National Institute for Health and Care Excellence

Consultation draft

Depression in adults: treatment and management

Appendix L: GRADE profiles

NICE Guideline

Appendices

May 2018

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- Organisation and service delivery (chapter 5)
- Service delivery
 - Collaborative care versus control

Quality assessment							No of patients Effect				Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collaborative care	Control	Relative (95% CI)	Absolute			
Depressi	Depression symptoms- 6 months (follow-up mean 6; Better indicated by lower values)												
46	randomised trials	very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.31 lower (0.39 to 0.23 lower)	⊕000 VERY LOW	CRITICAL	
Depressi	on symptoms	- Simple co	ollaborative care (follow-up mean	6 months; Bette	er indicated by low	er values)						
35		very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.32 lower (0.42 to 0.21 lower)	⊕OOO VERY LOW	CRITICAL	
Depressi	on symptoms	- Complex	collaborative car	e (follow-up mea	n 6 months; Be	tter indicated by lo	ower values)			l			
11	randomised trials	very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.28 lower (0.43 to 0.13 lower)	⊕OOO VERY LOW	CRITICAL	
Depressi	on symptoms	at follow-u	up (follow-up mea	n 12 months; Be	etter indicated b	y lower values)							
8	randomised trials	very serious ¹	very serious ³	no serious indirectness	no serious imprecision	none	2024	1996	-	SMD 0.22 lower (0.41 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL	
Depressi	on symptoms	at follow-u	up - Simple collab	orative care (fol	low-up mean 12	months; Better in	dicated by lowe	er values)					
5		very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	1029	1020	-	SMD 0.19 lower (0.28 to 0.09 lower)	⊕⊕OO LOW	CRITICAL	
Depressi	on symptoms	at follow-u	up - Complex coll	aborative care (f	ollow-up mean	12 months; Better	indicated by lov	wer values)				

3		very serious ¹	very serious ³	no serious indirectness	serious ⁴	none	995	976	-	SMD 0.27 lower (0.72 lower to 0.17 higher)	⊕OOO VERY LOW	CRITICAL
Non-resp	onse at follow	v-up (follov	v-up mean 12 mo	nths)				-				
10		very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	872/1732 (50.3%)	1156/1546 (74.8%)	RR 0.72 (0.63 to 0.81)	209 fewer per 1000 (from 142 fewer to 277 fewer)	⊕OOO VERY LOW	CRITICAL
								68.1%		191 fewer per 1000 (from 129 fewer to 252 fewer)		
Non-resp	onse at follov	v-up- Simp	le collaborative c	are (follow-up m	nean 12 months							
4		very serious ¹	serious ²	no serious indirectness	no serious imprecision ⁴	none	181/482 (37.6%)	247/413 (59.8%)	RR 0.66 (0.47 to 0.92)	203 fewer per 1000 (from 48 fewer to 317 fewer)	⊕OOO VERY LOW	CRITICAL
								39.4%		134 fewer per 1000 (from 32 fewer to 209 fewer)		
Non-resp	onse at follov	v-up - Com	plex collaborative	e care (follow-up	mean 12 mont	hs)						
6	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	691/1250 (55.3%)	909/1133 (80.2%)	RR 0.75 (0.66 to 0.85)	201 fewer per 1000 (from 120 fewer to 273 fewer)	⊕⊕OO LOW	CRITICAL
								75%		188 fewer per 1000 (from 112 fewer to 255 fewer)		
Antidepre	essant use- 6	months (fo	ollow-up mean 6 r	nonths)								
31		very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	-	-	RR 1.39 (1.26 to	-	⊕OOO VERY	CRITICAL
								0%	1.52)	-	LOW	
Antidepre	essant use- 6	months - S	Simple collaborati	ve care								
22		very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	-	-	RR 1.45 (1.26 to	-	⊕000 VERY	CRITICAL
								0%	1.66)	-	LOW	

10	randomised	very	no serious	no serious	no serious	none	-	-	RR 1.29 (1.2	-	$\oplus \oplus OO$	CRITICA
	trials	serious ¹	inconsistency	indirectness	imprecision			0%	to 1.38)		LOW	
ntide	pressant use at	follow-up	 (follow-up mean	12 months)				0%		-		
									T			Ī
	randomised trials	very serious ¹	serious ²	no serious indirectness	no serious imprecision4	none	1095/1626 (67.3%)	904/1634 (55.3%)	RR 1.21 (1.05 to 1.4)	116 more per 1000 (from 28 more to 221	⊕000 VERY	CRITICA
	uiais	Serious		indirectiless	Imprecision		(07.370)	(55.570)	(1.03 to 1.4)	more)	LOW	
										116 more per 1000		
								55%		(from 27 more to 220 more)		
ntide	pressant use at	follow-up	- Simple collabo	rative care (follo	w-up mean 12 m	onths)				,		
5	randomised	very	serious ²	no serious	serious ⁴	none	297/513	270/512	RR 1.22 (0.9	116 more per 1000	⊕OOO	CRITICAL
	trials	serious ¹	Serious	indirectness	Serious	lione	(57.9%)	(52.7%)	to 1.65)	(from 53 fewer to 343	VERY	CINITIOA
							, ,		,	more)	LOW	
										84 more per 1000		
								38%		(from 38 fewer to 247		
Antide	pressant use at	follow-up	- Complex collab	oorative care (fo	llow-up mean 12	months)				more)		
	randomised	1	no serious	no serious	no serious	la a a a	798/1113	634/1122	RR 1.26	147 more per 1000	0000	CRITICA
		very	inconsistency	indirectness	imprecision ⁴	none	(71.7%)	(56.5%)	(1.17 to	(from 96 more to 198	⊕⊕OO LOW	CRITICAL
	trials	serious1	III ICUI ISISICI ICV				(,	(,	1.35)	more)		
		serious ¹	inconsistency						1.33)			
ŀ		serious ¹	inconsistency						1.33)	161 more per 1000		
1		serious ¹	inconsistency					61.9%	1.55)	161 more per 1000 (from 105 more to 217		
1 Non-re	trials		,	care)				61.9%	1.55)	161 more per 1000		
Non-re	trials	onths (simp	ole collaborative	, 					, ,	161 more per 1000 (from 105 more to 217 more)		
Non-re	trials emission at 6 me	onths (simp	no serious	no serious	serious ⁴	none	64/115	66/96	RR 0.81	161 more per 1000 (from 105 more to 217 more)	⊕000 VEDV	CRITICA
Non-rε	trials	onths (simp	ole collaborative	, 	serious ⁴	none	64/115 (55.7%)		, ,	161 more per 1000 (from 105 more to 217 more)	⊕000 VERY LOW	CRITIC

2	randomised trials	serious ⁶	very serious ³	no serious indirectness	no serious imprecision ⁴	none	88/197 (44.7%)	156/198 (78.8%)	RR 0.58 (0.38 to 0.89)	331 fewer per 1000 (from 87 fewer to 488 fewer)	⊕OOO VERY LOW	CRITICAL		
Non-remi	Non-remission at follow-up - simple collaborative care (follow-up mean 12 months)													
1	trials	serious ⁶	no serious inconsistency	no serious indirectness	serious ⁷	none	47/110 (42.7%)	95/104 (91.3%)	RR 0.47 (0.37 to 0.59)	484 fewer per 1000 (from 375 fewer to 575 fewer)	⊕⊕OO LOW	CRITICAL		
Non-remi	ssion at follo	w-up - com	plex collaborative	e care (follow-up	mean 12 monti	ns)								
1	randomised trials	serious ⁶	no serious inconsistency	no serious indirectness	serious ⁷	none	41/87 (47.1%)	61/954 (6.4%)	RR 0.73 (0.56 to 0.95)	17 fewer per 1000 (from 3 fewer to 28 fewer)	⊕⊕OO LOW	CRITICAL		

¹ ROB high or unclear across multiple domains in most studies ² 12 >50%

2

6

8

9

Collaborative care versus other active intervention

			Quality asse	essment		No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collaborative care	Other comparison	Relative (95% CI)	Absolute		
Simple co	llaborative ca	are: Stand	ards CC vs patien	t centred CC- re	emission at fo	ollow-up (follow-up	o mean 12 mont	hs)				
	randomised trials			no serious indirectness	serious ²	none	27/65 (41.5%)	22/67 (32.8%)		89 more per 1000 (from 62 fewer to 322 more)	⊕⊕OO LOW	CRITICAL
								32.8%		89 more per 1000 (from 62 fewer to 321 more)		
Telebased	I CC vs Pract	ice based	CC- response- 6	months (follow-u	up mean 6 mo	onths)						

³ I2 >80%

⁴ 95% CI crosses one clinical decision threshold

⁵ ROB high or unclear across multiple domains

⁶ ROB high or unclear across a two to three domains

⁷ OIS not met (<300 events)

1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious ³	none	70/153 (45.8%)	25/165 (15.2%)	RR 3.02 (2.02 to 4.51)	306 more per 1000 (from 155 more to 532 more)	⊕⊕OO LOW	CRITICAL	
								15.2%	-	307 more per 1000 (from 155 more to 534 more)			
Telebase	Telebased CC vs practice based CC- response at follow-up (follow-up mean 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	73/138 (52.9%)	31/149 (20.8%)	RR 2.54 (1.79 to 3.61)	320 more per 1000 (from 164 more to 543 more)	⊕⊕OO LOW	CRITICAL	
								20.8%	-	320 more per 1000 (from 164 more to 543 more)			

¹ ROB high or unclear across two to three domains ² 95% CI crosses one clinical decision threshold

4

Stepped care versus control

			Quality asse	ssment			No of pa			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stepped care	Control	Relative (95% CI)	Absolute		
Remission	at endpoint							Į.				
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ^{2,3}	none	40/74 (54.1%)	29/74 (39.2%)	RR 1.38 (0.97 to 1.96)	149 more per 1000 (from 12 fewer to 376 more)	⊕⊕OO LOW	CRITICAL
								39.2%		149 more per 1000 (from 12 fewer to 376 more)		
Depressio	n symptoms a	t endpoin	t (measured with: F	PHQ-9; Better indi	cated by low	er values)						
1	randomised trials	serious¹	no serious inconsistency	no serious indirectness	serious ²	none	137	64	-	MD 1.4 lower (2.87 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL

³ OES not met (<300 events)

Antidepressant use (follow-up mean 6 months)

¹ ROB high or unclear in two to three domains ² 95% CI crosses one clinical decision threshold

⁵ 95% CI crosses two clinical decision thresholds

⁴ High or unclear ROB in most domains

very

serious4

no serious

inconsistency

no serious

indirectness

randomised

trials

³ OES not met (N<400)

5

S	
M	
11	
M	
1	

8

10

11

ROB high	n or unclear	across	multiple	domain

² I2 > 50% ³ ROB high or unclear across two to three domains

Medicati	ion manage	ment vei	rsus control									
			Quality as	sessment			No of patier	its		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medication management	Control	Relative (95% CI)	Absolute		
Mean cha	nge in depres	sion scor	es (Better indicate	d by lower value	s)							
11		very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.13 lower (0.32 lower to 0.06 higher)	⊕OOO VERY LOW	CRITICAL
Mean cha	nge in depres	sion scor	es at follow-up (fo	llow-up mean 12	months; Better	indicated by lower	values)					
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ⁴	none	113	106	-	MD 2 lower (4.86 lower to 0.86 higher)	⊕⊕OO LOW	CRITICAL
Antidepre	ssant use at	endpoint										
4	randomised trials	serious ³	serious ²	no serious indirectness	serious ⁵	none	-	-	Not estimable	-	⊕000 VERY LOW	CRITICAL
¹ ROB high	n or unclear ac	ross multip	ole domains									

none

very

serious⁵

28/86

(32.6%)

