206	7.8%	1.34 [0.93, 1.93]	
Subtotal (95% CI)		200		206	7.8%	1.34 [0.93, 1.93]	◆
Total events	52		40				
Heterogeneity: Not applicable Test for overall effect: Z = 1.57 (	P = 0.12)						
45.5.6 Pimavanserin							
Fava 2019	8	52	30	155	2.2%	0.79 [0.39, 1.62]	
Subtotal (95% CI)		52		155	2.2%	0.79 [0.39, 1.62]	-
Total events	8		30				
Heterogeneity: Not applicable Test for overall effect: Z = 0.63 (	P = 0.53)						
45.5.7 Quetiapine							
Bauer 2009 Tu Khalili 2010	51	330	18	163	4.3%	1.40 [0.85, 2.32]	+ <b>-</b>
El-Khalili 2010 Li 2013	79 0	298 49	23	148 46	6.0%	1.71 [1.12, 2.60] Not estimable	
Li 2013 Vicintyre 2007	11	49 29	13	46 29	3.0%	0.85 [0.46, 1.57]	
Subtotal (95% CI)		706	15	386	13.3%	1.33 [0.90, 1.95]	•
Total events Heterogeneity: Tau² = 0.05; Chi	141 ²= 3.47, df	= 2 (P =	54 0.18); I <sup>2</sup>	= 42%			
Fest for overall effect: Z = 1.45 (							
15.5.8 Risperidone							
<eitner 2009<="" td=""><td>12</td><td>64</td><td>7</td><td>33</td><td>1.7%</td><td>0.88 [0.38, 2.03]</td><td><u> </u></td></eitner>	12	64	7	33	1.7%	0.88 [0.38, 2.03]	<u> </u>
Mahmoud 2007	35	141	21	133	4.6%	1.57 [0.97, 2.56]	
Reeves 2008 Subtotal (95% CI)	1	12 217	4	11 177	0.3% 6.6%	0.23 [0.03, 1.75] 1.02 [0.48, 2.18]	
Fotal events	48	211	32		0.070	1.02 [0.40, 2.10]	
Heterogeneity: Tau² = 0.23; Chi Test for overall effect: Z = 0.05 (	₹= 4.21, df	= 2 (P =		= 52%			
45.5.9 Ziprasidone	,						
Dunner 2007	21	41	5	20	1.7%	2.05 [0.91, 4.63]	<u> </u>
Papakostas 2015	22	71	15	68	3.5%	1.40 [0.80, 2.47]	+
Subtotal (95% CI)		112		88	5.2%	1.59 [1.00, 2.53]	◆
Total events Heterogeneity: Tau² = 0.00; Chi	43 ²= 0.56, df	= 1 (P =	20 0.46); I²	= 0%			
Test for overall effect: Z = 1.95 (							
Fotal (95% CI)		5620		4392	100.0%	1.26 [1.13, 1.40]	•
Fotal events	825		525				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi	<sup>2</sup> = 27.65, c	lf = 26 (l	° = 0.38)	; I <b>=</b> 69	6		
Fest for overall effect: Z = 4.11 (							0.01 0.1 1 10 11

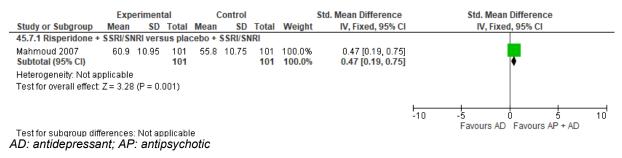
315 Depression in adults: Evidence review D FINAL (June 2022) <Insert Note here> AD: antidepressant; AP: antipsychotic

# Figure 277: Discontinuation due to side effects

Study or Subgroup	Experimen Events T			Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
5.6.1 Aripiprazole				_		
Berman 2007	6		178	4.4%	1.45 [0.42, 5.06]	
3erman 2009	11	177 3	3 172	4.3%	3.56 [1.01, 12.55]	
ava 2012/Mischoulon 2012	0		) 169		Not estimable	
(amijima 2013	15		2 195	3.2%	3.74 [0.86, 16.19]	
Kamijima 2018	6		3 203	3.7%	1.94 [0.49, 7.66]	
.enze 2015	2		2 90	1.8%	0.99 [0.14, 6.87]	
Aarcus 2008			2 190	2.8%	3.48 [0.73, 16.55]	
Subtotal (95% CI)	1	299	1197	20.3%	2.35 [1.31, 4.21]	◆
Fotal events Heterogeneity: Tau² = 0.00; Chi		16 ; (P = 0.78)				
Fest for overall effect: Z = 2.87 (	P = 0.004)					
15.6.2 Brexpiprazole						
Bauer 2019	27	444 13			2.07 [1.08, 3.95]	
Hobart 2018a		192 1		1.4%	4.21 [0.47, 37.32]	
Otsuka Pharmaceutical 2015			2 187	3.0%	4.55 [1.00, 20.77]	
Otsuka Pharmaceutical 2016	6	303 1		1.5%	2.50 [0.30, 20.51]	
Thase 2015a			) 191	0.8%	13.21 [0.75, 232.79]	
Thase 2015b	12		3 221	4.4%	1.94 [0.55, 6.80]	
Subtotal (95% CI)		1768	1369	27.5%	2.47 [1.50, 4.08]	-
⊺otal events Heterogeneity: Tau² = 0.00; Chi	64 = 2.66, df = 1	2( 5 (P = 0.75);				
est for overall effect: Z = 3.55 (	P = 0.0004)					
15.6.3 Brexpiprazole/quetiapin						
Hobart 2018b	6		2 206	2.7%	2.08 [0.42, 10.21]	
Subtotal (95% CI)	-	297	206	2.7%	2.08 [0.42, 10.21]	
Fotal events Jeteregeneity Net englischle	6	1	2			
Heterogeneity: Not applicable Fest for overall effect: Z = 0.90 (	P = 0.37)					
I5.6.4 Cariprazine						
Durgam 2016	54	550 8	3 269	13.0%	3.30 [1.59, 6.84]	<b>_</b>
Earley 2018	23		3 258	4.8%	7.35 [2.23, 24.19]	· · · · · · · · · · · · · · · · · · ·
ava 2018			2 81	2.2%	0.81 [0.14, 4.75]	
Subtotal (95% CI)	-	969	608	20.0%	3.21 [1.22, 8.49]	
Total events	80	1:	3			
Heterogeneity: Tau <sup>2</sup> = 0.38; Chi Test for overall effect: Z = 2.36 (	<sup>2</sup> = 4.19, df = 3					
	P = 0.02)					
I5.6.5 Olanzapine Thase 2007	27	200 (	5 206	7.9%	5.56 [2.19, 14.16]	
Subtotal (95% CI)	21	200	206	7.9%	5.56 [2.19, 14.16]	
Fotal events	27		5	110.0	0.00 [2:10, 1110]	
Heterogeneity: Not applicable	21		,			
Fest for overall effect: Z = 3.60 (	P = 0.0003)					
15.6.6 Pimavanserin						
ava 2019	1	52 2	2 155	1.2%	1.49 [0.14, 16.10]	
Subtotal (95% CI)		52	155	1.2%	1.49 [0.14, 16.10]	
Total events	1		2			
Heterogeneity: Not applicable			-			
Test for overall effect: Z = 0.33 (	P = 0.74)					
I5.6.7 Quetiapine Bauer 2009	30	330 (	5 163	8.0%	2.96 [1.17, 7.50]	
auer 2009 El-Khalili 2010	30 43	298 1		8.0%	2.96 [1.17, 7.50] 21.36 [2.97, 153.56]	
Li 2013	43 0		148 ) 46	1.070	21.36 [2.97, 153.56] Not estimable	
AcIntyre 2007	U 8		J 46 2 29	3.2%	4.00 [0.93, 17.25]	
Subtotal (95% CI)		29 . 706	2 29 386	3.2% 13.0%	4.00 [0.93, 17.25] 5.00 [1.65, 15.13]	
	81		300	13.070	5.00 [1.05, 15.15]	
⊺otal events Heterogeneity: Tau² = 0.46; Chi			-			
Feterogeneity: Tau== 0.46, Chi Fest for overall effect: Z = 2.85 (		z (r = 0.10),	, - 4770	•		
5.6.8 Risperidone						
(eitner 2009	6	64 1	I 33	1.6%	3.09 [0.39, 24.64]	
Aahmoud 2007	8		, 33 3 133	4.0%	2.52 [0.68, 9.28]	
Subtotal (95% CI)	-	205	166	5.6%	2.67 [0.88, 8.05]	
Total events	14					-
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi		1 (P = 0.87);	l² = 0%			
fest for overall effect: Z = 1.74 (						
5.6.9 Ziprasidone						
)unner 2007	16	41 (	) 20	0.9%	16.50 [1.04, 261.82]	
Papakostas 2015	10		0 68	0.9%	20.13 [1.20, 336.88]	
Subtotal (95% CI)		112	88	1.8%	18.19 [2.53, 130.85]	
Fotal events	26		)		. ,	
Heterogeneity: Tau² = 0.00; Chi	²= 0.01, df= 1		-			
Fest for overall effect: Z = 2.88 (	P = 0.004)					
Total (95% CI)		5608		100.0%	3.07 [2.36, 3.99]	•
	346	70	J			
Fotal events Jeteragonaity Tay? = 0.00; Obi				v		
∣otal events Heterogeneity: Tau² = 0.00; Chi Test for overall effect: Z = 8.38 (	<sup>2</sup> = 21.39, df =	: 24 (P = 0.62		%		0.01 0.1 1 10 10 Favours AP + AD Favours AD

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#### Figure 278: Quality of life endpoint

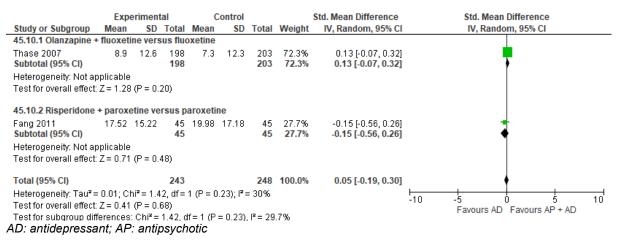


#### Figure 279: Quality of life change score

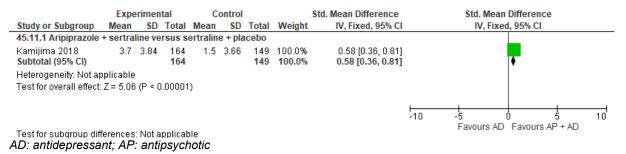
		eriment			Control	<b>-</b>		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD		Mean	SD	lotal	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
45.8.1 Aripiprazole + SSRI/SNI	RI versus	SSRI/S	SNRI + I	placebo					
Berman 2009	9.8	17.71	160	5.2	17.76	161	48.8%	0.26 [0.04, 0.48]	
Subtotal (95% CI)			160			161	48.8%	0.26 [0.04, 0.48]	•
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.31	(P = 0.02)	)							
45.8.2 Brexpiprazole + SSRI/S	NRI vers	us SSR	I/SNRI ·	+ placel	bo				
Otsuka Pharmaceutical 2016	7.13	14.5	286	5.92	14.68	120	51.2%	0.08 [-0.13, 0.30]	•
Subtotal (95% CI)			286			120	51.2%	0.08 [-0.13, 0.30]	•
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.76	(P = 0.45)	)							
Total (95% CI)			446			281	100.0%	0.17 [-0.00, 0.34]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i <sup>z</sup> = 1.27	df = 1 (l	P = 0.21	6): I <b>≥</b> = 2	1%				
Test for overall effect: Z = 1.92	•			-//					-10 -5 0 5 10
Test for subaroup differences:	• •		1 (P = 1	0.26) IZ	= 21.09	6			Favours AD Favours AP + AD
AD: antidepressant; AF		-			21.07	•			
AD. annuepressant, Ar	. anup	JSych	ouc						