23/84

to 1.89)

(27.4%)

RR 1.19 (0.75 | 52 more per 1000 (from 68

fewer to 244 more)

CRITICAL

 \oplus OOO \oplus

VERY LOW

⁴ OIS not met (<400 participants)

⁵ 95% CI crosses one clinical decision threshold

1 Care co-ordination versus control

			Quality ass	essment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CARE CO- ORDINATION	CONTROL	Relative (95% CI)	Absolute		
Mean cha	nge in depre	ssion scores	s at endpoint (Bet	ter indicated by	lower values)							
1		- ,	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.05 lower (0.35 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
Remissio	n (follow-up ı	mean 6 mon	ths; assessed wit	h: HAMD≤7)	'			•				
			no serious inconsistency	no serious indirectness	very serious ²	none	16/29 (55.2%)	8/28 (28.6%)	RR 1.93 (0.99 to 3.78)	266 more per 1000 (from 3 fewer to 794 more)	⊕⊕OO LOW	CRITICAL
Antidepre	essant adhere	ence at follow	w-up (follow-up m	 nean 12 months)				0%		-		
	randomised trials	serious ³	serious ⁴	no serious indirectness	serious ⁵	none	-	- 0%	RR 2.34 (0.84 to 6.56)	-	⊕OOO VERY LOW	CRITICAL

¹ ROB high or unclear across multiple domains

4 5 6

Integrated care versus control

			Quality as	sessment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INTEGRATED CARE	CONTROL	Relative (95% CI)	Absolute		
Mean char	nge in depres	ssion score	es at endpoint (Be	tter indicated by	lower values)						•	

² 95% CI crosses one clinical decision threshold and OIS not met (N<400)

³ ROB high or unclear in two to three domains

⁴ I2 > 50%

⁵ 95% CI crosses one clinical decision threshold

3	randomised trials	very serious ¹	serious ²	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.05 lower (0.26 lower to 0.16 higher)	⊕OOO VERY LOW	CRITICAL
Mean ch	ange in depres	ssion sco	res at endpoint - I	ntegrated care vs	control (Better	indicated by lower	r values)					
2	randomised trials	very serious ¹	serious ²	no serious indirectness	serious ³	none	0	-	-	SMD 0.19 lower (0.55 lower to 0.17 higher)	⊕OOO VERY LOW	CRITICAL
Mean ch	ange in depres	ssion sco	res at endpoint - I	ntegrated care vs	speciality refer	ral system (Better	indicated by high	ner values)	'			<u> </u>
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	SMD 0.08 higher (0.03 lower to 0.19 higher)	⊕⊕OO LOW	CRITICAL
Mean ch	ange in depres	ssion sco	res at follow-up (fo	ollow-up mean 12	2 months; Bette	r indicated by high	er values)					
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	serious ⁵	none	189	186	-	MD 0.01 higher (0.11 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
Antidepr	essant adhere	nce							Ļ	,		
2	randomised trials	very serious ¹	serious ²	no serious indirectness	very serious ⁶	none	-	-	Not estimable	-	⊕OOO VERY LOW	CRITICAL

¹ ROB high or unclear in multiple domains

6

7

Measurement-based care versus control

			Quality asse	ssment			No of patien	ıts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MEASUREMENT- BASED CARE	CONTROL	Relative (95% CI)	Absolute		

² I2 > 50%

³ 95% CI crosses one clinical decision threshold

⁴ ROB high or unclear in two to three domains

⁵ OIS not met (<400 participants) ⁶ 95% CI crosses two clinical decision thresholds

	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	53/61 (86.9%)	37/59 (62.7%)	RR 1.39 (1.11 to 1.73)	245 more per 1000 (from 69 more to 458 more)	⊕⊕⊕O MODERATE	CRITICA
								62.7%		245 more per 1000 (from 69 more to 458 more)		
missi	on (follow-up	mean 6 mo	nths; assessed	with: HAMD≤7)	•	·						
	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	45/61 (73.8%)	17/59 (28.8%)	RR 2.56 (1.67 to 3.93)	449 more per 1000 (from 193 more to 844 more)	⊕⊕⊕O MODERATE	CRITICA
								28.8%		449 more per 1000 (from 193 more to 844 more)		
press	ion symptom	s (follow-up	mean 6 month	s; measured wit	h: HAMD ch	ange score; Better	indicated by lower v	alues)				
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	61	59	-	MD 4.2 lower (6.21 to 2.19 lower)	⊕⊕⊕O MODERATE	CRITIC

¹ OIS not met (events<300) ² OIS not met (N<400)

1 2

Service delivery models for relapse prevention

			Quality asse	essment			No of patier	nts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RELAPSE PREVENTION	Control	Relative (95% CI)	Absolute		
Collabora	tive care (sim	ple)- depr	ession symptoms	at endpoint (Bet	ter indicated	by lower values)		,				
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	174	153	-	MD 0.09 lower (0.2 lower to 0.02 higher)	⊕000 VERY LOW	CRITICAL
Collabora	tive care (sim	ple)- relap	se at follow-up (fo	llow-up mean 12	2 months)			, ,			!	

1	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none		67/194 (34.5%)	,	3 more per 1000 (from 79 fewer to 114 more)	⊕⊕OO LOW	CRITICAL
			,				(0.110.73)	34.5%		3 more per 1000 (from 79 fewer to 114 more)	2011	
Stepped	care at follow-	up (follow	-up mean 12 mon	ths)						75 lewer to 114 more)		
1	randomised trials	- ,	no serious inconsistency	no serious indirectness	very serious⁴	none	24/74 (32.4%)	16/62 (25.8%)	,	67 more per 1000 (from 67 fewer to 297 more)	⊕OOO VERY LOW	CRITICAL
								25.8%		67 more per 1000 (from 67 fewer to 297 more)		

¹ ROB high or unclear in multiple domains ² OIS not met (<400 participants)

Settings for care

Crisis resolution team care versus standard care

											ı
										Quality	Importan
Design	k of as	onsistency l	Indirectness	Imprecision	Other considerations	Crisis resolution team care	Standard care	Relative (95% CI)	Absolute		
un (fallow un	maan 12 m	nontha: accor	and with Nu	mbor of part	ticinanta loct to fo	llow up by the one	d of the otu	ds/)			
-up (lollow-up i	mean 12 m	nonuns; asses	sea with: Nu	mber of pari	iicipants lost to lo	now-up by the end	i oi the stu	uy)			
domised very seriou				•	none	17/135 (12.6%)	17/125 (13.6%)	RR 0.93 (0.49 to 1.73)	10 fewer per 1000 (from 69 fewer to 99 more)	⊕OOO VERY	
							13.6%	_	10 fewer per 1000 (from	LOW	
erity (BPRS) (fo	ollow-up m	nean 8 weeks	; measured v	vith: Brief Ps	ychiatric Rating S	cale (BPRS) 8 wee	eks after cr	isis; Better ind			
domised very serior			serious ²	serious ⁴	none	107	104	-	SMD 0.29 lower (0.56 to 0.02 lower)	⊕OOO VERY	
										LOW	
ei dc s	up (follow-up omised very serio rity (BPRS) (following)	omised very no se incon rity (BPRS) (follow-up no se	pup (follow-up mean 12 months; assest omised very serious inconsistency very trity (BPRS) (follow-up mean 8 weeks omised very no serious	pup (follow-up mean 12 months; assessed with: Nu punised very no serious serious² inconsistency rity (BPRS) (follow-up mean 8 weeks; measured womised very no serious serious²	up (follow-up mean 12 months; assessed with: Number of part omised very no serious serious² very serious³ rity (BPRS) (follow-up mean 8 weeks; measured with: Brief Ps omised very no serious serious² serious⁴	pup (follow-up mean 12 months; assessed with: Number of participants lost to formised very no serious serious² very serious¹ inconsistency serious³ none rity (BPRS) (follow-up mean 8 weeks; measured with: Brief Psychiatric Rating Somised very no serious serious² serious⁴ none	pup (follow-up mean 12 months; assessed with: Number of participants lost to follow-up by the end of participants lost lost lost lost lost lost lost lo	pup (follow-up mean 12 months; assessed with: Number of participants lost to follow-up by the end of the sturbing serious of t	up (follow-up mean 12 months; assessed with: Number of participants lost to follow-up by the end of the study) omised very no serious serious² very serious³ none 17/135 17/125 RR 0.93 (0.49 to 1.73) rity (BPRS) (follow-up mean 8 weeks; measured with: Brief Psychiatric Rating Scale (BPRS) 8 weeks after crisis; Better incomised very no serious serious² serious⁴ none 107 104 -	pup (follow-up mean 12 months; assessed with: Number of participants lost to follow-up by the end of the study) Demised very	up (follow-up mean 12 months; assessed with: Number of participants lost to follow-up by the end of the study) omised very serious inconsistency no serious serious serious serious (12.6%) (13.6%) rity (BPRS) (follow-up mean 8 weeks; measured with: Brief Psychiatric Rating Scale (BPRS) 8 weeks after crisis; Better indicated by lower values) omised very no serious serious serious serious serious serious none (17/135 (17/125 (13.6%)) (13.6%)

³ 95% CI crosses one clinical decision threshold

⁴ 95% CI crosses two clinical decision thresholds

High risk of bias associated with randomisation method due to significant difference between groups and baseline and non-blind participants, intervention administrator(s) and outcome assessor(s)

² Not depression-specific population

³ 95% CI crosses line of no effect and threshold for both clinically important benefit (RR 0.75) and clinically important harm (RR 1.25)