Figure 280: C	Qualit	y o	f life	e phy	vsica	l co	mpon	ent score (PC	S) ch	ange	score		
	Exper	rimen	tal	(	Control			Std. Mean Difference		Std.	Mean Differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD.	Total	Weight	IV, Random, 95% CI		IV, I	Random, 95%	% CI	
45.9.1 Olanzapine + 1	fluoxetine	e vers	us fluc	oxetine									
Thase 2007 Subtotal (95% CI)	2.1	9	198 <b>198</b>	0.4	8.7	203 <b>203</b>	61.4% <b>61.4%</b>	0.19 [-0.00, 0.39] <b>0.19 [-0.00, 0.39]</b>			,		
Heterogeneity: Not ap	plicable												
Test for overall effect:	Z = 1.92	(P = 0	.06)										
45.9.2 Risperidone + Fang 2011	paroxeti 11.41		-		ne 11.43	45	38.6%	-0.20 [-0.61, 0.22]					
Subtotal (95% CI)	11.41	11.2	45	10.00	11.45	45	38.6%	-0.20 [-0.61, 0.22]			•		
Heterogeneity: Not ap	plicable										•		
Test for overall effect:	Z= 0.94	(P = 0	.35)										
Total (95% CI)			243				100.0%	0.04 [-0.33, 0.41]			•		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff AD: antidepressa	Z = 0.21 erences:	(P = 0 Chi² =	.83) = 2.79,	df = 1 (i					-10	-5 Favou	0 rs AD Favou	5 JIS AP + AD	10

#### Figure 281: Quality of life mental component score (MCS) change score



#### Figure 282: Global functioning change score

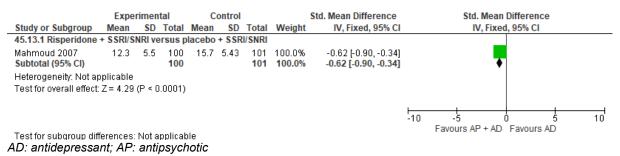


#### Figure 283: Functional remission (≤6 total score on SDS and all SDS domain scores ≤2)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	CI M-H, Fixed, 95% CI
45.12.1 Brexpiprazo	le + SSRI/S	NRI ver	sus SSR	I/SNRI ·	+ placebo	)	
Bauer 2019 Subtotal (95% CI)	68	444 <b>444</b>	73	442 <b>442</b>	100.0% <b>100.0%</b>	0.93 [0.68, 1.26] <b>0.93 [0.68, 1.26]</b>	-
Total events Heterogeneity: Not a Test for overall effect	•	° = 0.63	73				
Test for subgroup dif							0.01 0.1 1 10 10 Favours AD Favours AP + AD

AD: antidepressant; AP: antipsychotic

# Figure 284: Functional impairment endpoint



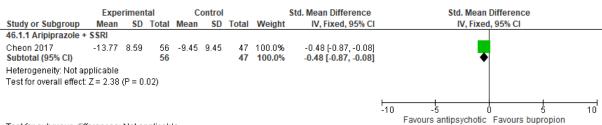
#### Figure 285: Functional impairment change score

		erimen		-	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
45.14.1 Aripiprazole versus pl									
Berman 2009		2.53	160		2.53	160	8.1%	-0.16 [-0.38, 0.06]	-
Kamijima 2013	-0.99	1.53	391	-0.46	1.54	195	12.1%	-0.35 [-0.52, -0.17]	
Subtotal (95% CI)			551			355	20.2%	-0.26 [-0.45, -0.08]	•
Heterogeneity: Tau² = 0.01; Ch Test for overall effect: Z = 2.84 (			(P = 0.1	9);   <b>*</b> =	42%				
45.14.2 Brexpiprazole versus	placebo								
Hobart 2018a	-1.6	2.76	191	-1.4	2.84	202	9.7%	-0.07 [-0.27, 0.13]	4
Otsuka Pharmaceutical 2015	-0.91	2.51	174	-0.69	2.49	172	8.7%	-0.09 [-0.30, 0.12]	4
Otsuka Pharmaceutical 2016	-0.99	2.16	285	-0.61	2.19	120	8.5%	-0.17 [-0.39, 0.04]	-
Thase 2015a	-1.35	2.27	179	-0.91	2.29	181	8.9%	-0.19 [-0.40, 0.01]	-
Thase 2015b	-1.27	2.02	451	-0.84	1.92	218	13.5%	-0.22 [-0.38, -0.05]	-
Subtotal (95% CI)			1280			893	49.2%	-0.15 [-0.24, -0.07]	•
Heterogeneity: Tau² = 0.00; Ch Test for overall effect: Z = 3.48 (			(P = 0.3	78); I² =	0%				
45.14.3 Brexpiprazole/quetiap									
Hobart 2018b	-0.76	1.64	290	-0.7	1.43	205	11.5%	-0.04 [-0.22, 0.14]	t
Subtotal (95% CI)			290			205	11.5%	-0.04 [-0.22, 0.14]	
Heterogeneity: Not applicable Test for overall effect: Z = 0.42 (	(P = 0.67	)							
45.14.4 Cariprazine versus pla	acebo								
Durgam 2016	-7.85	8.24	544	-6.6	8.12	264	15.7%	-0.15 [-0.30, -0.01]	-
Subtotal (95% CI)			544			264	15.7%	-0.15 [-0.30, -0.01]	•
Heterogeneity: Not applicable Test for overall effect: Z = 2.03 (	(P = 0.04	)							
45.14.5 Pimavanserin versus	placebo								
Fava 2019	-3.23	2.98		-2.03	2.52	127	3.5%	-0.45 [-0.79, -0.11]	-
Subtotal (95% CI)			45			127	3.5%	-0.45 [-0.79, -0.11]	•
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.58 (	(P = 0.01	0)							
Total (95% CI)			2710			1844	100.0%	-0.17 [-0.24, -0.11]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i <sup>2</sup> = 10.55	5, df = 9	9 (P = 0	.31); l² =	= 15%				-10 -5 0 5
Test for overall effect: Z = 5.15	(P < 0.00	001)							Favours AP + AD Favours AD
est for subaroup differences:	Chiž – 5	91 df:	= 4 (P =	0.21) 1	₹= 31	296			

AD: antidepressant; AP: antipsychotic

### Comparison 46. Augmenting with antipsychotic versus bupropion

#### Figure 286: Depression symptomatology change score



Test for subgroup differences: Not applicable

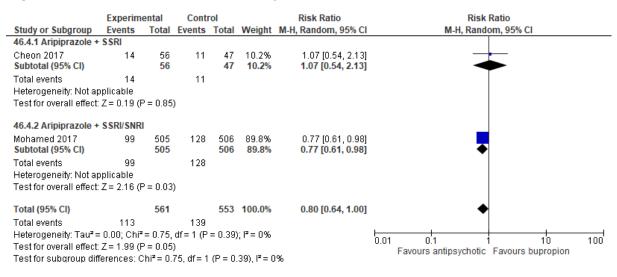
#### Figure 287: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
46.2.1 Aripiprazole +	SSRI									
Cheon 2017 Subtotal (95% CI)	31	56 <b>56</b>	16	47 <b>47</b>	36.8% <b>36.8%</b>	1.63 [1.02, 2.58] <b>1.63 [1.02, 2.58]</b>			•	
Total events	31		16							
Heterogeneity: Not ap	oplicable									
Test for overall effect:	Z = 2.06 (F	P = 0.04	)							
46.2.2 Aripiprazole +	SSRI/SNR	I								
Mohamed 2017 Subtotal (95% CI)	146	505 505	136	506 <mark>506</mark>	63.2% 63.2%	1.08 [0.88, 1.31] <b>1.08 [0.88, 1.31]</b>			•	
Total events	146		136							
Heterogeneity: Not ap	oplicable									
Test for overall effect:	Z=0.72 (F	P = 0.47	)							
Total (95% CI)		561		553	100.0%	1.25 [0.85, 1.85]			•	
Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:			•	= 0.11)	); I² = 62%	)	⊢ 0.01	0.1	1 10	100
Test for subgroup diff			·	(P = 0.	.11), I <sup>z</sup> = 6	i1.4%		Favours bupropion	Favours antipsyc	hotic

#### Figure 288: Response (ITT)

	Experime	ental	Contr	ol		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl		
46.3.1 Aripiprazole +	SSRI										
Cheon 2017 Subtotal (95% CI)	34	56 <b>56</b>	20	47 <b>47</b>	14.8% <b>14.8%</b>	1.43 [0.96, 2.11] <b>1.43 [0.96, 2.11]</b>			•		
Total events	34		20								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z=1.77 (F	P = 0.08	)								
46.3.2 Aripiprazole +	SSRI/SNRI	I									
Mohamed 2017 Subtotal (95% CI)	375	505 505	332	506 <mark>506</mark>	85.2% <b>85.2%</b>	1.13 [1.04, 1.23] <b>1.13 [1.04, 1.23]</b>			•		
Total events	375		332								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 2.98 (F	P = 0.00	3)								
Total (95% CI)		561		553	100.0%	1.17 [1.00, 1.38]			•		
Total events	409		352								
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup>	= 1.30,	df = 1 (P	= 0.25)	; <b>I</b> ² = 23%		0.01	0.1	<u> </u>	10	400
Test for overall effect:	Z = 1.90 (F	e = 0.06	)				0.01	Favours bupropion	Favoure an		100
Test for subgroup diff	erences: C	;hi <b>²</b> = 1.	28. df = 1	(P = 0.	26), I <sup>z</sup> = 2	1.7%			i avouis di	apsychotic	

#### Figure 289: Discontinuation due to any reason



#### Figure 290: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
46.5.1 Aripiprazole +	SSRI						
Cheon 2017 Subtotal (95% CI)	0	56 <b>56</b>	0	47 <b>47</b>		Not estimable Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					
46.5.2 Aripiprazole +	SSRI/SNR	I I					
Mohamed 2017 Subtotal (95% CI)	27	505 505	37	506 <mark>506</mark>	100.0% <b>100.0%</b>	0.73 [0.45, 1.18] <b>0.73 [0.45, 1.18]</b>	
Total events	27		37				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.28 (F	P = 0.20	)				
Total (95% CI)		561		553	100.0%	0.73 [0.45, 1.18]	•
Total events Heterogeneity: Not ap Test for overall effect: Test for subgroup diff	Z = 1.28 (F						0.01 0.1 1 10 100 Favours antipsychotic Favours bupropion

# Comparison 47. Augmenting with antipsychotic versus lithium

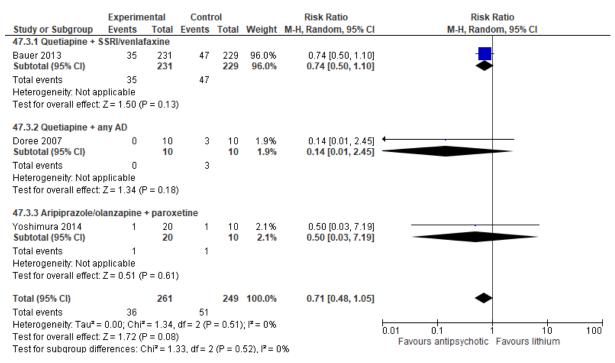
# Figure 291: Remission (ITT)

	Experim		Cont			Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
47.1.1 Quetiapine +	SSRI/venla	faxine					
Bauer 2013 Subtotal (95% CI)	73	231 231	60	229 229	71.8% <b>71.8%</b>	1.21 [0.90, 1.61] <b>1.21 [0.90, 1.61]</b>	
Total events	73		60				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 1.27 (F	P = 0.20	)				
47.1.2 Quetiapine + a	any AD						
Doree 2007	8	10	3	10	19.7%	2.67 [0.98, 7.22]	
Subtotal (95% CI)		10		10	19.7%	2.67 [0.98, 7.22]	
Total events	8		3				
Heterogeneity: Not a	pplicable						
Test for overall effect	:: Z = 1.93 (F	P = 0.05	)				
47.1.3 Aripiprazole/o	olanzapine	+ parox	etine				
Yoshimura 2014	3	20	2	10	8.5%	0.75 [0.15, 3.79]	
Subtotal (95% CI)		20		10	8.5%	0.75 [0.15, 3.79]	
Total events	3		2				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.35 (F	P = 0.73	)				
Total (95% CI)		261		249	100.0%	1.35 [0.82, 2.22]	•
Total events	84		65				
Heterogeneity: Tau <sup>2</sup> =	= 0.07; Chi <sup>a</sup>	²= 2.66,	df = 2 (P	= 0.26	); <b>I</b> ² = 25%	6	0.01 0.1 1 10 100
Test for overall effect	: Z = 1.20 (F	P = 0.23	)				0.01 0.1 1 10 100 Favours lithium Favours antipsychotic
Test for subgroup dif	ferences: C	⊃hi <b>²</b> = 2.	66, df = 2	2 (P = 0	.26), I <b>ž</b> = 2	24.7%	ravours nunum ravours anupsycholic

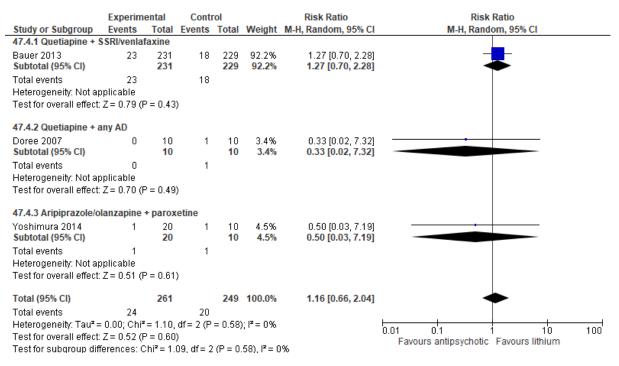
# Figure 292: Response (ITT)

	Experim		Contr			Risk Ratio	Risk Ratio				
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl				
47.2.1 Quetiapine + SSRI/venlafaxine											
Bauer 2013 Subtotal (95% CI)	120	231 231	102	229 <b>229</b>	89.7% <b>89.7%</b>	1.17 [0.96, 1.41] <b>1.17 [0.96, 1.41]</b>	<b>↓</b>				
Total events	120		102								
Heterogeneity: Not ap	oplicable										
Test for overall effect:	Z = 1.58 (F	P = 0.11	)								
17.0.0.0 // .											
47.2.2 Quetiapine + a	-										
Doree 2007	8	10	5	10	6.8%	1.60 [0.80, 3.20]					
Subtotal (95% CI)	_	10	_	10	6.8%	1.60 [0.80, 3.20]					
Total events	8		5								
Heterogeneity: Not ap											
Test for overall effect:	Z = 1.33 (F	P = 0.18	)								
47.2.3 Aripiprazole/o	lanzapine	+ parox	etine								
Yoshimura 2014	7	20	4	10	3.5%	0.88 [0.33, 2.30]					
Subtotal (95% CI)		20		10	3.5%	0.88 [0.33, 2.30]					
Total events	7		4								
Heterogeneity: Not ap	oplicable										
Test for overall effect:	Z=0.27 (F	P = 0.79	)								
Total (95% CI)		261		249	100.0%	1.18 [0.98, 1.41]	•				
Total events	135		111								
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>a</sup>	= 1.13.	df = 2 (P	= 0.57)	); I <b>ž</b> = 0%						
Test for overall effect:	•						0.01 0.1 1 10 100 Favours lithium Favours antipsychotic				
Test for subgroup diff	Test for subgroup differences: Chi <sup>2</sup> = 1.12, df = 2 (P = 0.57), l <sup>2</sup> = 0%										

#### Figure 293: Discontinuation due to any reason



#### Figure 294: Discontinuation due to side effects

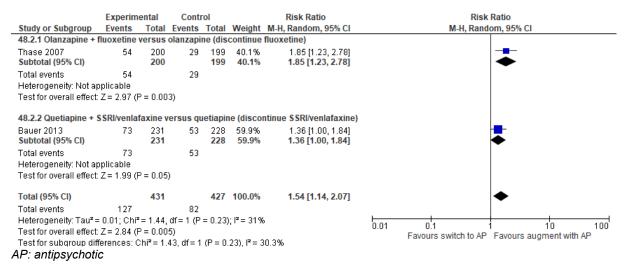


#### Comparison 48. Augmenting with antipsychotic versus switch to antipsychotic

#### Figure 295: Depression symptomatology change score

	Experimental Control			5	Std. Mean Difference	std. Mean Difference			
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Fixed, 95% CI	CI IV, Fixed, 95% CI
48.1.1 Olanzapine +	fluoxetin	e vers	sus ola	nzapine					
Thase 2007 <b>Subtotal (95% CI)</b>	-12.6	10.3	198 <b>198</b>	-8.9	9	197 <b>197</b>	100.0% <b>100.0%</b>	-0.38 [-0.58, -0.18] - <b>0.38 [-0.58, -0.18]</b>	
Heterogeneity: Not a Test for overall effect			).0002)						· · · · · · · · · · · · · · · · · · ·
Test for subgroup dit AP: antipsychot		: Not a	pplical	ble					-10 -5 0 5 10 Favours augment with AP Favours switch to AP

#### Figure 296: Remission (ITT)



#### Figure 297: Response (ITT)

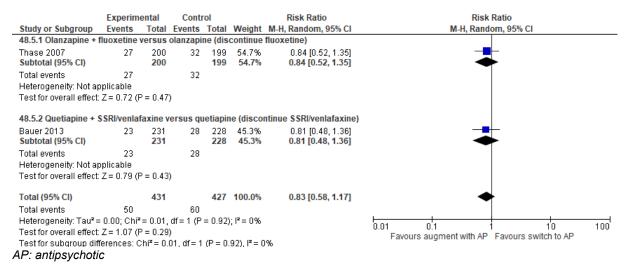
	Exporime	entel	Contr			Risk Ratio	Risk Ratio
	Experime						
Study or Subgroup	Events				-	M-H, Random, 95% Cl	M-H, Random, 95% Cl
48.3.1 Olanzapine +	fluoxetine v	ersus	olanzapiı	ne (dis	continue	fluoxetine)	
Thase 2007 Subtotal (95% CI)	80	200 200	51	199 <b>199</b>	46.0% <b>46.0%</b>	1.56 [1.17, 2.09] 1.56 [1.17, 2.09]	<b>★</b>
Total events	80	200	51	155	40.0%	1.50 [1.17, 2.05]	•
Heterogeneity: Not ap	oplicable						
Test for overall effect:	•	= 0.00	3)				
48.3.2 Quetiapine + 9	SSRI/venlaf	axine v	ersus qu	etiapir	ne (disco	ntinue SSRI/venlafaxine)	
Bauer 2013	120	231	114	228	54.0%	1.04 [0.87, 1.24]	÷
Subtotal (95% CI)		231		228	54.0%	1.04 [0.87, 1.24]	•
Total events	120		114				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z= 0.42 (F	= 0.68	)				
Total (95% CI)		431		427	100.0%	1.25 [0.84, 1.88]	•
Total events	200		165				
Heterogeneity: Tau <sup>2</sup> =				= 0.02)			
Test for overall effect: Test for subgroup dif			~	(P – 0	Favours switch to AP Favours augment with AP		
AP: antipsychoti		m = 0.	, ui = 1	() = 0.	.027,1 = 0		

#### Figure 298: Discontinuation due to any reason

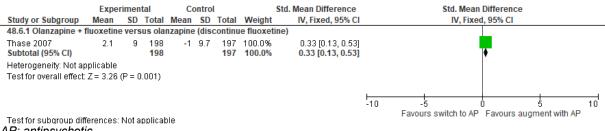
	Experime	ental	Control			Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
48.4.1 Olanzapine +	fluoxetine v	/ersus	olanzapi	ne (dis	continue	fluoxetine)				
Thase 2007 <b>Subtotal (95% CI)</b>	52	200 <b>200</b>	72	199 <b>199</b>	63.5% <mark>63.5%</mark>	0.72 [0.53, 0.97] 0.72 [0.53, 0.97]	<b>→</b>			
Total events	52		72							
Heterogeneity: Not a	pplicable									
Test for overall effect	:: Z = 2.17 (P	= 0.03	)							
48.4.2 Quetiapine +	SSRI/venlaf	axine v	ersus qu	etiapir	ne (disco	ntinue SSRI/venlafaxine)				
Bauer 2013 Subtotal (95% CI)	35	231 <b>231</b>	49	228 228	36.5% <b>36.5%</b>		<b>→</b>			
Total events	35		49							
Heterogeneity: Not a	pplicable									
Test for overall effect	: Z=1.74 (P	= 0.08	)							
Total (95% CI)		431		427	100.0%	0.71 [0.56, 0.90]	•			
Total events	87		121							
Heterogeneity: Tau <sup>2</sup> :	= 0.00; Chi <sup>z</sup>	= 0.01,	df = 1 (P	0.01 0.1 1 10 100						
Test for overall effect	: Z = 2.79 (P	9 = 0.00	5)	Favours augment with AP Favours switch to AP						
Test for subgroup differences: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.94), l <sup>2</sup> = 0%										
AP: antipsychot	ic									

AP: antipsychotic

#### Figure 299: Discontinuation due to side effects



#### Figure 300: Quality of life physical component score (PCS) change score



AP: antipsychotic

#### Std. Mean Difference Std. Mean Difference Experimental Control Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI Study or Subgroup 48.7.1 Olanzapine + fluoxetine versus olanzapine (discontinue fluoxetine) 8.9 12.6 198 6.7 11.2 197 100.0% 198 197 100.0% Thase 2007 Subtotal (95% CI) 0.18 [-0.01, 0.38] 0.18 [-0.01, 0.38] Heterogeneity: Not applicable Test for overall effect: Z = 1.83 (P = 0.07) -10 -5 10 ń Ś Favours switch to AP Favours augment with AP Test for subgroup differences: Not applicable AP: antipsychotic

# Figure 301: Quality of life mental component score (MCS) change score

# Comparison 49. Augmenting with antipsychotic versus switch to bupropion

#### Figure 302: Remission (ITT)

	Experim	ental	I Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Events Total		Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
49.1.1 Aripiprazole	+ SSRI/SNR						
Mohamed 2017 Subtotal (95% CI)	146	505 505	114	511 <b>511</b>	100.0% <b>100.0%</b>	1.30 [1.05, 1.60] <b>1.30 [1.05, 1.60]</b>	•
Total events Heterogeneity: Not a Test for overall effect	••	P = 0.02	114				
Test for subgroup di	fferences: N	lot appl	icable				0.01 0.1 1 10 100 Favours bupropion Favours AP

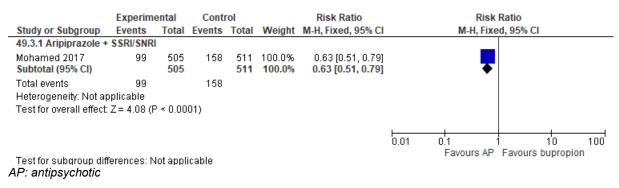
AP: antipsychotic

# Figure 303: Response (ITT)

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
49.2.1 Aripiprazole +	+ SSRI/SNR						
Mohamed 2017 <b>Subtotal (95% Cl)</b>	375	505 505	319	511 <b>511</b>	100.0% <b>100.0%</b>	1.19 [1.09, 1.29] <b>1.19 [1.09, 1.29]</b>	,
Total events Heterogeneity: Not a Test for overall effect		P < 0.00	319 01)				
Test for subaroup di	fferences: N	lot appl	icable				0.01 0.1 1 10 100 Favours bupropion Favours AP

ifferences: Not applicable AP: antipsychotic

# Figure 304: Discontinuation due to any reason



#### Figure 305: Discontinuation due to side effects

	Experime	ental	Contr	ol		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H	, Fixed, 95% (	CI	
49.4.1 Aripiprazole +	SSRI/SNRI										
Mohamed 2017 Subtotal (95% Cl)	27	505 <b>505</b>	51	511 <b>511</b>	100.0% <b>100.0%</b>	0.54 [0.34, 0.84] 0.54 [0.34, 0.84]					
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.00	51 7)								
Test for subgroup dif AP: antipsychotic	ferences: N	lot appl	icable				L 0.01	0.1 Favour	1 s AP Favour	10 s buprop	100 ion

#### Comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/placebo)

# Figure 306: Remission (ITT)

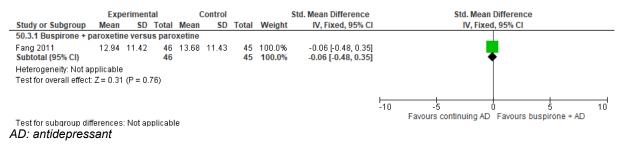
	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI		
50.1.1 Buspirone + p	paroxetine	versus	paroxeti	ne					
Fang 2011 Subtotal (95% CI)	15	46 <b>46</b>	21	45 <b>45</b>	100.0% <b>100.0%</b>	0.70 [0.42, 1.18] <b>0.70 [0.42, 1.18]</b>			
Total events Heterogeneity: Not a Test for overall effect	• •	<sup>o</sup> = 0.18	21						
Test for subgroup di	fferences: N	lot appl	icable				.01 0.1 1 Favours continuing AD Favours	10 buspirone + AD	100

Test for subgroup differences: Not applicable AD: antidepressant

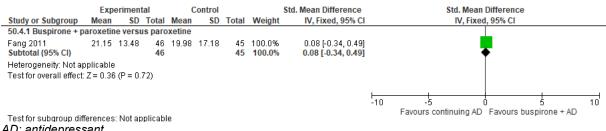
# Figure 307: Response (ITT)

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
50.2.1 Buspirone + S	SRI versus	s placel	00 + SSR				
Appelberg 2001 Subtotal (95% CI)	17	51 <b>51</b>	16	51 <b>51</b>	25.3% <b>25.3%</b>	1.06 [0.61, 1.86] 1.06 [0.61, 1.86]	<b>*</b>
Total events	17		16				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.21 (F	P = 0.83	)				
50.2.2 Buspirone + p	aroxetine	versus	paroxetii	ie			
Fang 2011	26	46	30	45	74.7%	0.85 [0.61, 1.18]	-
Subtotal (95% CI)		46		45	74.7%	0.85 [0.61, 1.18]	•
Total events	26		30				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.99 (F	P = 0.32	)				
Total (95% CI)		97		96	100.0%	0.90 [0.68, 1.19]	•
Total events	43		46				
Heterogeneity: Tau² =	: 0.00; Chi <b>²</b>	= 0.50,	df = 1 (P	= 0.48)	); I <b>ž</b> = 0%		
Test for overall effect:			,				Favours continuing AD Favours buspirone + AD
Test for subgroup dif		hi² = 0.	46. df = 1	(P = 0.	.50), I <sup>2</sup> = 0	1%	
AD: antidepressa	ant						

#### Figure 308: Quality of life physical component score (PCS) change score

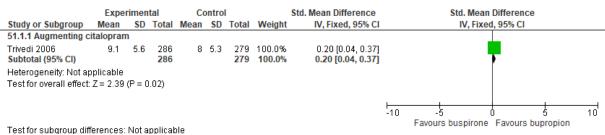


#### Figure 309: Quality of life mental component score (MCS) change score

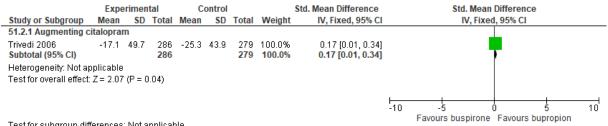


# Comparison 51. Augmenting with buspirone versus bupropion

#### Figure 310: Depression symptomatology endpoint

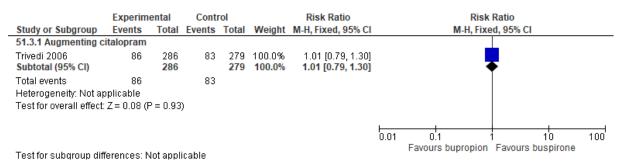


# Figure 311: Depression symptomatology change score



Test for subgroup differences: Not applicable

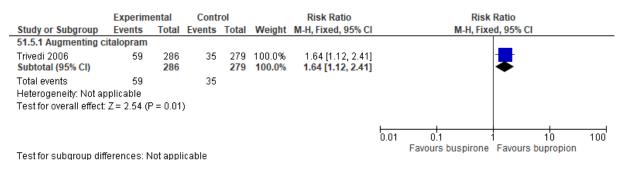
# Figure 312: Remission (ITT)



# Figure 313: Response (ITT)

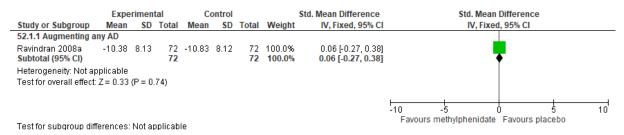
	Experimental Control			Risk Ratio		Risk	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
51.4.1 Augmenting ci	talopram									
Trivedi 2006 Subtotal (95% CI)	77	286 <b>286</b>	88	279 <b>279</b>	100.0% <b>100.0%</b>	0.85 [0.66, 1.10] <b>0.85 [0.66, 1.10]</b>				
Total events Heterogeneity: Not ap Test for overall effect: .	•	P = 0.23	88							
							⊢ 0.01	0.1 Favours bupropion	1 10	100

## Figure 314: Discontinuation due to side effects

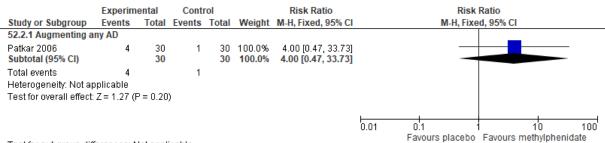


# Comparison 52. Augmenting with methylphenidate versus placebo

# Figure 315: Depression symptomatology change score

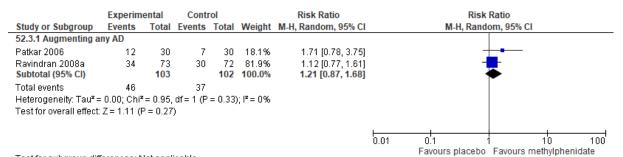


#### Figure 316: Remission (ITT)

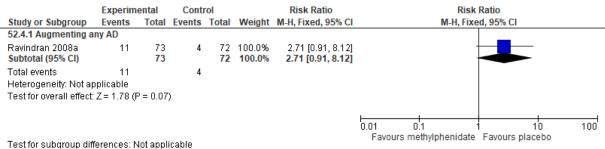


Test for subgroup differences: Not applicable

#### Figure 317: Response (ITT)



# Figure 318: Discontinuation due to any reason



#### Figure 319: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio		Risk	Ratio	
Study or Subgroup	· · · ·		Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl			
52.5.1 Augmenting a	ny AD									
Patkar 2006	2	30	2	30	58.0%	1.00 [0.15, 6.64]			<b></b>	
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 <sup>2</sup> =	= 2.18; Chi <sup>z</sup>	= 2.42,	df = 1 (P	= 0.12)	); I² = 59%	6				
Test for overall effect:	Z = 0.80 (F	P = 0.43	)							
							0.01	0.1	1 10	100
								rs methylphenidate		100

Test for subgroup differences: Not applicable

#### Comparison 53. Augmenting with lithium versus continuing with antidepressant (+/placebo)

# Figure 320: Depression symptomatology endpoint

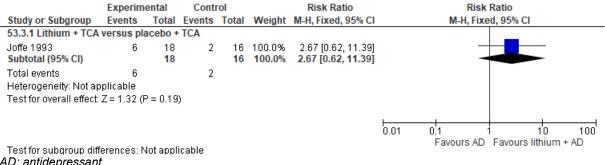
	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
53.1.1 Lithium + TCA	versus p	placet	00 + TC	Α					
Joffe 1993	12.1	7.3	17	14.9	8	16	48.9%	-0.36 [-1.05, 0.33]	
Stein 1993 Subtotal (95% CI)	21.6	6.7	16 <b>33</b>	22.7	11.9	18 <b>34</b>	51.1% <b>100.0%</b>	-0.11 [-0.78, 0.56] - <b>0.23 [-0.71, 0.25]</b>	<b>→</b>
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	•			= 1 (P =	0.61);	I <sup>2</sup> = 0%			
reactor overall effect.	. 2 - 0.34	() = 0							
Test for subaroup dif	ferences:	Nota	nnlicat	nlo					Favours lithium + AD Favours AD

rences: Not applicable AD: antidepressant

# Figure 321: Depression symptomatology change score

	Expo	rimen	tal	6	ontro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean				SD	lotal	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
53.2.1 Lithium + TCA	versus	placet	00 + TC	Α					
Joffe 1993	-8.1	4.83	17	-3.8	5.5	16	29.6%	-0.81 [-1.53, -0.10]	-#-
Stein 1993	-7.3	4.9	16	-7.9	9.6	18	31.8%	0.08 [-0.60, 0.75]	+
Subtotal (95% CI)			33			34	61.3%	-0.36 [-1.23, 0.51]	◆
Heterogeneity: Tau <sup>2</sup> =	0.27; CI	hi <sup>z</sup> = 3.	14, df=	= 1 (P =	0.08)	; <b>I2</b> = 68	3%		
Test for overall effect:	•								
53.2.2 Lithium + any	AD versi	us any	AD						
Girlanda 2014	-7	8.2	27	-6.1	5.7	22	38.7%	-0.12 [-0.69, 0.44]	+
Subtotal (95% CI)			27			22	38.7%	-0.12 [-0.69, 0.44]	<b></b>
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.43	(P = 0	1.67)						
Total (95% CI)			60			56	100.0%	-0.26 [-0.76, 0.23]	•
Heterogeneity: Tau <sup>2</sup> =	0.08; CI	hi² = 3.	47, df=	= 2 (P =	0.18)	; l² = 42	2%		
Test for overall effect:	Z = 1.05	(P = 0	1.29)						-10 -5 0 5 10 Favours lithium + AD Favours AD
Test for subgroup diff	erences	∶Čhi <b></b> ≇⊧	= 0.20.	df = 1 (F	<sup>o</sup> = 0.	65), I <sup>2</sup> =	= 0%		
AD: antidepressar									

#### Figure 322: Remission (ITT)

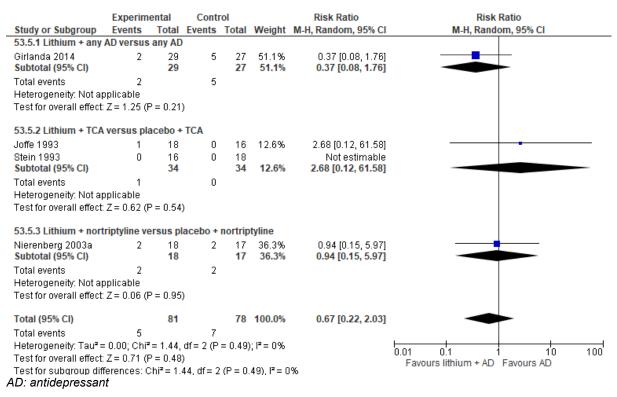


AD: antidepressant

#### Figure 323: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
53.4.1 Lithium + cital	opram ver	sus pla	cebo + c	italopr	am		
Baumann 1996 Subtotal (95% CI)	6	10 <b>10</b>	2	14 <b>14</b>	53.1% <b>53.1%</b>	4.20 [1.06, 16.68] 4.20 [1.06, 16.68]	
Total events	6		2				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.04 (F	P = 0.04)	)				
53.4.2 Lithium + nort	riptyline ve	ersus pl	acebo +	nortrip	tyline		
Nierenberg 2003a Subtotal (95% CI)	2	18 <b>18</b>	3	17 17	46.9% 46.9%	0.63 [0.12, 3.32] 0.63 [0.12, 3.32]	
Total events Heterogeneity: Not ap	2 plicable		3				
Test for overall effect:	•	e = 0.59)	)				
Total (95% CI)		28		31	100.0%	1.72 [0.27, 11.05]	
Total events	8		5				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff AD: antidepressa	Z = 0.58 (F ferences: C	e = 0.57)	)				0.01 0.1 1 10 100 Favours continuing AD Favours lithium + AD
AD. annuepiessa							