⁴ N<400

⁵ Events<300

1 Acute day hospital care versus innatient care

			Quality as:	sessment			No of pa	tients		Effect		
			·								Quality	Importan
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acute day hospital care	Inpatient care	Relative (95% CI)	Absolute		
ost to fo	ollow-up (follo	w-up 3-14	months; assessed	with: Number o	f participants lo	st to follow-up by	the end of the	study)				
3	randomised	serious ¹	no serious	serious ²	serious ³	none	310/907	270/856	RR 1.25	79 more per 1000	⊕OOO	<u> </u>
	trials		inconsistency				(34.2%)	(31.5%)	(0.96 to	(from 13 fewer to 199	VERY	
									1.63)	more)	LOW	
								17.8%		44 more per 1000 (from 7 fewer to 112 more)		
Death (su	uicide) (follow	-up mean 1	4 months; assess	ed with: Number	r of participants	that committed su	iicide during th	ne study pe	riod)			
1	randomised	very	no serious	no serious	very serious ⁵	none	0/596	3/521	RR 0.12	5 fewer per 1000	⊕OOO	
	randomised trials	very serious ⁴	no serious inconsistency	no serious indirectness	very serious ⁵	none	0/596 (0%)	3/521 (0.6%)	(0.01 to	(from 6 fewer to 8	VERY	
I					very serious ⁵	none				(from 6 fewer to 8 more)		
					very serious ⁵	none		(0.6%)	(0.01 to	(from 6 fewer to 8 more) 5 fewer per 1000	VERY	
l					very serious ⁵	none			(0.01 to	(from 6 fewer to 8 more)	VERY	
Remissio	trials	serious ⁴	inconsistency	indirectness	,		(0%)	0.6%	(0.01 to 2.41)	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8	VERY LOW	(HAM-D))
Remissio	trials	serious ⁴	inconsistency	indirectness	,		(0%)	0.6%	(0.01 to 2.41)	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more)	VERY LOW	(HAM-D))
Remissio	trials on of psychiat	serious⁴ ric sympto	inconsistency ms (follow-up 3-13	indirectness 3 months; assess	sed with: Preser	nt State Examination	(0%) on: Index of De	(0.6%) 0.6%	(0.01 to 2.41)	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De	VERY LOW	(HAM-D))
Remissio	trials on of psychiat	serious⁴ ric sympto	inconsistency ms (follow-up 3-13	indirectness 3 months; assess	sed with: Preser	nt State Examination	(0%) on: Index of De	(0.6%) 0.6% finition≤4/< 33/71	(0.01 to 2.41) 7 on Hamilto RR 0.91	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De	VERY LOW	(HAM-D))
Remissio	trials on of psychiat	serious⁴ ric sympto	inconsistency ms (follow-up 3-13	indirectness 3 months; assess	sed with: Preser	nt State Examination	(0%) on: Index of De	(0.6%) 0.6% finition≤4/< 33/71	(0.01 to 2.41) 7 on Hamilto RR 0.91 (0.65 to	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De 42 fewer per 1000 (from 163 fewer to 121 more)	very LOW pression one of the control of the contr	(HAM-D))
Remissio	trials on of psychiat	serious⁴ ric sympto	inconsistency ms (follow-up 3-13	indirectness 3 months; assess	sed with: Preser	nt State Examination	(0%) on: Index of De	(0.6%) 0.6% finition≤4/< 33/71	(0.01 to 2.41) 7 on Hamilto RR 0.91 (0.65 to	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De 42 fewer per 1000 (from 163 fewer to 121 more) 33 fewer per 1000 (from 129 fewer to 96	very LOW pression one of the control of the contr	(HAM-D))
2	on of psychiat randomised trials	ric sympton very serious ⁶	ms (follow-up 3-13 no serious inconsistency	indirectness months; assess serious ²	sed with: Preser	nt State Examination reporting bias ⁸	(0%) on: Index of De 33/80 (41.3%)	(0.6%) 0.6% finition≤4/< 33/71 (46.5%) 36.9%	(0.01 to 2.41) 67 on Hamilto RR 0.91 (0.65 to 1.26)	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De 42 fewer per 1000 (from 163 fewer to 121 more) 33 fewer per 1000 (from 129 fewer to 96 more)	very LOW pression one of the control of the contr	n (HAM-D))
2	on of psychiat randomised trials e (follow-up n	ric sympton very serious ⁶	ms (follow-up 3-13 no serious inconsistency	indirectness months; assess serious ² h: Number of pe	very serious ⁷	reporting bias ⁸	(0%) on: Index of De 33/80 (41.3%) on Hamilton R	(0.6%) 0.6% ofinition≤4/< 33/71 (46.5%) 36.9% ating Scale	(0.01 to 2.41) 7 on Hamilto RR 0.91 (0.65 to 1.26)	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De 42 fewer per 1000 (from 163 fewer to 121 more) 33 fewer per 1000 (from 129 fewer to 96 more) ion (HAM-D))	very LOW pression one of the control of the contr	n (HAM-D))
2	on of psychiat randomised trials	ric sympton very serious ⁶	ms (follow-up 3-13 no serious inconsistency	indirectness months; assess serious ²	sed with: Preser	nt State Examination reporting bias ⁸	(0%) on: Index of De 33/80 (41.3%)	(0.6%) 0.6% finition≤4/< 33/71 (46.5%) 36.9%	(0.01 to 2.41) 67 on Hamilto RR 0.91 (0.65 to 1.26)	(from 6 fewer to 8 more) 5 fewer per 1000 (from 6 fewer to 8 more) on Rating Scale for De 42 fewer per 1000 (from 163 fewer to 121 more) 33 fewer per 1000 (from 129 fewer to 96 more)	very LOW pression one of the control of the contr	n (HAM-D))

								40%		152 fewer per 1000 (from 296 fewer to 200 more)	⊕OOO VERY LOW
						with: Comprehens; change score); B				PRS; change score)/	Brief Psychia
	randomised	very	serious ¹²	serious ²	no serious	none	682	599	-	SMD 0.05 higher	⊕000
	trials	serious ¹¹			imprecision					(0.22 lower to 0.33	VERY
										higher)	LOW
			post-admission) re); Better indica			ured with: Compre	nensive Psych	opathologic	cal Rating Sc	ale (CPRS; change sc	ore)/Brief Ps
	randomised	very	very serious ¹³	serious ²	serious ¹⁴	none	663	586	-	SMD 0.19 lower (0.81	⊕000
	trials	serious ¹¹	, , , , , , , , , , , , , , , , , , , ,							lower to 0.42 higher)	VERY
										in the second second	LOW
iration	randomised	very	no serious	serious ²	no serious	none none	800	735	lower values	SMD 0.55 higher	⊕000
	trials	serious ¹¹	inconsistency		imprecision					(0.44 to 0.65 higher)	VERY
		SCHOOS	inconcionation							(c. 11 to 0.00 mg/lol)	LOW
admis				ed with: Numb	·	lmitted to hospital)				(c. r to d.oo nignoly	
admis	randomised			ed with: Numb	·	Imitted to hospital)	39/183	47/189	RR 0.79	52 fewer per 1000	LOW ⊕OOO
admis	ssion (follow-u	p mean 12	months; assess		er of patients read			47/189 (24.9%)	(0.41 to	52 fewer per 1000 (from 147 fewer to	⊕OOO VERY
eadmis	randomised	p mean 12	months; assess		er of patients read		39/183			52 fewer per 1000	LOW ⊕OOO
eadmis	randomised	p mean 12	months; assess		er of patients read		39/183	(24.9%)	(0.41 to	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000	⊕OOO VERY
eadmis	randomised	p mean 12	months; assess		er of patients read		39/183		(0.41 to	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000 (from 127 fewer to	⊕OOO VERY
	randomised trials	p mean 12 serious ¹⁵	serious ¹²	serious ²	er of patients read very serious ⁵		39/183 (21.3%)	(24.9%)	(0.41 to 1.52)	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000	⊕OOO VERY
	randomised trials	p mean 12 serious ¹⁵	serious ¹²	serious ²	er of patients read very serious ⁵	reporting bias ⁸	39/183 (21.3%)	(24.9%)	(0.41 to 1.52)	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000 (from 127 fewer to	⊕OOO VERY
	randomised trials	serious ¹⁵	serious ¹²	serious ²	er of patients read very serious ⁵	reporting bias ⁸	39/183 (21.3%)	(24.9%) 21.5% onths of adn	(0.41 to 1.52)	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000 (from 127 fewer to 112 more)	⊕OOO VERY LOW
	randomised trials ge (follow-up randomised	serious ¹⁵	serious ¹² serious ¹² nths; assessed w	serious ²	er of patients read very serious ⁵	reporting bias ⁸	39/183 (21.3%) tal within 3 mo	(24.9%) 21.5% enths of adn 33/48	(0.41 to 1.52) nission)	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000 (from 127 fewer to 112 more)	⊕OOO VERY LOW
	randomised trials ge (follow-up randomised	serious ¹⁵	serious ¹² serious ¹² nths; assessed w	serious ²	er of patients read very serious ⁵	reporting bias ⁸	39/183 (21.3%) tal within 3 mo	(24.9%) 21.5% enths of adn 33/48	(0.41 to 1.52) nission)	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000 (from 127 fewer to 112 more) 275 fewer per 1000 (from 62 fewer to 412 fewer)	⊕OOO VERY LOW
	randomised trials ge (follow-up randomised	serious ¹⁵	serious ¹² serious ¹² nths; assessed w	serious ²	er of patients read very serious ⁵	reporting bias ⁸	39/183 (21.3%) tal within 3 mo	(24.9%) 21.5% enths of adn 33/48	(0.41 to 1.52) nission)	52 fewer per 1000 (from 147 fewer to 129 more) 45 fewer per 1000 (from 127 fewer to 112 more) 275 fewer per 1000 (from 62 fewer to 412	⊕OOO VERY LOW

		. 47			. 2							
1	randomised	serious ¹⁷	no serious	serious ²	serious ³	reporting bias8	12/38	6/45	RR 2.37	183 more per 1000	⊕000	
	trials		inconsistency				(31.6%)	(13.3%)	(0.98 to	(from 3 fewer to 628	VERY	
									5.71)	more)	LOW	
										182 more per 1000		
								13.3%		(from 3 fewer to 626		
										more)		
Service	utilisation: Out	tnatient co	ntact (follow-up n	nean 4 months	assessed with: I	Number of participa	nts making o	utpatient co	ntacts within	4 months post-admis	sion)	
				, ,						- I III O III O POOL WUIII O	,	
1	randomised	serious ¹⁷	no serious	serious ²	very serious ⁵	reporting bias8	14/38	12/45	RR 1.38	101 more per 1000	⊕OOO	
•	trials	Scrious	inconsistency	5011005	very serious	reporting blue	(36.8%)	(26.7%)	(0.73 to	(from 72 fewer to 432	VERY	
	uiais		inconsistency				(30.070)	(20.7 70)	2.62)	more)	LOW	
									2.02)	more)	LOVV	
										101 1000		
								26.7%		101 more per 1000 (from 72 fewer to 433		
								20.7%		`		
	1	<u> </u>	L	<u> </u>		1				more)		
Satisfac	tion (follow-up	mean 4 m	onths; assessed	with: Number of	participants sat	isfied or very satisf	ied with their	treatment)				
			1	1 .		1	1					
1	randomised	very	no serious	serious ²	serious ¹⁶	reporting bias8	31/38	19/45	RR 1.93	393 more per 1000	⊕OOO	
	trials	serious ¹⁷	inconsistency				(81.6%)	(42.2%)	(1.33 to	(from 139 more to	VERY	
									2.81)	764 more)	LOW	
										·		
										392 more per 1000		
								42.2%		(from 139 more to		
										764 more)		
Satisfac	tion (follow-up	mean 2 m	onths: measured	with: Cliet Asse	esment of Treat	ment (CAT); Better	indicated by I	ower values	1	,		
Gatioiao	uon (ionon up		onino, mododi od	0			indicated by i	ono. raidoe	,			
1	randomised	very	no serious	serious ²	no serious	none	596	521	-	SMD 0.03 higher	⊕ООО	
•	trials	serious ¹¹	inconsistency	5011005	imprecision	none	000	021		(0.09 lower to 0.15	VERY	
	uiais	Serious	inconsistency		Imprecision					higher)	LOW	
I										riigher)	LOW	
Quality of	of life (2-month	is post-adr	nission) (follow-u	p mean 2 month	ns; measured wi	th: Manchester sho	rt assessmen	t of quality of	of life (MANS	A); Better indicated by	lower valu	ues)
1	randomised	very	no serious	serious ²	no serious	none	596	521	-	SMD 0.01 higher	⊕000	
	trials	serious ¹¹	inconsistency		imprecision					(0.11 lower to 0.13	VERY	
										higher)	LOW	
ĺ	1				1							
Quality of	of life (14-mont	ths post-ac	lmission) (follow-	up mean 14 moi	nths; measured	with: Manchester s	nort assessm	ent of qualit	y of life (MAI	NSA); Better indicated	by lower va	alues)
			,,									
1	randomised	very	no serious	serious ²	no serious	none	596	521	-	SMD 0.01 higher	⊕ООО	
	trials	serious ¹¹	inconsistency		imprecision					(0.11 lower to 0.13	VERY	
		311000								higher)	LOW	
										ilighter)	LOVV	
								1		l		

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¹ Randomisation method was unclear (or high risk associated with it due to significant baseline differences). Non-blind participants, intervention administrator(s) and unclear blinding of, or nonblind, outcome assessor(s)

² Non depression-specific population

³ 95% CI crosses both line of no effect and threshold for clinically important harm (RR 1.25)

⁴ High risk of bias associated with randomisation method due to significant difference between groups at baseline. Non-blind participants, intervention administrator(s) and outcome assessor(s). Unclear risk of attrition bias (drop-out>20% but difference between groups<20% and ITT analysis used)

⁵ 95% CI crosses line of no effect and both threshold for clinically important benefit (RR 0.75) and clinically important harm (RR 1.25)

⁶ Unclear randomisation method and method of allocation concealment. Non-blind participants and intervention administrator(s) and unclear blinding of outcome assessment

- ⁷ 95% CI crosses line of no effect and threshold for clinically important harm (RR 0.75) and clinically important benefit (RR 1.25)
- ⁸ Data cannot be extracted for all outcomes (measure of variance not reported)
- ⁹ Unclear blinding of allocation concealment. Non-blind participants and intervention administrator(s) and unclear blinding of outcome assessment. Unclear risk of attrition bias (drop-out>20% but difference between groups<20% and ITT analysis used)
- ¹⁰ A non-standard definition of response selected (e.g. 47% rather than 50%)
- ¹¹ High risk of bias associated with randomisation method due to significant difference between groups at baseline. Non-blind participants, intervention administrator(s) and outcome assessment. Unclear risk of attrition bias (drop-out>20% but difference between groups<20% and ITT analysis used)
- ¹² I-squared>50%
- ¹³ I-squared>80%
- ¹⁴ 95% CI crosses both line of no effect and threshold for clinically important benefit (SMD -0.5)
- ¹⁵ Non-blind participants, intervention administrator(s) and outcome assessment
- 12 ¹⁶ Events<300

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- ¹⁷ Unclear randomisation method and allocation concealment, and non-blind participants, intervention administrator(s) and outcome assessment
- ¹⁸ Non-blind participants and intervention administrator(s) and non-blind, or unclear blinding of, outcome assessment. Unclear risk of attrition bias (drop-out>20% but difference between groups<20%)
- ¹⁹ 95% CI crosses both line of no effect and threshold for clinically important benefit (RR 1.25)

Non-acute day hospital care versus outpatient care

			Quality asses	sment			No of patients			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-acute day hospital care versus outpatient care		Relative (95% CI)	Absolute		
Lost to fo	llow-up (follo	w-up 6-24	months; assesse	d with: Numb	er of particip	ants lost to follow	v-up by the end of the stu	ıdy)				
	randomised trials	serious ¹	serious ²	serious ³	very serious ⁴	reporting bias⁵	24/136 (17.6%)	30/145 (20.7%)		39 fewer per 1000 (from 157 fewer to 352 more)	⊕000 VERY LOW	
								20.7%		39 fewer per 1000 (from 157 fewer to 352 more)		
Death (all	causes) (follo	ow-up mea	an 24 months; ass	essed with: I	Number of pa	rticipants who die	ed due to any causes dur	ing the	study period)	,		
	randomised trials		no serious inconsistency	serious ³	very serious ⁴	none	2/48 (4.2%)	1/58 (1.7%)	RR 2.42 (0.23 to 25.85)	24 more per 1000 (from 13 fewer to 428 more)	⊕000 VERY LOW	
								1.7%		24 more per 1000 (from 13 fewer to 422 more)		

randomised	serious ⁷	very serious8	serious ³	very serious ⁹	none	75	69	-	SMD 0.08 higher (0.72	⊕ООО
trials									lower to 0.88 higher)	VERY
										LOW
			(follow-up 8	3-12 months; m	easured with: Psy	chiatric Evaluation Fo	orm (change	e score)/Pres	ent State Examination	(change sco
indicated by lo	wer values	5)								
	. 7		. 3	. 10	() 11	70	00		0110 0 15 1 (0 10	
randomised	serious ⁷	no serious	serious ³	serious ¹⁰	reporting bias ¹¹	73	66	-	SMD 0.15 lower (0.49	⊕000
trials		inconsistency							lower to 0.19 higher)	VERY
										LOW
-1		0.40 41		41			ali andra ar Alica	- 4		
sion as inpatie	nt (follow-u	ip 6-12 months;	assessed wil	tn: Number of p	participants admit	ted into inpatient care	during the	study period		
randomised	serious ¹²	no serious	serious ³	very serious ⁴	⁴ none	16/136	12/145	RR 1.26	22 more per 1000	⊕000
trials	SCHOUS	inconsistency	SCHOOS	very serious	TIONE	(11.8%)		-	(from 40 fewer to 170	VERY
uiais		inconsistency				(11.070)	(0.576)	(0.32 to 3.00)	`	LOW
									more)	LOW
									21 more per 1000	
							8%		(from 38 fower to 165	
							8%		(from 38 fewer to 165 more)	
ction (follow-u	p 4-6 mont	hs; assessed wit	th: Number o	of participants s	satisfied or very sa	atisfied with their trea			(from 38 fewer to 165 more)	
					,		tment)	DD 4 (0 474	more)	
randomised		hs; assessed with very serious ⁸	th: Number of serious ³	very	satisfied or very sa	59/92	tment) 67/106		more) 0 fewer per 1000 (from	⊕000
					,		tment)		0 fewer per 1000 (from 335 fewer to 708	VERY
randomised				very	,	59/92	tment) 67/106		more) 0 fewer per 1000 (from	
randomised				very	,	59/92	tment) 67/106		0 fewer per 1000 (from 335 fewer to 708 more)	VERY
randomised				very	,	59/92	67/106 (63.2%)		0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from	VERY
randomised				very	,	59/92	tment) 67/106		0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703	VERY
randomised trials	serious ¹	very serious ⁸	serious ³	very serious ¹³	none	59/92 (64.1%)	67/106 (63.2%)	2.12)	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more)	VERY LOW
randomised trials	serious ¹	very serious ⁸	serious ³	very serious ¹³	none	59/92 (64.1%)	67/106 (63.2%)	2.12)	0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703	VERY LOW
randomised trials	serious ¹	very serious ⁸	serious ³	very serious ¹³ an 6 months; m	none neasured with: Glo	59/92 (64.1%)	67/106 (63.2%) 62.8%	2.12)	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low	VERY LOW
randomised trials functioning (6	serious ¹ -months po	very serious ⁸ pst-admission) (f	serious ³	very serious ¹³	none neasured with: Glo	59/92 (64.1%)	67/106 (63.2%)	2.12)	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low SMD 0.04 higher (0.53	VERY LOW er values)
randomised trials functioning (6	serious ¹	very serious ⁸	serious ³	very serious ¹³ an 6 months; m	none neasured with: Glo	59/92 (64.1%)	67/106 (63.2%) 62.8%	2.12)	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low	VERY LOW er values) #000 VERY
randomised trials functioning (6	serious ¹ -months po	very serious ⁸ pst-admission) (f	serious ³	very serious ¹³ an 6 months; m	none neasured with: Glo	59/92 (64.1%)	67/106 (63.2%) 62.8%	2.12)	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low SMD 0.04 higher (0.53	VERY LOW er values)
randomised trials functioning (6 randomised trials	serious ¹ -months po	very serious ⁸ pst-admission) (f	serious ³ ollow-up me	very serious ¹³ an 6 months; m	none neasured with: Glo	59/92 (64.1%) obal Assessment Scal	67/106 (63.2%) 62.8% le (GAS; cha	2.12) ange score); l	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low SMD 0.04 higher (0.53 lower to 0.61 higher)	ver values) or values) or values) or values)
randomised trials functioning (6 randomised trials	serious ¹ -months po	very serious ⁸ pst-admission) (f	serious ³ ollow-up me	very serious ¹³ an 6 months; m	none neasured with: Glo	59/92 (64.1%) obal Assessment Scal	67/106 (63.2%) 62.8% le (GAS; cha	2.12) ange score); l	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low SMD 0.04 higher (0.53	ver values) or values) or values) or values)
randomised trials functioning (6 randomised trials	serious ¹ -months povery serious ¹⁴ 2-months povery	very serious ⁸ pst-admission) (f	serious ³ ollow-up me	very serious ¹³ an 6 months; m	none neasured with: Glo	59/92 (64.1%)	67/106 (63.2%) 62.8% le (GAS; cha	2.12) ange score); l	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low SMD 0.04 higher (0.53 lower to 0.61 higher)	ver values) or values) or values) or values)
randomised trials functioning (6 randomised trials	serious ¹ -months povery serious ¹⁴ 2-months p	very serious ⁸ pst-admission) (for no serious inconsistency post-admission) (for no serious post-admission) (for no seriou	serious ³ ollow-up me	very serious ¹³ an 6 months; m very serious ⁹ ean 12 months	none neasured with: Glo	59/92 (64.1%) obal Assessment Scal	67/106 (63.2%) 62.8% le (GAS; cha	2.12) ange score); l	more) 0 fewer per 1000 (from 335 fewer to 708 more) 0 fewer per 1000 (from 333 fewer to 703 more) Better indicated by low SMD 0.04 higher (0.53 lower to 0.61 higher)	POOO VERY LOW

	• ,		oost-admission) (f by lower values)	ollow-up 4-6	months; me	asured with: Socia	Adjustment Scale-Self F	Report (SAS-SR; chan	ge score)/Social Func	tioning S	cale (SFS;
change s	core, better	iliulcateu	by lower values)									
2	randomised	serious ⁷	no serious	serious ³	serious15	reporting bias11	74	67	-	SMD 0.2 lower (0.54	⊕000	
	trials		inconsistency							lower to 0.14 higher)	VERY	
											LOW	
	• ,		•	•	12 months; n	neasured with: Soc	cial Adjustment Scale-Se	If Repor	t (SAS-SR; ch	ange score)/Social Fu	nctioning	Scale
(SFS; cha	ange score); E	setter indi	cated by lower va	lues)								
2	randomised	serious ⁷	no serious	serious ³	serious ¹⁵	reporting bias ¹¹	73	67	_	SMD 0.31 lower (0.65	⊕OOO	
=	trials	CONTOGO	inconsistency	Conodo	Conodo	roporting blac	10	O,		lower to 0.03 higher)	VERY	
			,							3 · ,	LOW	

¹ Unclear randomisation method and non-blind participants and intervention administrator(s)

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Community mental health teams (CMHTs) versus standard care

Quality assessment	No of patients	Effect	Quality	Importance

² I-squared>50%

³ Non-depression specific population

^{4 95%} CI crosses line of no effect and threshold for both clinically important benefit (RR 0.75) and clinically important harm (RR 1.25)

⁵ Data cannot be extracted or is not reported for all outcomes

⁶ Unclear randomisation method and non-blind participants and intervention administrator(s). Unclear risk of attrition bias (drop-out>20% but difference between groups<20% and ITT analysis used)

⁷ Unclear randomisation method and non-blind participants and intervention administrator(s). Risk of attrition bias is unclear or high (drop-out>20% and ITT analysis not used)

⁸ I-squared>80%

^{9 95%} CI crosses line of no effect and threshold for both clinically important benefit (SMD -0.5) and clinically important harm (SMD 0.5)

¹⁰ N<400

¹² Data is not reported for longest follow-up

¹² Unclear randomisation method and method of allocation concealment. Non-blind participants and intervention administrator(s) and unclear blinding of outcome assessment. Unclear risk of attriiton bias (drop-out>20%)

¹³ 95% CI crosses line of no effect and threshold for both clinically important harm (RR 0.75) and clinically important benefit (RR 1.25)

¹⁴ Unclear randomisation method and method of allocation concealment. Non-blind participants and intervention administrator(s) and unclear blinding of outcome assessment. High risk of attrition bias as drop-out>20%, difference between groups>20% and completer analysis used