#### Figure 324: Discontinuation due to any reason



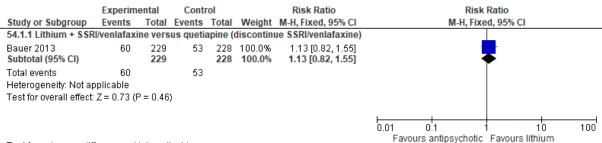
#### Figure 325: Discontinuation due to side effects

	Experim	ental	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
53.6.1 Lithium + TC/	A versus pl	acebo +	TCA							
Joffe 1993	1	18	0	16	100.0%	2.68 [0.12, 61.58]				
Stein 1993	0	16	0	18		Not estimable				
Subtotal (95% CI)		34		34	100.0%	2.68 [0.12, 61.58]				
Total events	1		0							
Heterogeneity: Not a	pplicable									
Test for overall effect	t: Z = 0.62 (I	<sup>o</sup> = 0.54	)							
								01		100
								urs lithium + AD	Favours AD	100
	~ .						1 4 4 0	aro nanami · AD	r avoara AD	

Test for subgroup differences: Not applicable AD: antidepressant

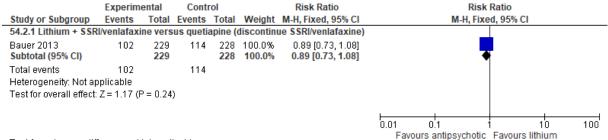
# Comparison 54. Augmenting with lithium versus switch to antipsychotic

#### Figure 326: Remission (ITT)



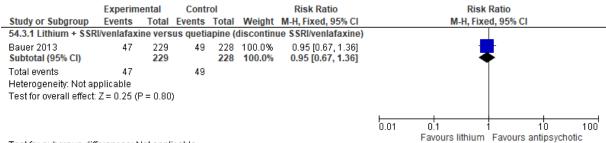
Test for subgroup differences: Not applicable

# Figure 327: Response (ITT)



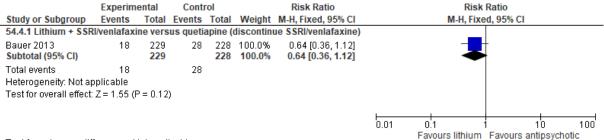
Test for subgroup differences: Not applicable

#### Figure 328: Discontinuation due to any reason



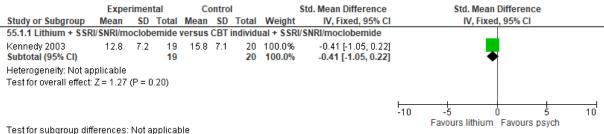
Test for subgroup differences: Not applicable

# Figure 329: Discontinuation due to side effects

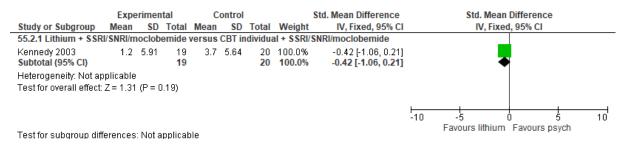


# Comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

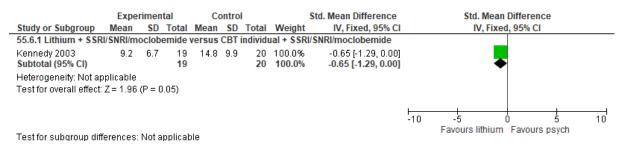
#### Figure 330: Depression symptomatology endpoint



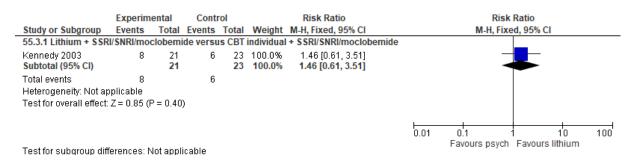
#### Figure 331: Depression symptomatology change score



#### Figure 332: Depression symptomatology at 1-month follow-up

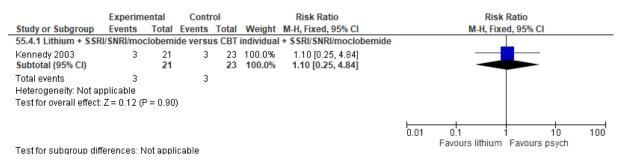


# Figure 333: Remission (ITT)

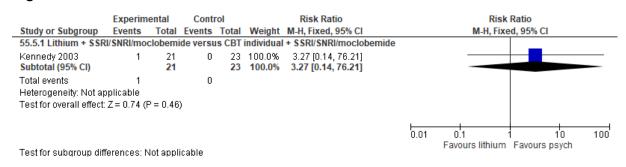


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#### Figure 334: Discontinuation due to any reason

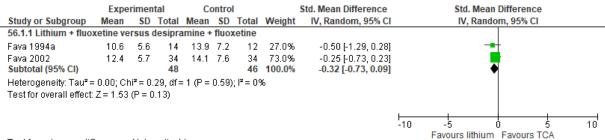


#### Figure 335: Discontinuation due to side effects



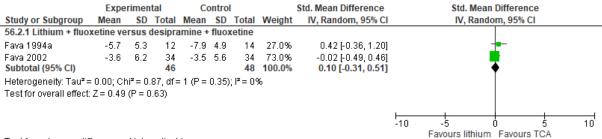
#### Comparison 56. Augmenting with lithium versus augmenting with TCA

#### Figure 336: Depression symptomatology endpoint



#### Test for subgroup differences: Not applicable

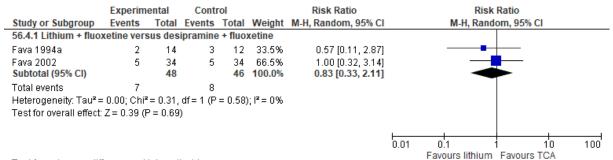
#### Figure 337: Depression symptomatology change score



# Figure 338: Remission (ITT)

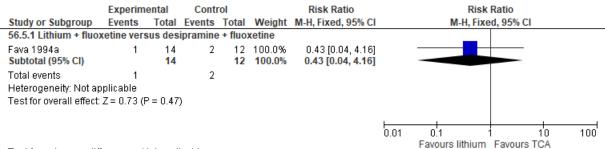
	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
56.3.1 Lithium + fluo	xetine vers	sus des	ipramine	e + fluo	xetine				
Fava 1994a	4	14	3	12	27.9%	1.14 [0.32, 4.12]		<b>_</b>	
Fava 2002 Subtotal (95% CI)	8	34 <b>48</b>	10	34 <b>46</b>	72.1% 100.0%	0.80 [0.36, 1.78] 0.88 [0.45, 1.74]		-	
Total events Heterogeneity: Tau² Test for overall effect	•			= 0.64)	); I² = 0%				
Test for subgroup dit	ferences:♪	Vot appl	icable				L	0.1 1 10 Favours TCA Favours lithium	100

# Figure 339: Discontinuation due to any reason



Test for subgroup differences: Not applicable

#### Figure 340: Discontinuation due to side effects



# Comparison 57. Augmenting with omega-3 fatty acids versus placebo

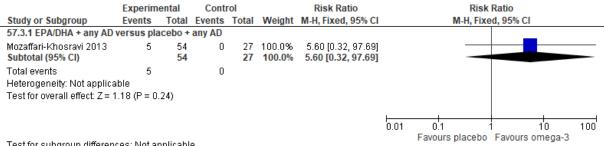
#### Figure 341: Depression symptomatology endpoint

	Exp	erimen	tal	С	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI
57.1.1 Omega-3 + sertra	line vers	us plac	cebo +	sertral	ine					
Jahangard 2018 Subtotal (95% CI)	6	2.38	25 <b>25</b>	17.2	3.52	25 <b>25</b>	32.7% <b>32.7%</b>	-3.67 [-4.60, -2.74] - <b>3.67 [-4.60, -2.74]</b>		•
Heterogeneity: Not applic	able									
Test for overall effect: Z =	7.72 (P <	0.000	01)							
57.1.2 EPA + SSRI versus	s placeb	o + SSF	રા							
Nemets 2002 Subtotal (95% CI)	11.6		10 <b>10</b>	20	8.8	10 <b>10</b>	32.6% <b>32.6%</b>	-1.06 [-2.01, -0.11] - <b>1.06 [-2.01, -0.11]</b>		_ <b>+</b> _
Heterogeneity: Not applic Test for overall effect: Z =		: 0.03)								
57.1.3 EPA/DHA + any AD	) versus	placeb	o + any	AD						
Mozaffari-Khosravi 2013 Subtotal (95% CI)	11.96	3.39	41 <b>41</b>	13.7	2.75	21 <b>21</b>	34.6% <b>34.6%</b>	-0.54 [-1.07, -0.00] - <b>0.54 [-1.07, -0.00]</b>		•
Heterogeneity: Not applic	able									
Test for overall effect: Z =	1.97 (P =	0.05)								
Total (95% CI)			76			56	100.0%	-1.73 [-3.59, 0.12]		-
Heterogeneity: Tau <sup>2</sup> = 2.5 Test for overall effect: Z = Test for subgroup differer	1.83 (P =	: 0.07)							-10	-5 0 5 10 Favours omega-3 Favours placebo

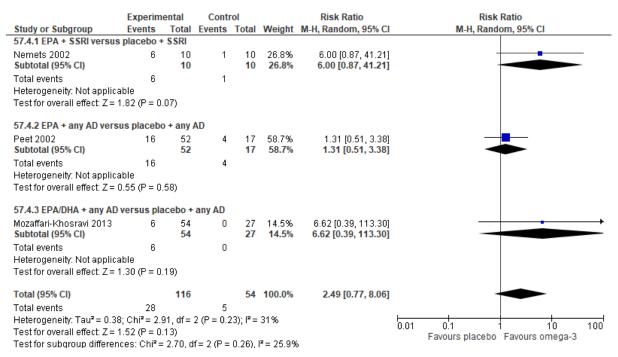
# Figure 342: Depression symptomatology change score

	Expe	eriment	al	С	Std. Mean Difference	nce Std. Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
57.2.1 Omega-3 + sertral	ine vers	us plac	ebo +	sertral	ine						-
Jahangard 2018 Subtotal (95% Cl)	-31.2	6	25 <b>25</b>	-15.4	5.42	25 <b>25</b>		-2.72 [-3.50, -1.94] - <b>2.72 [-3.50, -1.94]</b>		•	
Heterogeneity: Not applica	able										
Test for overall effect: Z = 6	6.79 (P <	0.0000	11)								
57.2.2 EPA + SSRI versus	placebo	o + SSR	1								
Nemets 2002 Subtotal (95% CI)	-12.4	4.46	10 <b>10</b>	-2.3	6.95	10 <b>10</b>		-1.66 [-2.70, -0.61] - <b>1.66 [-2.70, -0.61]</b>		•	
Heterogeneity: Not applica Test for overall effect: Z = 3		0.002)									
57.2.3 EPA/DHA + any AD	versus	placebo	) + any	AD							
Mozaffari-Khosravi 2013 Subtotal (95% CI)	-3.84	3.4	41 <b>41</b>	-1.9	2.29	21 <b>21</b>	35.6% <b>35.6%</b>	-0.62 [-1.16, -0.08] -0.62 [-1.16, -0.08]		*	
Heterogeneity: Not applica Test for overall effect: Z = 2		0.02)									
Total (95% CI)			76				100.0%	-1.65 [-3.02, -0.27]			
Heterogeneity: Tau <sup>2</sup> = 1.30	);Chi²=	19.05, (	lf = 2 (	P < 0.0	001); F	²= 90%	5		-10	-5 0 5	10
Test for overall effect: Z = 2	2.35 (P =	0.02)								Favours omega-3 Favours placebo	10
Test for subgroup differen	ces: Chi	<sup>2</sup> = 19.0	5. df =	2 (P <	0.0001	l), l <sup>z</sup> = 8	39.5%			· · · · · · · · · · · · · · · · · · ·	