¹⁵ 95% CI crosses both line of no effect and threshold for clinically important benefit (SMD-0.5)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Community mental health teams (CMHTs) versus standard care	Control	Relative (95% CI)	Absolute	
ost to fo	llow-up (folio	ow-up mea	an 3 months; ass	essed with: N	lumber of pa	rticipants lost to	follow-up by the end of the s	tudy)			
	randomised trials		no serious inconsistency	serious ²	very serious ³	reporting bias⁴	8/48 (16.7%)	7/52 (13.5%)	RR 1.24 (0.49 to 3.16)	32 more per 1000 (from 69 fewer to 291 more)	⊕000 VERY LOW
								13.5%		32 more per 1000 (from 69 fewer to 292 more)	
eath (all	causes) (foll	low-up me	ean 3 months; as	sessed with:	Number of p	articipants who d	ied due to any causes during	g the stu	dy period)		
	randomised trials		no serious inconsistency		very serious ³	reporting bias ⁴	1/48 (2.1%)	2/52 (3.8%)	RR 0.54 (0.05 to 5.78)	18 fewer per 1000 (from 37 fewer to 184 more)	⊕OOO VERY LOW
								3.9%		18 fewer per 1000 (from 37 fewer to 186 more)	
ymptom	severity (fol	low-up m	ean 3 months; me	easured with:	Comprehen	sive Psychopatho	logical Rating Scale (CPRS)	at endpo	oint; Better i	ndicated by lower val	ues)
	randomised trials		no serious inconsistency	serious ²	serious ⁵	reporting bias ⁴	48	52	-	SMD 0.06 lower (0.45 lower to 0.33 higher)	⊕OOO VERY LOW
dmissio	n as inpatien	t (follow-	up mean 3 month	s; assessed v	with: Numbe	r of participants a	dmitted into inpatient care d	uring the	e study perio	l od)	
	randomised trials		no serious inconsistency	serious ²	serious ⁶	reporting bias⁴	7/48 (14.6%)	16/52 (30.8%)	RR 0.47 (0.21 to 1.05)	163 fewer per 1000 (from 243 fewer to 15 more)	⊕000 VERY LOW
								30.8%		163 fewer per 1000 (from 243 fewer to 15 more)	
dmissio	n as inpatien	t for >10	days (follow-up m	nean 3 month	s; assessed	with: umber of pa	rticipants admitted into inpa	itient car	e for more the	nan 10 days during th	e study period
	randomised trials		no serious inconsistency	serious ²	serious ⁷	reporting bias4	2/48 (4.2%)	11/52 (21.2%)	RR 0.2 (0.05 to 0.84)	169 fewer per 1000 (from 34 fewer to 201 fewer)	

Satisfacti	on (follow-up	mean 3 i	months; assessed	d with: Numb	er of particip	ants satisfied wit	h their treatment)	21.2%		170 fewer per 1000 (from 34 fewer to 201 fewer)	⊕OOO VERY LOW	
	randomised trials		no serious inconsistency	serious ²	serious ⁵	reporting bias ⁴	34/41 (82.9%)	25/46 (54.3%)	RR 1.53 (1.13 to	288 more per 1000 (from 71 more to 576	⊕000 VERY	
									2.06)	more)	LOW	
								54.4%		288 more per 1000 (from 71 more to 577 more)		
Satisfacti	on (follow-up	mean 3 i	months; measure	d with: Servi	ce Satisfaction	on Score; Better i	ndicated by lower values)					
	randomised trials		no serious inconsistency	serious ²	serious ⁵	reporting bias ⁴	41	46	-	SMD 0.85 higher (0.41 to 1.29 higher)	⊕000 VERY	
			nd non blind partic								LOW	

¹ Unclear randomisation method and non-blind participants and intervention administrator(s)

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First-line treatment (chapter 7)

- NMA sub-analysis 10
- Pairwise comparisons: Nortriptyline for depression in older adults 11
- 12 Nortriptyline versus placebo

Quality assessment	No of patients	Effect	Quality	Importance

² Non-depression specific population

³ 95% CI crosses line of no effect and threshold for both clinically important benefit (RR 0.75) and clinically important harm (RR 1.25) ⁴ Data cannot be extracted for all outcomes (no measure of variance reported)

⁵ N<400

⁶ 95% CI crosses both line of no effect and threshold for clinically important benefit (RR 0.75)

⁷ Events<300

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nortriptyline	Placebo	Relative (95% CI)	Absolute		
Depressio	n symptomat	ology at e	ndpoint - milder de	epression (measi	ured with: HA	MD; Better indica	ted by lower	values)				,
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	12	11	-	MD 8.10 lower (13.17 to 3.03 lower)	⊕⊕OO LOW	CRITICAL
Depressio	n symptomat	ology at e	ndpoint - more sev	vere (measured w	vith: HAMD; I	Better indicated by	lower values	5)				
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	41	45	-	MD 5.3 lower (8.89 to 1.71 lower)	⊕⊕OO LOW	CRITICAL
Remission	n at endpoint	- milder de	epression (assesse	ed with: CGI/HAN	ID)							
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	7/12 (58.3%)	1/11 (9.1%)	RR 6.42 (0.93 to 44.16)	493 more per 1000 (from 6 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Treatment	discontinuat	ions due t	o side effects - mi	der depression								
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias	2/25 (8%)	0/28 (0%)	RR 5.58 (0.28 to 110.89)	-	⊕OOO VERY LOW	CRITICAL
Remission	n at endpoint	- more sev	vere depression (a	ssessed with: CC	SI/HAMD)							
	randomised trials	serious ¹	serious ⁵	no serious indirectness	serious ³	none	37/60 (61.7%)	22/65 (33.8%)	RR 2.14 (0.81 to 5.72)	386 more per 1000 (from 64 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Treatment	discontinuat	ions - moi	re severe depressi	on								
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	39/99 (39.4%)	29/94 (30.9%)	RR 1.25 (0.85 to 1.82)	77 more per 1000 (from 46 fewer to 253 more)	⊕⊕OO LOW	CRITICAL
Treatment	discontinuat	ions due t	o side effects - mo	re severe depres	sion							
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	10/38 (26.3%)	1/35 (2.9%)	RR 9.21 (1.24 to 68.31)	235 more per 1000 (from 7 more to 1000 more)	⊕⊕OO LOW	CRITICAL

¹ High ROB in one domain and unclear in several others ² OIS not met (<400 participants) ³ 95% CI crosses one clinical decision threshold

- ⁴ 95% CI crosses two clinical decision thresholds
- ⁵ I2 >50% but <80%

Nortriptyline versus sertraline

			Quality asse	essment			No of pa	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nortriptyline	Sertraline	Relative (95% CI)	Absolute		
Depressio	n symptomat	ology: mil	der symptom seve	erity (measured w	rith: HAMD; o	change in score; c	ompleter anal	lysis; Bett	er indicated by	higher values)		
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	52	58	-	MD 2.10 lower (3.55 to 0.65 lower)	⊕000 VERY LOW	CRITICAL
Response	(assessed wi	th: HAMD)	•	•							
	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ⁴	none	86/110 (78.2%)	54/110 (49.1%)	RR 1.59 (1.29 to 1.97)	290 more per 1000 (from 142 more to 476 more)	⊕⊕OO LOW	CRITICAL

¹ High risk of bias in most domains

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Pairwise comparisons: Acupuncture

Acupuncture versus sham acupuncture

			Quality asse	essment			No of	patients		Effect	Quality	Importance	
No of studies	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations Acupuncture Sham acupuncture (95% CI) Absolute												
Discontin	Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants lost to follow-up due to adverse events)												

² OIS not met (<400 participants)
³ High risk of bias for allocation concealment and reporting bias

⁴ 95% CI crosses 1 clinical decision threshold

2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/53 (1.9%)	0/54 (0%)	RR 3.1 (0.13 to 73.12)	-	⊕OOO VERY LOW	
Discontin	uation for an	y reason	(follow-up 8-12 we	eks; assessed	with: Number	r of participants lo	st to follow-up	for any reaso	n (including ac	lverse events))	<u> </u>	
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	7/53 (13.2%)	8/51 (15.7%)	RR 0.92 (0.24 to 3.55)	13 fewer per 1000 (from 119 fewer to 400 more)	⊕OOO VERY LOW	
Remissio	n (follow-up r	mean 8 we	eeks; assessed w	ith: HAMD endp	oint score of	7 or below)						
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ⁴	none	14/25 (56%)	1/22 (4.5%)	RR 12.32 (1.76 to 86.26)	515 more per 1000 (from 35 more to 1000 more)	⊕⊕OO LOW	
Respons	e (follow-up n	nean 8 we	eks; assessed wi	th: reduction of	at least 50%	from the baseline	score on HAN	ID)				
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ⁴	none	18/25 (72%)	4/22 (18.2%)	RR 3.96 (1.58 to 9.93)	538 more per 1000 (from 105 more to 1000 more)	⊕⊕OO LOW	
Depression	on symptoma	tology (fo	llow-up 8-12 weel	ks; measured wi	ith: HAMD ch	ange score; Bette	r indicated by	lower values)				
2		very serious ⁵	very serious ⁶	no serious indirectness	very serious ⁷	none	48	44	-	SMD 0.56 lower (1.8 lower to 0.69 higher)	⊕OOO VERY LOW	

¹ Randomisation method and method for allocation concealment are not reported

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Acupuncture + AD/TAU versus AD/TAU

Quality assessment	No of patients	Effect	Quality	Importance

² 95% CI crosses line of no effect and two clinical decision thresholds (RR 0.8 and 1.25) and events<300

³ Allocation sequence not concealed

⁴ Criterion for optimal information size not met (<400 participants)
⁵ Randomisation method not reported; unclear allocation concealment and unclear blinding of paticipants in one of the studies and allocations sequence generation not concealed in the other study

⁶ I-square>80%

⁷ 95% CI crosses line of no effect and two clinical decision thresholds (+0.5 and -0.5)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture + AD/TAU	AD/TAU	Relative (95% CI)	Absolute	
Discontin	uation due to	side effe	cts (follow-up mea	an 6 weeks; asse	essed with: Num	ber of participants	lost to follow-up	due to a	adverse event	es)	
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	6/160 (3.8%)	4/95 (4.2%)		2 fewer per 1000 (from 32 fewer to 114 more)	⊕OOO VERY LOW
								3.9%		2 fewer per 1000 (from 29 fewer to 106 more)	
Discontin	uation for any	y reason (follow-up 3-13 we	eks; assessed w	vith: Number of	participants lost to	follow-up due to	adverse	events)		
7	randomised trials	serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	81/584 (13.9%)	46/351 (13.1%)	RR 1.04 (0.74 to 1.46)	5 more per 1000 (from 34 fewer to 60 more)	⊕OOO VERY LOW
								10.4%		4 more per 1000 (from 27 fewer to 48 more)	
Remissio	n (follow-up n	nean 6 we	eks; assessed wi	th: HAMD endpo	oint score of 7 o	r below)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	28/109 (25.7%)	11/48 (22.9%)	RR 1.12 (0.61 to 2.06)	28 more per 1000 (from 89 fewer to 243 more)	⊕OOO VERY LOW
								22.9%		27 more per 1000 (from 89 fewer to 243 more)	
Respons	e (follow-up m	nean 6 wee	eks; assessed wit	h: reduction of a	nt least 50% from	n the baseline sco	re on HAMD)	•			•
)	randomised trials	very serious ¹	serious ⁴	no serious indirectness	serious ³	none	102/157 (65%)	43/95 (45.3%)	RR 1.37 (0.91 to 2.06)	167 more per 1000 (from 41 fewer to 480 more)	⊕OOO VERY LOW
								45.3%		168 more per 1000 (from 41 fewer to 480 more)	
Depressi	on symptoma	tology (fo	llow-up 3-13 week	s; measured wit	h: HAMD/PHQ-9	/BDI-II change sco	ore; Better indicat	ted by lo	wer values)		
		very	very serious ⁵	no serious	no serious	none	504	334		SMD 0.85 lower (1.4 to	⊕000