#### Figure 343: Remission (ITT)



# Figure 344: Response (ITT)

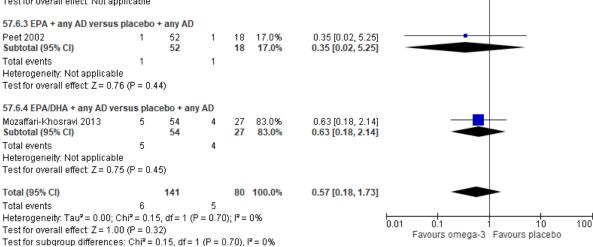


#### Figure 345: Discontinuation due to any reason

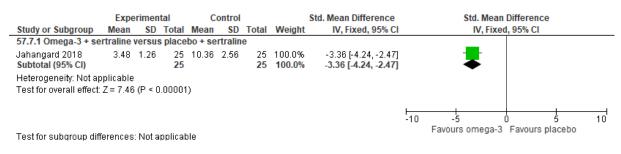
	Experime		Contr			Risk Ratio Risk Ratio				
Study or Subgroup 57.5.1 Omega-3 + sertra	Events line versus				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
Jahangard 2018 Subtotal (95% CI)	0	25 <b>25</b>	0	25 25		Not estimable <mark>Not estimable</mark>				
Total events Heterogeneity: Not applic			0							
Test for overall effect: No	t applicable									
57.5.2 EPA + \$\$RI versu	s placebo +	SSRI								
Nemets 2002 Subtotal (95% CI)	0	10 <b>10</b>	1	10 <b>10</b>	4.7% <b>4.7%</b>	0.33 [0.02, 7.32] 0.33 [0.02, 7.32]				
Total events Heterogeneity: Not applic Test for overall effect: Z =		49)	1							
57.5.3 EPA + any AD vers		-		40	22.00	0 50 10 47 4 601				
Peet 2002 Subtotal (95% CI)	6	52 <b>52</b>	4	18 <mark>18</mark>	33.8% <b>33.8%</b>	0.52 [0.17, 1.63] <b>0.52 [0.17, 1.63]</b>				
Total events Heterogeneity: Not applic	6 able		4							
Test for overall effect: Z =		26)								
57.5.4 EPA/DHA + any AI	) versus pla	cebo +	any AD							
Mozaffari-Khosravi 2013 Subtotal (95% CI)	13	54 54	6	27 27	61.5% <b>61.5%</b>	1.08 [0.46, 2.53] <b>1.08 [0.46, 2.53]</b>	<u>+</u>			
Total events	13	54	6	21	01.5%	1.00 [0.40, 2.33]				
Heterogeneity: Not applic Test for overall effect: Z =		85)								
Total (95% CI)		141		80	100.0%	0.80 [0.41, 1.56]	-			
Total events	19		11				_			
Heterogeneity: Tau² = 0.0			2 (P = 0.5	51); I² =	0%		0.01 0.1 1 10 100			
Test for overall effect: Z =							Favours omega-3 Favours placebo			
Test for subgroup differe	nces: Chí² =	1.34, df	r= 2 (P =	0.51),	If = 0%					

#### Experimental Control **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% CI 57.6.1 Omega-3 + sertraline versus placebo + sertraline Jahangard 2018 Π 25 Π 25 Not estimable 25 Subtotal (95% CI) 25 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable 57.6.2 EPA + \$\$RI versus placebo + \$\$RI Nemets 2002 0 10 0 10 Not estimable Subtotal (95% CI) 10 10 Not estimable 0 Total events 0 Heterogeneity: Not applicable Test for overall effect: Not applicable 57.6.3 EPA + any AD versus placebo + any AD 18

# Figure 346: Discontinuation due to side effects

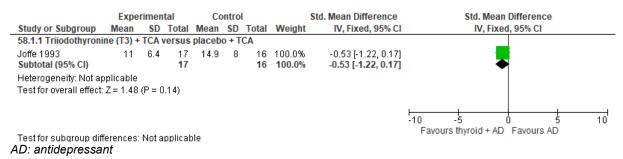


# Figure 347: Sleeping difficulties endpoint

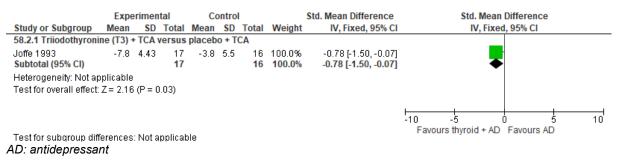


# Comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant (+/- placebo)

# Figure 348: Depression symptomatology endpoint



# Figure 349: Depression symptoms change score



# Figure 350: Remission (ITT)

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
58.3.1 Thyroid hormo	ne + paro	xetine v	ersus pa	aroxeti	ne		
Fang 2011	18	48	21	45	61.1%	0.80 [0.50, 1.30]	
Subtotal (95% CI)		48		45	61.1%	0.80 [0.50, 1.30]	•
Total events	18		21				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.89 (F	P = 0.37	)				
58.3.2 Triiodothyronii	ne (T3) + T	CA vers	sus place	ebo + T	CA		
Joffe 1993	7	17	2	16	38.9%	3.29 [0.80, 13.57]	
Subtotal (95% CI)		17		16	38.9%	3.29 [0.80, 13.57]	
Total events	7		2				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.65 (F	P = 0.10	)				
Total (95% CI)		65		61	100.0%	1.39 [0.35, 5.53]	
Total events	25		23				
Heterogeneity: Tau² =	0.75; Chi <sup>z</sup>	= 3.58,	df = 1 (P	= 0.06)	; I² = 72%		
Test for overall effect:	Z=0.47 (F	P = 0.64	)				Favours AD Favours thyroid + AD
Test for subgroup diff		≻hi² = 3.	42. df = 1	(P = 0.	06), <b>i</b> ² = 7	0.8%	
AD: antidepressan	t						

#### Figure 351: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		CI	
58.4.1 Thyroid horm	one + paro	xetine v	ersus pa	aroxeti	ne				
Fang 2011 Subtotal (95% CI)	28	48 <b>48</b>	30	45 <b>45</b>	100.0% <b>100.0%</b>	0.88 [0.64, 1.20] <b>0.88 [0.64, 1.20]</b>		-	
Total events Heterogeneity: Not a Test for overall effect		P = 0.41	30 )						
Test for subaroun di	¥	let en ul	isabla				L	0.1 1 Favours AD Favou	10 100 Irs thyroid + AD

Test for subgroup differences: Not applicable AD: antidepressant

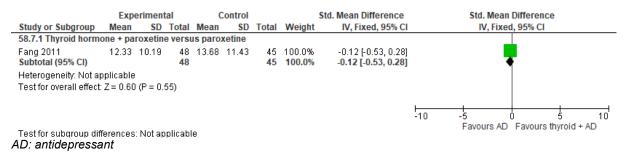
# Figure 352: Discontinuation due to any reason

	Experime	ental	Cont	rol		Risk Ratio			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% C				
58.5.1 Triiodothyroni	ne (T3) + TCA versus placebo + T(				CA							
Joffe 1993 Subtotal (95% CI)	0	17 <b>17</b>	0	16 <b>16</b>		Not estimable Not estimable						
Total events Heterogeneity: Not ap Test for overall effect:	•	able	0				L	<b> </b>			100	
Test for subgroup diff AD: antidepressan		lot appl	icable						AD Favour		100	

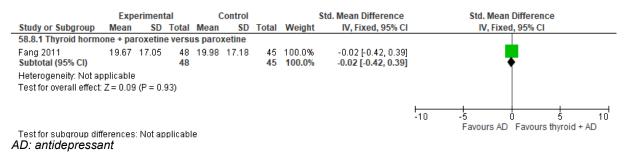
#### Figure 353: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	ht M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl						
58.6.1 Triiodothyronii	ne (T3) + T	CA ver	sus place	ebo + T	CA							
Joffe 1993 Subtotal (95% CI)	0	17 <b>17</b>	0	16 <b>16</b>		Not estimable Not estimable						
Total events Heterogeneity: Not ap Test for overall effect:	•	able	0									
Test for subgroup diff AD: antidepressant		Vot appl	icable				0.01 Favor	0.1 urs thyroid +	AD Favours A	10 D	100	

#### Figure 354: Quality of life physical component score (PCS) change score

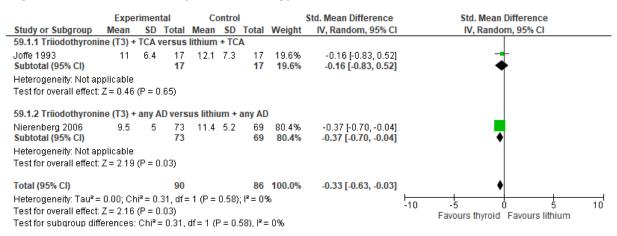


#### Figure 355: Quality of life mental component score (MCS) change score

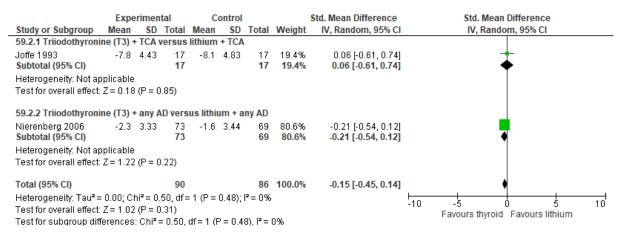


# Comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

#### Figure 356: Depression symptomatology endpoint



# Figure 357: Depression symptomatology change score



# Figure 358: Remission (ITT)

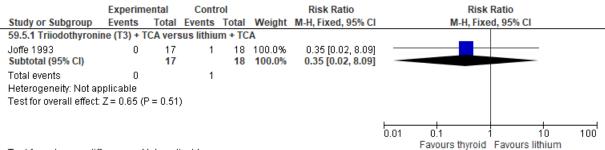
	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Ra	ndom, 95% Cl			
59.3.1 Triiodothyronii	ne (T3) + T	CA vers	sus lithiu	m + TC	A						
Joffe 1993	7	17	6	18	41.5%	1.24 [0.52, 2.94]					
Subtotal (95% CI)		17		18	41.5%	1.24 [0.52, 2.94]		◆			
Total events	7		6								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z=0.48 (F	P = 0.63	)								
59.3.2 Triiodothyronii	ne (T3) + a	ny AD v	ersus lit	hium +	any AD						
Nierenberg 2006	18	73	9	69	58.5%	1.89 [0.91, 3.92]					
Subtotal (95% CI)		73		69	58.5%	1.89 [0.91, 3.92]		-			
Total events	18		9								
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z=1.71 (F	P = 0.09	)								
Total (95% CI)		90		87	100.0%	1.58 [0.91, 2.77]		•			
Total events	25		15								
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	²= 0.56,	df = 1 (P	= 0.46)	); I² = 0%		0.01 0.1		100		
Test for overall effect:	Z = 1.62 (F	<sup>o</sup> = 0.11)	)					m Favours thyroid	100		
Test for subgroup diff	erences: C	Chi <b>²</b> = 0.	54. df = 1	(P = 0)	46), I <sup>2</sup> = 0	1%	, avours nunu	in ravous ulyrolu			

# Figure 359: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
59.4.1 Triiodothyron	ine (T3) + a	iny AD v	ersus lit	hium +	any AD		
Nierenberg 2006 Subtotal (95% CI)	17	73 <b>73</b>	11	69 <mark>69</mark>	100.0% <b>100.0%</b>	1.46 [0.74, 2.89] <b>1.46 [0.74, 2.89]</b>	
Total events Heterogeneity: Not a Test for overall effect		<sup>o</sup> = 0.28	11 )				
Test for subaroup dit	ffarannae: N	lot anni	icable				0.01 0.1 1 10 100 Favours lithium Favours thyroid

Test for subgroup differences: Not applicable

# Figure 360: Discontinuation due to any reason



Test for subgroup differences: Not applicable

#### Figure 361: Discontinuation due to side effects

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
59.6.1 Triiodothyronir	ne (T3) + 1				_		
Joffe 1993 Subtotal (95% CI)	0	17 17	1	18 <b>18</b>	6.5% <b>6.5%</b>	0.35 [0.02, 8.09] 0.35 [0.02, 8.09]	
Total events	0		1	10	0.3%	0.55 [0.02, 6.09]	
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.65 (I	P = 0.51	)				
59.6.2 Triiodothyronir	ne (T3) + a	any AD v	ersus litl	hium +	any AD		_
Nierenberg 2006 Subtotal (95% CI)	7	73 <b>73</b>	16	69 69	93.5% <b>93.5%</b>	0.41 [0.18, 0.94] <b>0.41 [0.18, 0.94]</b>	
Total events	7		16				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.10 (I	P = 0.04	)				
Total (95% CI)		90		87	100.0%	0.41 [0.18, 0.91]	-
Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: . Test for subgroup diffe	Z = 2.20 (I	P = 0.03	)		•		0.01 0.1 1 10 100 Favours thyroid Favours lithium