Depression	Depression symptomatology (less severe) (follow-up 3-13 weeks; measured with: PHQ/HAMD/HADS-D change score; Better indicated by lower values)													
4		very serious¹	. ,		no serious imprecision	none	331	220	-	SMD 1.83 lower (2.92 to 0.73 lower)	⊕OOO VERY LOW			
Depression	Depression symptomatology (more severe) (follow-up 6-12 weeks; measured with: BDI-II/HAMD change score; Better indicated by lower values)													
4		very serious ¹		no serious indirectness	serious ³	none	173	114	-	SMD 0.23 lower (0.77 lower to 0.31 higher)	⊕000 VERY LOW			

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses two clinical decision thresholds

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Acupuncture versus SSRI 7

			Quality asse	ssment			No of patie	ents		Effect	Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	SSRI	(95% CI)				
Discontin	uation due to	side effect	s (follow-up mean	6 weeks; assesso	ed with: Num	ber of participants	lost to follow	v-up d	ue to adverse ev	vents)			
1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	0/50 (0%)	0/25 (0%)	not pooled	not pooled	⊕⊕OO LOW		
Discontin	uation for any	reason (fo	llow-up mean 6 wo	eeks; assessed w	ith: Number	of participants los	t to follow-up	for ar	ny reason includ	ing adverse events)		l	
1	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	14/50 (28%)	0/25 (0%)	RR 14.78 (0.92 to 238.15)	-	⊕⊕OO LOW		
Depression	Depression symptomatology (follow-up 6-24 weeks; measured with: HAMD/MADRS change score; Better indicated by lower values)												

³ 95% CI crosses one clinical decision threshold

⁴ I2>50%

⁵ I2>80%

2	randomised trials	very serious ¹	very serious ⁴	no serious indirectness	serious ⁵	none	60	49	-	SMD 0.48 lower (0.87 to 0.08 lower)	⊕000 VERY LOW	
Response	(follow-up me	ean 6 weel	s; assessed with:	reduction of at le	ast 50% fron	n the baseline scor	e on HAMD)					
1	randomised trials	very serious ¹		no serious indirectness	serious³	none		15/25 (60%)	,	150 more per 1000 (from 84 fewer to 486 more)	⊕OOO VERY LOW	

¹ Risk of bias is high or unclear across multiple domains

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Acupuncture + TAU versus counselling + TAU

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			Quality as	sessment			No of p	patients		Effect	Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture + TAU	Counselling + TAU	(95% CI) Absolute				
Discontir	continuation for any reason (follow-up mean 13 weeks; assessed with: Number of participants lost to follow-up for any reason including adverse events)												
1	randomised trials			no serious indirectness	very serious ²	none	53/302 (17.5%)	65/302 (21.5%)	RR 0.82 (0.59 to 1.13)	39 fewer per 1000 (from 88 fewer to 28 more)	⊕000 VERY LOW		
Depressi	Depression symptomatology (follow-up mean 13 weeks; measured with: PHQ-9 change score; Better indicated by lower values)												
1	randomised trials				no serious imprecision	none	249	237	-	SMD 0.05 lower (0.22 lower to 0.13 higher)	⊕⊕⊕O MODERATE		

² OIS not met (events<300) ³ 95% CI crosses one clinical decision threshold

⁴ I2>80%

⁵ OIS not met (N<400)

¹ No attempts at blinding ² 95% CI crosses both line of no effect and clinical decision threshold (RR 0.8)

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Acupuncture + counselling versus TAU

			Quality asse	essment			No of patien	ts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture + counselling	TAU	Relative (95% CI)	Absolute		
Discontin	ontinuation for any reason (follow-up mean 8 weeks; assessed with: Number of participants lost to follow-up for any reason including adverse events)											
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	3/40 (7.5%)	5/40 (12.5%)	RR 0.6 (0.15 to 2.34)	50 fewer per 1000 (from 106 fewer to 167 more)	⊕OOO VERY LOW	
								12.5%		50 fewer per 1000 (from 106 fewer to 167 more)		
Depression	on symptomat	tology (fol	low-up mean 8 we	eks; measured v	vith: HADS-D	change score; Be	etter indicated by lo	wer valu	ues)			
1	randomised trials	· ,	no serious inconsistency	no serious indirectness	serious ³	none	37	35	-	SMD 1.39 lower (1.91 to 0.87 lower)	⊕000 VERY LOW	

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses two clinical decision thresholds

Pairwise comparisons: Behavioural couples therapy

Behavioural couples therapy versus CBT

			Quality asse	essment			No of patient	ts		Effect	Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural couples therapy	СВТ	Relative (95% CI)	Absolute				
Depressio	Depression symptomatology at endpoint (across severity) (follow-up 10-78 weeks; measured with: BDI/HAMD; Better indicated by lower values)													

³ OIS not met (N<400)

4	randomised trials	very serious ¹	serious ²	no serious indirectness	serious ³	none	67	68	-	SMD 0.03 higher (0.49 lower to 0.54 higher)	#000 VERY LOW	CRITICAL
Depressi	on symptoma	tology at	endpoint (milder	depression) (follo	ow-up 16-78 v	weeks; measured	with: BDI/HAMD; E	Better ind	icated by lowe	er values)		!
3	randomised trials	very serious ¹	serious ²	no serious indirectness	very serious ⁴	none	52	53	-	SMD 0.14 higher (0.49 lower to 0.78 higher)	⊕000 VERY LOW	CRITICAL
Depressi	on symptoma	tology at	endpoint (more s	evere depression) (follow-up	mean 10 weeks; m	neasured with: BDI	l; Better ii	ndicated by lo	wer values)		
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	15	15	-	SMD 0.34 lower (1.07 lower to 0.38 higher)	⊕000 VERY LOW	CRITICAL
Remissio	on (assessed v	with: BDI<	10)	1							L	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	13/19 (68.4%)	16/19 (84.2%)	RR 0.81 (0.57 to 1.17)	160 fewer per 1000 (from 362 fewer to 143 more)	⊕000 VERY LOW	CRITICAL
								0%		-		
Treatmen	nt discontinua	tion rates	(across severity)	(follow-up 15-78	weeks; asse	essed with: Numbe	er of participants d	liscontinu	ing for any re	ason)		
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	20/72 (27.8%)	9/70 (12.9%)	RR 1.97 (0.98 to 3.98)	125 more per 1000 (from 3 fewer to 383 more)	⊕⊕OO LOW	CRITICAL
								15.5%		150 more per 1000 (from 3 fewer to 462 more)		
Treatmen	nt discontinua	tion rates	(milder depressi	on) (follow-up 16	-78 weeks; as	ssessed with: Nun	nber of participant	ts discont	inuing for any	reason)		
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	17/60 (28.3%)	6/58 (10.3%)	RR 2.49 (1.11 to 5.61)	154 more per 1000 (from 11 more to 477 more)	⊕⊕OO LOW	CRITICAL
								14.3%		213 more per 1000 (from 16 more to 659 more)		
Treatmen	nt discontinua	tion rates	(more severe de	pression) (follow-	up mean 15	weeks; assessed	with: Number of pa	articipant	s discontinuir	ng for any reason)		

1	randomised trials	serious ¹	no serious inconsistency	 very serious ⁴	none	3/12 (25%)	3/12 (25%)	RR 1 (0.25 to 4)	0 fewer per 1000 (from 188 fewer to 750 more)	⊕000 VERY LOW	CRITICAL
							25%		0 fewer per 1000 (from 188 fewer to 750 more)		

¹ High or unclear ROB in most domains

4

6

Behavioural couples therapy versus waitlist

			Quality asse	essment		No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural couples therapy versus waitlist control	Control	Relative (95% CI)	Absolute			
Depression	Depression symptomatology at endpoint (more severe depression) (follow-up mean 10 weeks; measured with: BDI; Better indicated by lower values)												
1		very serious ¹		no serious indirectness	serious ²	none	15	15	-	MD 12.07 lower (18.32 to 5.82 lower)	⊕OOO VERY LOW	CRITICAL	
Treatmen	Treatment discontinuation rates (more severe depression) (follow-up mean 15 weeks; assessed with: Number of participants discontinuing for any reason)												
1	randomised trials	serious ¹		no serious indirectness	very serious ³	none	3/12 (25%)	(0%)	RR 7 (0.4 to 122.44)	-	⊕000 VERY LOW	CRITICAL	
								0%		-			

¹ High or unclear ROB in most domains

10 Behavioural couples therapy versus waitlist

Quality assessment	No of patients	Effect	Quality	Importance

² I2 <80% but >50%

³ 95% confidence interval crosses one clinical decision threshold

⁴ 95% CI crosses two clinical decision thresholds

⁵ Events<300

² OIS not met (<400 participants) ³ 95% CI crosses two clinical decision thresholds

Risk of

Other

Behavioural

Waitlist

Relative

No of

4

5

Behavioural couples therapy (BCT) versus IPT (interpersonal therapy)

			Quality asse	essment			No of patients	•		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural couples therapy	IPT	Relative (95% CI)	Absolute		
Depression	n symptomat	ology at e	ndpoint (milder de	pression) (follow	up mean 78	weeks; measured	with: BDI; Better in	dicate	d by lower va	alues)		
1	randomised very no serious no seriou			no serious indirectness	serious ²	reporting bias ³	20	20	-	MD 1.56 higher (5.07 lower to 8.19 higher)	⊕000 VERY LOW	CRITICAL
Treatment	discontinuat	ion rates (milder depression) (follow-up mear	n 78 weeks; a	assessed with: Nu	mber of participants	disco	ntinuing for	any reason)		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	none	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	⊕000 VERY LOW	CRITICAL
								10%		0 fewer per 1000 (from 84 fewer to 542 more)		

¹ High or unclear ROB in most domains

² OIS not met (<400 participants)

³ 95% CI crosses two clinical decision thresholds

- ¹ High or unclear ROB in most domains ² 95% CI crosses one clinical decision threshold
- ³ Data not reported for all outcomes
 - ⁴ 95% CI crosses two clinical decision thresholds

Behavioural couples therapy versus combined BCT and CBT

			Quality ass	essment			No	of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural couples therapy	Combined BCT and CBT (individual CBT for the depressed wife)	Relative (95% CI)	Absolute		
Depressi	on symptom	atology a	t endpoint (milde	er depression)	(measured w	vith: HAMD; Bette	r indicated by lo	wer values)				
		- ,	no serious inconsistency	no serious indirectness	serious ²	none	19	21	-	MD 4.12 higher (0.66 lower to 8.9 higher)	⊕OOO VERY LOW	CRITICAL
Remissio	on (milder de	pression	(assessed with:	BDI<10)								
		very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	13/19 (68.4%)	12/21 (57.1%)	RR 1.2 (0.74 to 1.94)	114 more per 1000 (from 149 fewer to 537 more)	⊕000 VERY LOW	CRITICAL
								57.1%		114 more per 1000 (from 148 fewer to 537 more)		
Treatmer	nt discontinu	ation rate	es (milder depres	sion) (assesse	ed with: Num	ber of participant	s discontinuing	for any reason)				
1	randomised trials			no serious indirectness	serious ²	none	8/27 (29.6%)	0/21 (0%)	RR 13.36 (0.81 to 218.99)	-	⊕⊕OO LOW	CRITICAL
	ingloor DOD i							0%		-		

¹ High or unclear ROB in most domains

8

5

² 95% CI crosses one clinical decision threshold

³ 95% CI crosses two clinical decision thresholds

3

2 Pairwise comparisons: Omega-3 fatty acids

Omega-3 fatty acids versus placebo

			Quality ass	essment			No of par	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-3 fatty acids	Placebo	Relative (95% CI)	Absolute		
Remission	n (milder dep	ression) (follo	ow-up 3-8 weeks;	assessed with:	BDI=>10 or HAM	ID <=7 at endpoint)					
2		no serious risk of bias	serious ¹	no serious indirectness	very serious ²	reporting bias ³	44/143 (30.8%)	21/74 (28.4%)	RR 1.43 (0.48 to 4.29)	122 more per 1000 (from 148 fewer to 934 more)	⊕000 VERY LOW	CRITICAL
Response	(milder depr	ession) (follo	w-up mean 8 wee	ks; assessed wi	th: HAMD reduc	ed by >50% at end	lpoint)					1
1			no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	52/131 (39.7%)	28/65 (43.1%)	RR 0.92 (0.65 to 1.31)	34 fewer per 1000 (from 151 fewer to 134 more)	⊕000 VERY LOW	CRITICAL
Treatmen	t discontinua	l tion (milder d	l lepression) (follov	v-up 3-8 weeks;	assessed with: I	Number of particip	ants discont	inuing fo	r any reason)			
3	randomised trials	very serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision ⁵	none ³	20/203 (9.9%)	23/136 (16.9%)	RR 0.56 (0.32 to 1)	74 fewer per 1000 (from 115 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Discontin	uation due to	side effects	(milder depressio	n) (follow-up me	ean 8 weeks; ass	sessed with: Numb	er of particip	oants dis	continuing du	e to side effects)		
1			no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	1/131 (0.76%)	0/65 (0%)	RR 1.5 (0.06 to 36.32)	-	⊕OOO VERY LOW	CRITICAL
Depression	on symptoma	tology (meas	ured with: HAMD;	change score;	completer analys	sis; Better indicate	ed by lower v	alues)				1
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	55	51	-	MD 0.50 lower (2.01 lower to 1.01 higher)	⊕000 VERY LOW	CRITICAL

¹ I²>50%

² 95% CI crosses two clinical decision thresholds

5

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

			Quality ass	essment			No of p	atients	E	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-3 fatty acids + SSRI/antidepressants	Placebo + SSRI/antidepressants	Relative (95% CI)	Absolute		
Remissi	on (more se	vere depr	ession) (follow-u	ip mean 8 wee	eks; assesse	d with: HAMD <=	7 at endpoint)					
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	8/18 (44.4%)	4/22 (18.2%)	RR 2.44 (0.88 to 6.82)	262 more per 1000 (from 22 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Respons	se (more sev	ere depre	ession) (follow-u	p mean 8 weel	ks; assessed	with: HAMD red	uced by >50% at endpoir	nt)				
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	13/16 (81.3%)	8/16 (50%)	RR 1.63 (0.94 to 2.8)	315 more per 1000 (from 30 fewer to 900 more)	⊕OOO VERY LOW	CRITICAL
Treatme	nt discontin	uation (m	ilder depression) (follow-up m	ean 12 week	s; assessed with	: Number of participants	discontinuing for any re	eason)			
	randomised trials	_	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	6/18 (33.3%)	5/17 (29.4%)	RR 1.13 (0.42 to 3.03)	38 more per 1000 (from 171 fewer to 597 more)	⊕OOO VERY LOW	CRITICAL
Treatme	nt discontin	uation (m	ore severe depr	ession) (follow	-up mean 8	weeks; assessed	with: Number of particip	pants discontinuing for a	iny reason)		
	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	none ³	7/40 (17.5%)	11/42 (26.2%)	RR 0.68 (0.29 to 1.62)	84 fewer per 1000 (from 186 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL

³ Data not reported for all outcomes

⁴ Unclear allocation concealment in 2 of the studies, unclear/high selective reporting of outcomes for 2 of the studies and incomplete outcome data for one of the studies

⁵ 95% CI crosses one clinical decision threshold

⁶ Unclear concealment and incomplete outcome data

Disconti	nuation due	to side ef	fects (more sev	ere depressio	n) (follow-up	mean 8 weeks; a	assessed with: Number of	f participants discontinu	uing due to	side effects)	
2	randomised trials			no serious indirectness	very serious ⁵	reporting bias ³	2/40 (5%)		,	24 more per 1000 (from 19 fewer to 460 more)	

¹ High or unclear risk in multiple ROB domains

6

7

8

5

Pairwise comparisons: Psychosocial interventions (peer support)

Peer support versus waitlist

			Quality asses	ssment			No of patie	ents		Effect	Quality	Importance
No of studies	Design	Inconsistency	Other considerations	Peer support group	Waitlist	Relative (95% CI)	Absolute					
Depression	n symptoms at	endpoint (milder depression)	follow-up mean 4	weeks; meas	sured with: BDI; Be	tter indicated by	y lower v	values)			
	1 randomised very no serious no serious serious² reporting bias³ inconsistency indirectness					reporting bias ³	19	67	-	MD 7.66 lower (9.77 to 4.41 lower)	⊕OOO VERY LOW	

¹ Unclear allocation concealment and non-blind participants, intervention administrators and outcome assessment

11

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

Quality assessment	No of patients	Effect	Quality	mportance

² 95% CI crosses one clinical decision threshold

³ Data not reported for all outcomes

⁴ Unclear risk across multiple ROB domains

⁵ 95% CI crosses two clinical decision thresholds

^{10 &}lt;sup>2</sup> N<40

³ Data is not reported or cannot be extracted for all outcomes

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peer support (online support group)	Attention- placebo control	Relative (95% CI)	Absolute	
Treatmen	t discontinua	ation (milder	depression) (foll	ow-up mean 12	weeks; asse	ssed with: Numbe	er of participants v	vho discontinu	ed for any re	ason)	
1		no serious risk of bias		no serious indirectness	serious ¹	reporting bias ²	36/89 (40.4%)	11/82 (13.4%)	RR 3.02 (1.65 to 5.52)	271 more per 1000 (from 87 more to 606 more)	
								13.4%		271 more per 1000 (from 87 more to 606 more)	

¹ Events<300

Peer support group versus CBT group

			Quality asse	ssment			No of patients			Effect	Quality	Importance
No of studies	Design Inconsistency Indirectness mnrecision							CBT group	Relative (95% CI)	Absolute		
Depression	n symptoms a	t endpoint	(milder depression)	(follow-up mean	4 weeks; me	asured with: BDI; I	Better indicated	d by lowe	er values)			
	randomised very no serious no serious serious² reporting bia inconsistency indirectness					reporting bias ³	19	50	-	MD 1.09 lower (3.42 lower to 1.24 higher)	⊕000 VERY LOW	

¹ Unclear allocation concealment and non-blind participants, intervention administrators and outcome assessment

7 Peer support group versus self-help (without support)

Quality assessment	No of patients	Effect	Quality	Importance

² Data is not reported or cannot be extracted for all outcomes

² 95% CI crosses one clinical decision threshold

³ Data is not reported or cannot be extracted for all outcomes

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peer support group	Self-help (without support)	Relative (95% CI)	Absolute		
Depression	on symptoms a	t endpoin	t (milder depressio	on) (follow-up me	an 4 weeks; ı	measured with: BD	DI/CES-D chan	ge score; Better i	indicated	by lower values)		
2	randomised trials			no serious indirectness	serious ²	none ³	19	50	-	MD 0.24 lower (0.54 lower to 0.06 higher)	⊕⊕OO LOW	

¹ Unclear allocation concealment and non-blind participants, intervention administrators and outcome assessment

Peer support + any antidepressant versus any antidepressant

			Quality ass	essment			No of patients Effect				Quality	Importance
No of studies	studies Design bias Inconsistency Indirectness Imprecision conside						Peer support + and antidepressant	Any antidepressant	Relative (95% CI)	Absolute		
Remissio	on (milder syn	nptom se	verity) (follow-up	mean 36 weeks	s; assessed v	with: CIS-R>7)						
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	12/33 (36.4%)	8/30 (26.7%)	RR 1.36 (0.65 to 2.87)	96 more per 1000 (from 93 fewer to 499 more)	⊕⊕OO LOW	

¹ Unclear allocation concealment and non-blind participants, intervention administrators and outcome assessment, attrition bias

Social intervention + any antidepressant versus any antidepressant

			Quality ass	essment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Social intervention + any antidepressant	,	Relative (95% CI)	Absolute	-	
Remissio	n (follow-up	mean 36	weeks; assessed	with: CIS-R >7)							

OIS not met (<400 participants)
 Data is not reported or cannot be extracted for all outcomes

² 95% CI crosses one clinical decision threshold

1	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious ¹	none	11/37 (29.7%)	8/30 (26.7%)	RR 1.11 (0.51 to 2.42)	29 more per 1000 (from 131 fewer to 379 more)		
Depressi	on symptom	atology (Copy) (follow-up	mean 36 weeks	; measured	with: HAMD; endp	ooint data; completer a	ınalysis; Better in	dicated by	higher values)		
	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	31	28	-	MD 0.10 lower (3.09 lower to 2.89 higher)	⊕⊕OO LOW	

¹ 95% CI crosses 2 clinical decision thresholds

Pairwise comparisons: bright light therapy

Sham light therapy + fluoxetine versus bright light therapy + fluoxetine

			Quality asse	essment			No of p	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sham light therapy +fluoxetine	Bright light therapy + fluoxetine versus	Relative (95% CI)	Absolute	Quality	importance
Respons	e (follow-up	mean 8 we	eks; assessed w	ith: MADRS)						<u>'</u>		•
1				no serious indirectness	serious ¹	none	22/29 (75.9%)	9/31 (29%)	RR 2.61 (1.45 to 4.7)	467 more per 1000 (from 131 more to 1000 more)		CRITICAL
Remission	on (MADRS) -	Milder syr	mptom severity (f	ollow-up mean	8 weeks)							
1				no serious indirectness	serious ¹	none	17/29 (58.6%)	6/31 (19.4%)	RR 3.03 (1.39 to 6.61)	393 more per 1000 (from 75 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Depressi	on symptom	atology (M	ADRS; change s	core; complete	analysis) - I	Milder symptom s	everity (follow-u	p mean 8 weeks;	Better indic	ated by higher valu	ies)	

² Unclear allocation concealment and non-blind participants, intervention administrators and outcome assessment, attrition bias

³ N<400

1	randomised	no serious	no serious	no serious	serious ²	none	29	31	-	MD 8.1 higher	⊕⊕⊕О	CRITICAL
	trials	risk of bias	inconsistency	indirectness						(3.27 to 12.93	MODERATE	
										higher)		

^{1 &}lt;300 events

Bright light therapy versus placebo

			Quality assess	sment			No of patients	s		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light therapy versus placebo	Control	Relative (95% CI)	Absolute		
Depression	n symptomat	ology - milde	r depression sever	ity (follow-up me	an 3 weeks;	measured with: H	AMD; change score;	ITT ana	lysis; Be	tter indicated by lo	wer values)	
	randomised trials			no serious indirectness	serious ¹	none	42	47	-	MD 2.6 lower (3.55 to 1.65 lower)	⊕⊕⊕O MODERATE	CRITICAL

N<400

5

6 Pairwise comparisons: attention modification bias

7 Attention modification bias versus attention placebo

			Quality asse	essment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Attention bias modification	Attention placebo	Relative (95% CI)	Absolute		
Depressio values)	n symptomat	ology - mo	ore severe to milde	r symptom sever	ity (follow-u	p mean 21 weeks;	measured with: BD	I-II;change sc	ore; ITT a	analysis; Better indica	ted by lo	ower
	randomised trials			no serious indirectness	serious ²	none	27	27	-	MD 0.71 lower (2.82 lower to 1.4 higher)	⊕⊕OO LOW	CRITICAL

² N<400

Light therapy

3 4

Is bright light effective for depression with a seasonal pattern/SAD compared with waitlist control?