#### Comparison 60. Switching to ECT versus switching to paroxetine

#### Figure 362: Depression symptomatology endpoint

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI	
Folkerts 1997	12.5	3.9	21	23	10.4	18	100.0%	-1.35 [-2.06, -0.65]				
Total (95% Cl) Heterogeneity: Not ap	nlicahla		21			18	100.0%	-1.35 [-2.06, -0.65]	<b></b>	•		<b>I</b>
Test for overall effect:	•	(P = 0	.0002)						-10	-5 Favours ECT	Ó Favours AD	5 10 <sup>°</sup> )

# Figure 363: Depression symptomatology change score

	Experimental Control							Std. Mean Difference	Std. Mean	Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	l, 95% CI		
Folkerts 1997	-18.6	3.25	21	-9.6	7.29	18	100.0%	-1.61 [-2.34, -0.87]		-			
Total (95% CI)			21			18	100.0%	-1.61 [-2.34, -0.87]		•			
Heterogeneity: Not applicable Test for overall effect: Z = 4.29 (P < 0.0001)									-10	-5 ( Favours ECT	Favours AD	5	10
AD: antidepressa	nt												

# Figure 364: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Folkerts 1997	15	21	5	19	100.0%	2.71 [1.22, 6.04]	
Total (95% CI)		21		19	100.0%	2.71 [1.22, 6.04]	◆
Total events	15		5				
Heterogeneity: Not ap	oplicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 2.45 (F	° = 0.01	)				Favours AD Favours ECT

AD: antidepressant

# Figure 365: Discontinuation due to any reason

	Experim	ental	Cont	ol		Risk Ratio	Risk Ratio
Study or Subgroup	ly or Subgroup Events Total		Events Tota		Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Folkerts 1997	0	21	1	19	100.0%	0.30 [0.01, 7.02]	
Total (95% CI)		21		19	100.0%	0.30 [0.01, 7.02]	
Total events	0		1				
Heterogeneity: Not ap	pplicable						0.01 0.1 1 10 100
Test for overall effect	: Z = 0.74 (F	°=0.46	)				0.01 0.1 1 10 100 Favours ECT Favours AD

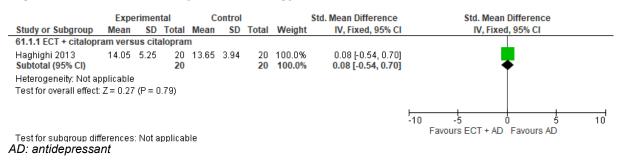
AD: antidepressant

# Figure 366: Discontinuation due to side effects

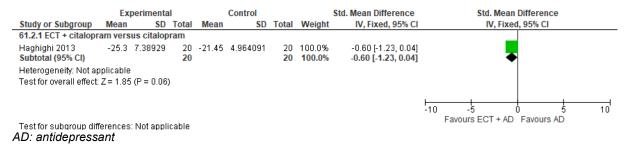
	Experim	ental	Contr	ol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
Folkerts 1997	0	21	0	19		Not estimable				
Total (95% CI)		21		19		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	oplicable						0.01		<u> </u>	0 100
Test for overall effect:	Not applic	able					0.01	Favours ECT	Favours AD	

# Comparison 61. Augmenting with ECT versus continuing with antidepressant

#### Figure 367: Depression symptomatology endpoint



#### Figure 368: Depression symptomatology change score



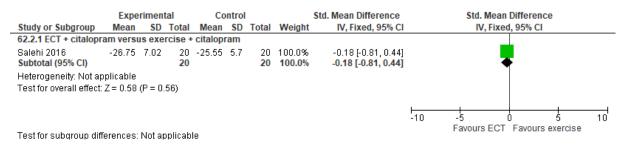
# Comparison 62. Augmenting with ECT versus augmenting with exercise

#### Figure 369: Depression symptomatology endpoint

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std.	Mean Differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95%	CI	
62.1.1 ECT + citalopr	am vers	us exe	ercise	+ citalo	oram								-
Salehi 2016 Subtotal (95% CI)	15.35	4.03	20 <b>20</b>	14.8	4.87		100.0% <b>100.0%</b>	0.12 [-0.50, 0.74] 0.12 [-0.50, 0.74]			•		
Heterogeneity: Not ap Test for overall effect:			).70)										
									⊢ -10			5	10
Ta at fan anderson die	-									Favours	ECT Favou	irs exercise	

Test for subgroup differences: Not applicable

#### Figure 370: Depression symptomatology change score

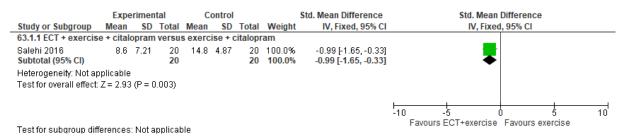


# Figure 371: Remission (ITT)

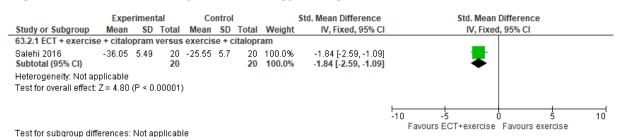
	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
62.3.1 ECT + citalopr	am versus	в ехегсі	se + cita	lopram	1		
Salehi 2016 Subtotal (95% CI)	2	20 <b>20</b>	2	20 <b>20</b>	100.0% <b>100.0%</b>	1.00 [0.16, 6.42] <b>1.00 [0.16, 6.42]</b>	
Total events Heterogeneity: Not ap Test for overall effect:	•	° = 1.00	2				
Test for subgroup dif	ferences: N	lot appl	icable				0.01 0.1 1 10 100 Favours exercise Favours ECT

#### Comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

#### Figure 372: Depression symptomatology endpoint



# Figure 373: Depression symptomatology change score

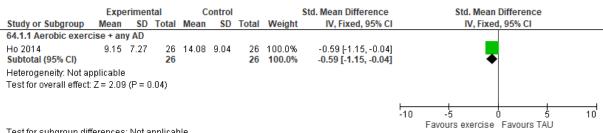


# Figure 374: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
63.3.1 ECT + exercis	se + citalop	ram ve	rsus exe	rcise +	citalopra	Im		
Salehi 2016 Subtotal (95% CI)	13	20 <b>20</b>	2	20 <b>20</b>	100.0% <b>100.0%</b>	6.50 [1.68, 25.16] 6.50 [1.68, 25.16]		
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	2 7)					
Taat far aubaraun di	foronaa: b	let en ni	iaabla				⊢ 0.01	0.1 1 10 100 Favours exercise Favours ECT+exercise

# Comparison 64. Augmenting with exercise versus TAU

#### Figure 375: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

#### Figure 376: Depression symptomatology change score

	Expe	rimen	tal	C	ontrol			Std. Mean Difference		Std. Mea	n Differ	ence	
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Ran	dom, 95	% CI	
64.2.1 Aerobic exerc	ise + SS	RI/SNR	1										
Danielsson 2014 Subtotal (95% CI)	-10.3	7.5	22 22	-4.6	7.6	20 <b>20</b>	44.1% <b>44.1%</b>	-0.74 [-1.37, -0.11] - <b>0.74 [-1.37, -0.11]</b>		-	•		
Heterogeneity: Not ap	plicable												
Test for overall effect:	Z = 2.31	(P = 0.	02)										
64.2.2 Aerobic exerc	ise + any	AD											
Ho 2014 Subtotal (95% CI)	-10.08	9.41	26 <b>26</b>	-4.69	7.33	26 <b>26</b>	55.9% <mark>55.9%</mark>	-0.63 [-1.19, -0.07] - <b>0.63 [-1.19, -0.07]</b>			•		
Heterogeneity: Not ap Test for overall effect:		(P = 0.	03)										
Total (95% CI)			48			46	100.0%	-0.68 [-1.10, -0.26]			•		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff	Z= 3.19	(P = 0.	001)	`			)%		⊢ -10	-5 Favours exercis	0 e Favo	5 ours TAU	10

# Figure 377: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
64.3.1 Aerobic exerc	ise + SSRI	/SNRI					
Danielsson 2014 Subtotal (95% CI)	7	22 <b>22</b>	3	20 <b>20</b>	26.5% <b>26.5%</b>	2.12 [0.63, 7.11] 2.12 [0.63, 7.11]	
Total events	7		3				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.22 (F	P = 0.22	)				
64.3.2 Aerobic exerc	ise + any /	AD					
Ho 2014 Subtotal (95% CI)	14	26 <b>26</b>	7	26 <b>26</b>	73.5% <b>73.5%</b>	2.00 [0.97, 4.14] <b>2.00 [0.97, 4.14]</b>	
Total events	14		7				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.87 (F	P = 0.06	)				
Total (95% CI)		48		46	100.0%	2.03 [1.09, 3.79]	◆
Total events	21		10				
Heterogeneity: Tau² =	0.00; Chi <sup>z</sup>	= 0.01,	df = 1 (P	= 0.93)	; I² = 0%		
Test for overall effect:	Z = 2.23 (F	P = 0.03	)				Favours TAU Favours exercise
Test for subgroup diff	erences: C	¦hi² = 0.1	01. df = 1	(P = 0.	93), I <sup>z</sup> = 0	1%	

# Figure 378: Response (ITT)

	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	CI M-H, Fixed, 95% CI
64.4.1 Aerobic exer	cise + SSR	/SNRI					
Danielsson 2014 Subtotal (95% CI)	9	22 <b>22</b>	5	20 <b>20</b>	100.0% <b>100.0%</b>	1.64 [0.66, 4.07] <b>1.64 [0.66, 4.07]</b>	
Total events Heterogeneity: Not a Test for overall effect		P = 0.29	5				
Test for subgroup di	ferences: N	lot appl	icable				0.01 0.1 1 10 10 Favours TAU Favours exercise

# Figure 379: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
64.5.1 Aerobic exerc	ise + SSRI	/SNRI					
Danielsson 2014 Subtotal (95% CI)	4	22 <b>22</b>	4	20 <b>20</b>	39.7% <b>39.7%</b>	0.91 [0.26, 3.16] 0.91 [0.26, 3.16]	-
Total events	4		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.15 (F	P = 0.88	)				
64.5.2 Aerobic exerc	ise + any /	AD					
Ho 2014 Subtotal (95% CI)	7	26 <b>26</b>	5	26 <b>26</b>	60.3% <mark>60.3%</mark>	1.40 [0.51, 3.85] <b>1.40 [0.51, 3.85]</b>	
Total events	7		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.65 (F	P = 0.51	)				
Total (95% CI)		48		46	100.0%	1.18 [0.54, 2.59]	-
Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup diff	Z=0.41 (F	e = 0.68	)		•	%	0.01 0.1 1 10 100 Favours exercise Favours TAU

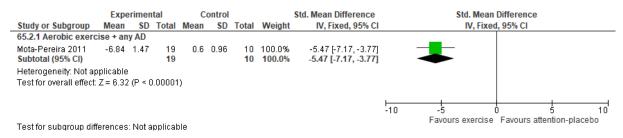
# Comparison 65. Augmenting with exercise versus attention-placebo

#### Figure 380: Depression symptomatology endpoint

	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference		Sto	i. Mean I	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI			IV, Fixed	, 95% CI		
65.1.1 Tai chi group	+ escital	opram	1											
Lavretsky 2011 Subtotal (95% CI)	5.1	3.5	33 <b>33</b>	6.7	4.4	35 <b>35</b>	100.0% <b>100.0%</b>	-0.40 [-0.88, 0.08] - <b>0.40 [-0.88, 0.08]</b>			•			
Heterogeneity: Not a Test for overall effect			.11)											
									⊢ -10	-5			5	10
Test for subaroup dif	ferences:	Nota	nnlical	hle						Favours e	xercise	Favours atte	ntion-pla	cebo

fferences: Not applica

# Figure 381: Depression symptomatology change score



# Figure 382: Remission (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
65.3.1 Aerobic exerc	ise + any /	AD						
Mota-Pereira 2011	5	22 22	0	11 <b>11</b>	14.4% <b>14.4%</b>	5.74 [0.35, 95.29]		
Subtotal (95% CI) Total events	5	~~~~	0		14.470	5.74 [0.35, 95.29]		
Heterogeneity: Not ap	plicable		-					
Test for overall effect:	•	° = 0.22	)					
65.3.2 Tai chi group	+ escitalop	oram						
Lavretsky 2011 Subtotal (95% CI)	21	36 <b>36</b>	18	37 <b>37</b>	85.6% <b>85.6%</b>	1.20 [0.78, 1.85] <b>1.20 [0.78, 1.85]</b>		
Total events	21		18					
Heterogeneity: Not ap	oplicable							
Test for overall effect:	Z = 0.83 (F	° = 0.41	)					
Total (95% CI)		58		48	100.0%	1.50 [0.47, 4.77]		
Total events	26		18					
Heterogeneity: Tau <sup>2</sup> =	= 0.36; Chi <sup>z</sup>	= 1.34,	df = 1 (P	= 0.25)	); <b>I</b> ² = 25%		0.01 0.1 1 10	10
Test for overall effect:	Z = 0.69 (F	P = 0.49	)				Favours attention-placebo Favours exercise	
Test for subgroup dif	ferences: C	⊳hi² = 1.	17, df = 1	(P = 0.	28), I <sup>2</sup> = 1	4.2%	r avours auction pracebo i r avours exercise	

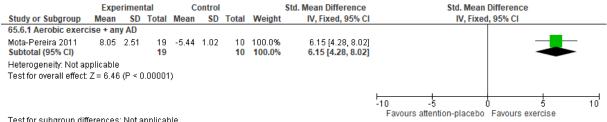
# Figure 383: Response (ITT)

	Experime	ental	Control			Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
65.4.1 Aerobic exerc	ise + any A	٩D								
Mota-Pereira 2011 Subtotal (95% CI)	4	22 22	0	11 <b>11</b>	3.2% <b>3.2%</b>	4.70 [0.28, 80.14] <b>4.70 [0.28, 80.14]</b>				
Total events Heterogeneity: Not ap	4 pplicable		0							
Test for overall effect:		e = 0.29	)							
65.4.2 Weight trainin	ig group + a	any AD								
Mather 2002 Subtotal (95% CI)	23	43 <b>43</b>	14	43 <b>43</b>	96.8% <b>96.8%</b>	1.64 [0.98, 2.74] <b>1.64 [0.98, 2.74]</b>				
Total events Heterogeneity: Not ap	23 Dicable		14							
Test for overall effect:	•	° = 0.06	)							
Total (95% CI)		65		54	100.0%	1.70 [1.03, 2.81]	◆			
Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subgroup dif	Z = 2.06 (F	° = 0.04	)			1%	0.01 0.1 1 10 10 Favours attention-placebo Favours exercise			

# Figure 384: Discontinuation due to any reason

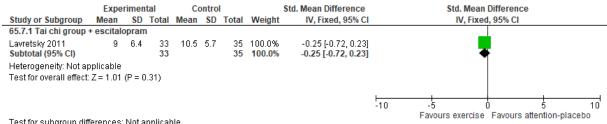
	Experim	ental	Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
65.5.1 Aerobic exerc	ise + any /	٨D					
Mota-Pereira 2011	3	22	1	11	39.4%	1.50 [0.18, 12.80]	
Subtotal (95% CI)		22		11	39.4%	1.50 [0.18, 12.80]	
Total events	3		1				
Heterogeneity: Not ap							
Test for overall effect:	Z = 0.37 (F	P = 0.71	)				
65.5.2 Tai chi group +	Loscitalon	ram					
Lavretsky 2011			2	27	60.6W	4 54 10 27 0 001	
Subtotal (95% CI)	3	36 <b>36</b>	2	37 37	60.6% 60.6%	1.54 [0.27, 8.69] 1.54 [0.27, 8.69]	
Total events	3	50	2	51	00.070	104 [0.21, 0.00]	
Heterogeneity: Not ap	-		2				
Test for overall effect:	•	P = 0.62	<b>`</b>				
		0.02	, ,				
65.5.3 Weight trainin	g group + a	any AD					
Mather 2002	0	43	0	43		Not estimable	
Subtotal (95% CI)		43		43		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					
Total (95% CI)		101		91	100.0%	1.53 [0.40, 5.86]	
Total events	6		3				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.00.	df = 1 (P	= 0.98)	; I² = 0%		
Test for overall effect:							0.01 0.1 1 10 100 Favours exercise Favours attention-placebo
Test for subgroup diff	erences: C	;hi² = 0.1	00. df = 1	(P = 0.	98), I <sup>2</sup> = 0	1%	Favours exercise Favours allention-placebo

# Figure 385: Global functioning change score



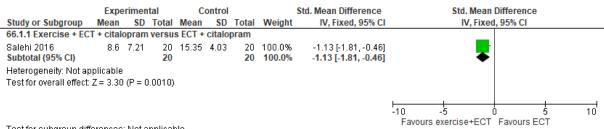
Test for subgroup differences: Not applicable

#### Figure 386: Sleeping difficulties endpoint



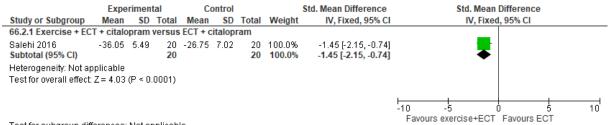
# Comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

#### Figure 387: Depression symptomatology endpoint



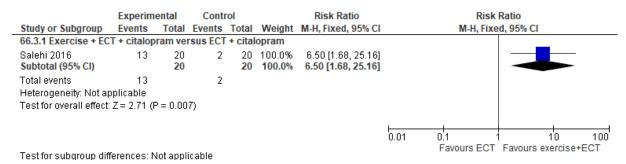
Test for subgroup differences: Not applicable

# Figure 388: Depression symptomatology change score



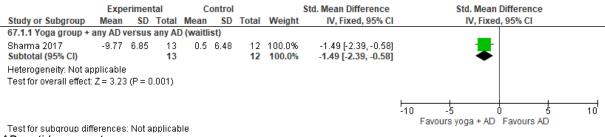
Test for subgroup differences: Not applicable

# Figure 389: Remission (ITT)

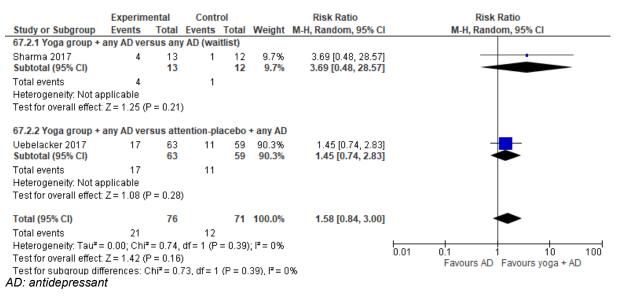


#### Comparison 67. Augmenting with yoga versus continuing with antidepressant (+/waitlist or attention-placebo)

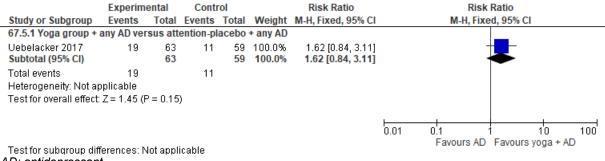
#### Figure 390: Depression symptomatology change score



#### Figure 391: Remission (ITT)

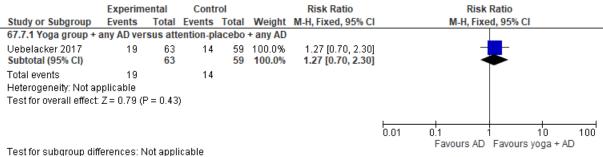


#### Figure 392: Remission (ITT) at 3-month follow-up



AD: antidepressant

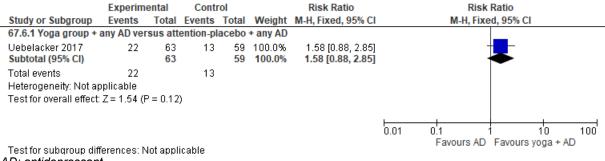
#### Figure 393: Remission (ITT) at 6-month follow-up



# Figure 394: Response (ITT)

	Experime	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
67.3.1 Yoga group + a	any AD ver	sus any	AD (wa	itlist)			
Sharma 2017 Subtotal (95% CI)	6	13 <b>13</b>	1	12 <b>12</b>	23.7% <b>23.7%</b>	5.54 [0.78, 39.57] 5.54 [0.78, 39.57]	
Total events	6		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.71 (P	= 0.09)	)				
67.3.2 Yoga group + a	any AD ver	sus atte	ention-pl	acebo	+ any AD		
Uebelacker 2017 Subtotal (95% CI)	21	63 63	13	59 <mark>59</mark>	76.3% <b>76.3%</b>	1.51 [0.84, 2.74] <b>1.51 [0.84, 2.74]</b>	
Total events Heterogeneity: Not ap	21 plicable		13				
Test for overall effect:	•	= 0.17)	)				
Total (95% CI)		76		71	100.0%	2.06 [0.68, 6.19]	
Total events	27		14				
Heterogeneity: Tau² =	0.32; Chi <b>ž</b>	= 1.59,	df = 1 (P	= 0.21)	; I <sup>z</sup> = 37%	)	0.01 0.1 1 10 100
Test for overall effect:	Z = 1.29 (P	= 0.20)	)				Favours AD Favours yoga + AD
Test for subgroup diff	erences: C	hi² = 1.	53, df = 1	(P = 0.	22), <b>I<sup>2</sup> =</b> 3	4.8%	
AD: antidepressan	t						

## Figure 395: Response (ITT) at 3-month follow-up



AD: antidepressant

# Figure 396: Response (ITT) at 6-month follow-up

	Experimental Control			Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M	-H, Fixed, 95% C	1	
67.8.1 Yoga group +	any AD ver	rsus att	ention-pl	acebo	+ any AD					
Uebelacker 2017 Subtotal (95% CI)	23	63 <mark>63</mark>	14	59 <b>59</b>	100.0% <b>100.0%</b>	1.54 [0.88, 2.70] <b>1.54 [0.88, 2.70]</b>		-		
Total events Heterogeneity: Not a Test for overall effect		P = 0.13	14 )							
Test for subgroup di	ferences: N	Vot appl	icable				0.01 0.1 Favor	urs AD Favours	10 ; yoga + A	100 D

# Figure 397: Discontinuation due to any reason

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
67.4.1 Yoga group + a	any AD ver	sus any	y AD (wa	itlist)			
Sharma 2017	2	13	0	12	35.0%	4.64 [0.25, 87.91]	
Subtotal (95% CI)		13		12	35.0%	4.64 [0.25, 87.91]	
Total events	2		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.02 (F	P = 0.31	)				
67.4.2 Yoga group + a	any AD ver	sus att	ention-pl	acebo	+ any AD		
Uebelacker 2017	5	63	13	59	65.0%	0.36 [0.14, 0.95]	
Subtotal (95% CI)		63		59	65.0%	0.36 [0.14, 0.95]	$\bullet$
Total events	5		13				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.07 (F	P = 0.04	)				
Total (95% CI)		76		71	100.0%	0.88 [0.08, 9.88]	
Total events	7		13				
Heterogeneity: Tau <sup>2</sup> =	2.10; Chi <sup>2</sup>	= 2.68,	df = 1 (P	= 0.10)	); I <sup>z</sup> = 63%	5	
Test for overall effect: .	Z = 0.10 (F	P = 0.92	)				Favours voga + AD Favours AD
Test for subgroup diffe	erences: C	≎hi <b>²</b> = 2.	62. df = 1	(P = 0)	.11), I² = 6	1.8%	ravous joga - AD - ravous AD