			Quality asse	eemant					Summary	of findings		
			Quanty asse	33116111			No of p	atients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Waitlist	Relative (95% CI)	Absolute	Quality	
Leaving s	study early for	r any reason (c	overall) (total num	ber not completi	ng study)	L						
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	3/42 (7.1%)	3/40 (7.5%)	RR 0.95 (0.21 to 4.32)	0 fewer per 100 (from 6 fewer to 25 more)	⊕⊕OO LOW	
								8.7%		0 fewer per 100 (from 7 fewer to 29 more)		
Leaving	study early du	e to side effec	ts - Light box vs v	vaitlist control								
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	0/16 (0%)	0/15 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE	
Leaving s	study early - L	ight room vs v	vaitlist control					0%		not pooled		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	1/26 (3.8%)	1/25 (4%)	RR 0.96 (0.06 to 14.55)	0 fewer per 100 (from 4 fewer to 54 more)	⊕⊕⊕O MODERATE	
								0%	,	0 fewer per 100 (from 0 fewer to 0 more)		
Mean sel	f rated SAD de	epression sco	res at endpoint - L	ight room vs wa	itlist control (m	easured with: SIG	H-SAD-SR	t; Better in	idicated by Id	wer values)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	24	24	-	MD 12.8 lower (18.52 to 7.08 lower)	⊕⊕⊕O MODERATE	
Mean clir	ician rated S	AD depression	scores at endpoi	nt - Light box vs	waitlist control	(measured with:	SIGH-SAD	; Better in	dicated by lo	wer values)		

¹ Unclear how treatment allocation was concealed ² 95% CI crosses both clinical decision threshold (SMD -0.5 and 0.5)

	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	16	15	-	MD 10.4 lower (15.99 to 4.81 lower)	⊕⊕⊕O MODERATE
ean clir	nician rated ty	pical depress	ion scores at end	point - Light box	x vs waitlist con	trol (measure	d with: HRSD-2	1; Better	indicated by lo	ower values)	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	15	-	MD 6.3 lower (10.34 to 2.26 lower)	⊕⊕⊕⊕ HIGH
ean sel	f-rated depres	ssion score - o	overall (Better ind	icated by lower	values)						
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	39	-	MD 1.15 lower (1.63 to 0.67 lower)	⊕⊕⊕⊕ HIGH
ean sel	f rated depres	sion scores a	t endpoint - Light	room vs waitlis	t control (meas	ured with: HR	SD-21-SR; Bette	er indicate	ed by lower va	llues)	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	24	24	-	MD 7.7 lower (11.58 to 3.82 lower)	⊕⊕⊕O MODERATE
ean sel	f rated depres	sion scores a	t endpoint - Light	t box vs waitlist	control (measu	red with: BDI;	Better indicated	l by lowe	r values)		
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	16	15	-	MD 10.9 lower (16.99 to 4.81 lower)	⊕⊕⊕O MODERATE
ean clir	ician rated at	ypical depres	sion scores at en	dpoint - Light bo	ox vs waitlist co	ntrol (measur	ed with: SAD su	ıbscale; E	Better indicate	d by lower values)	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	16	15	-	MD 4 lower (6.73 to 1.27 lower)	⊕⊕⊕O MODERATE
ean sel	f rated atypica	al depression	scores at endpoi	nt - Light room v	s waitlist contro	ol (measured v	with: SAD-SR su	ubscale o	of SIGH-SAD);	Better indicated by Id	wer values)
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	24	24	-	MD 5.2 lower (7.39 to 3.01 lower)	⊕⊕⊕O MODERATE
n remi	ission (SIGH-S	SAD-SR) (ove	rall)						1		
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/42 (47.6%)	36/40 (90%)	RR 0.53 (0.38 to 0.74)	42 fewer per 100 (from 23 fewer to 56 fewer)	⊕⊕⊕⊕ HIGH
								88%		41 fewer per 100 (from 23 fewer to 55	

1		no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	12/26 (46.2%)	24/25 (96%)	RR 0.48 (0.31 to 0.73)	50 fewer per 100 (from 26 fewer to 66 fewer)	⊕⊕⊕O MODERATE	
								96%		50 fewer per 100 (from 26 fewer to 66 fewer)		
Non remi	ssion (SIGH-S	SAD-SR) - Ligh	t box vs waitlist c	ontrol								
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	8/16 (50%)	12/15 (80%)	RR 0.62 (0.36 to 1.08)	30 fewer per 100 (from 51 fewer to 6 more)	⊕⊕⊕O MODERATE	
								80%		30 fewer per 100 (from 51 fewer to 6 more)		
Non resp	onse (SIGH-S	AD) - Light roo	om vs waitlist con	trol	•	•						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	13/26 (50%)	25/25 (100%)	RR 0.50 (0.34 to 0.73)	50 fewer per 100 (from 27 fewer to 66 fewer)	⊕⊕⊕O MODERATE	
								100%	,	50 fewer per 100 (from 27 fewer to 66 fewer)		

¹ Inconclusive effect size

3 Is bright light effective for depression with a seasonal pattern/SAD compared with attentional control?

			Quality asse	ssment					Summary of	findings		
			•				No o	f patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Attentional control	Relative (95% CI)	Absolute	Quality	
Leaving s	study early fo	r any reason (overall)		<u> </u>	<u> </u>						
5				no serious indirectness	very serious ¹	none	18/134 (13.4%)	18/124 (14.5%)	RR 0.92 (0.51 to 1.64)	1 fewer per 100 (from 7 fewer to 9 more)	⊕⊕OO LOW	

² Single study

								13.1%		1 fewer per 100 (from 6 fewer to 8 more)	
ing	study early fo	r any reason	- Light box vs de	activated negati	ive ion generato	r					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	8/41 (19.5%)	9/40 (22.5%)	RR 0.87 (0.37 to	3 fewer per 100 (from 14 fewer to 23 more)	⊕⊕OO LOW
								22.5%	2.02)	3 fewer per 100 (from 14 fewer to 23 more)	
ing	study early fo	r any reason	- Low dose (<500	00lux hours/day)	LED light vs ne	gative ion ge	nerator				
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	1/15 (6.7%)	2/11 (18.2%)	RR 0.37 (0.04 to	11 fewer per 100 (from 17 fewer to 46 more)	⊕⊕OO LOW
								18.2%	3.55)	11 fewer per 100 (from 17 fewer to 46 more)	
ing	study early fo	r any reason	- Light box vs hig	gh dose (>300lu	x) dim red light	box					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	6/33 (18.2%)	5/26 (19.2%)	RR 0.95 (0.32 to	1 fewer per 100 (from 13 fewer to 34 more)	⊕⊕OO LOW
							(10.270)	19.2%	2.76)	1 fewer per 100 (from 13 fewer to 34 more)	
	study early fo	r any reason	- Light box vs lov	w-density ionisa	tion						
ving			no serious	no serious	very serious ²	none		2/25 (00/)		1 more per 100 (from 7 fewer to 49	
ving	randomised trials	no serious limitations	inconsistency	indirectness			2/23 (8.7%)	2/25 (8%)	RR 1.09 (0.17 to 7.1)	more)	⊕⊕OO LOW

	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	1/10 (10%)	0/12 (0%)	RR 3.55 (0.16 to 78.56)	0 more per 100 (from 0 fewer to 0 more) 0 more per 100 (from 0 fewer to 0 more)	⊕⊕OO LOW
aving	study early fo	r any reason	- Low dose (<500	00lux hours/day) light visor vs n	o light visor				,	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	0/12 (0%)	0/10 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
		ļ						0%		not pooled	
aving	study early di	ue to lack of e	efficacy - Low dos	se (<5000lux ho	urs/day) LED lig	ht vs negative	ion generator				
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	0/15 (0%)	1/11 (9.1%)	RR 0.25 (0.01 to	7 fewer per 100 (from 9 fewer to 42 more)	⊕⊕OO LOW
								9.1%	5.62)	7 fewer per 100 (from 9 fewer to 42 more)	
porte	d side effects	(overall)									
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	25/45 (55.6%)	21/36 (58.3%)	RR 0.98 (0.73 to 1.32)	1 fewer per 100 (from 16 fewer to 19 more)	⊕⊕OO LOW
								44.6%	1.02)	1 fewer per 100 (from 12 fewer to 14 more)	
porte	d side effects	- Low dose (5000lux hours/da	ay) LED light vs	negative ion ge	nerator					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	2/15 (13.3%)	1/11 (9.1%)	RR 1.47 (0.15 to 14.21)		⊕⊕⊕O MODERATE
								9.1%	14.21)	4 more per 100 (from 8 fewer to 120 more)	

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious	none	23/30 (76.7%)	20/25 (80%)	RR 0.96 (0.73 to 1.27)	3 fewer per 100 (from 22 fewer to 22 more) 3 fewer per 100 (from 22 fewer to 22 more)	⊕⊕OO LOW	
Mean cli	nician rated S	AD depression	n scores at endp	oint (overall) (m	easured with: §	SIGH-SAD; Better	r indicated b	y lower values	s)	,		
6	randomised trials	no serious limitations	serious ³	no serious indirectness	serious ¹	none	139	131	-	MD 2.78 lower (6.81 lower to 1.26 higher)	⊕⊕OO LOW	
Mean cli values)	nician rated S	AD depressio	n scores at endpo	oint - Low dose	(<5000lux hour	rs/day) LED light	vs negative	ion generator	(measured)	with: SIGH-SAD; Bet	ter indicated	by lower
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	14	9	-	MD 4.7 lower (10.34 lower to 0.94 higher)	⊕⊕⊕O MODERATE	
Mean cli	nician rated S	AD depression	n scores at endp	oint - Light viso	r vs dim light v	isor (measured v	vith: SIGH-S	AD; Better ind	icated by lov	wer values)		
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ³	none	64	58	-	MD 0.86 higher (7.56 lower to 9.29 higher)	⊕⊕OO LOW	
Mean cli	nician rated S	AD depressio	n scores at endp	oint - Light box	vs low-density	ionisation (meas	sured with: S	I SIGH-SAD; Bet	ter indicated	by lower values)		
2	randomised trials	no serious limitations	serious ²	no serious indirectness	no serious imprecision	none	40	42	-	MD 8.56 lower (14.73 to 2.39 lower)	⊕⊕⊕O MODERATE	
Mean cli	nician rated S	AD depressio	n scores at endp	oint - Low dose	(<5000lux hou	rs/day) light box	vs no light b	oox (measured	with: SIGH-	SAD; Better indicate	d by lower v	alues)
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	9	12	-	MD 1.4 higher (4.93 lower to 7.73 higher)	⊕⊕OO LOW	
Mean cli	nician rated S	AD depression	n scores at endp	oint - Low dose	(<5000lux hour	rs/day) light viso	r vs no light	visor (measur	ed with: SIG	H-SAD; Better indic	ated by lowe	r values)
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	12	10	-	MD 0.2 lower (6.22 lower to 5.82 higher)	⊕⊕OO LOW	

	ilinician rated t	ypicai depres	ssion scores at en	dpoint (measur	ea with Hami	7 177111100 21, 0	etter mulcateu	by lower val	ues)			
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ¹	none	106	103	-	SMD 0.07 lower (0.51 lower to 0.37 higher)	⊕⊕OO LOW	
an c	linician rated t	ypical depres	ssion scores at en	dpoint - Light v	isor vs dim lig	ht visor (measur	ed with: HAMD)-17/HRSD-21	; Better ind	icated by lower value	s)	
	randomised trials	no serious limitations	serious ³	no serious indirectness	serious ⁴	none	64	58	-	SMD 0.05 higher (0.52 lower to 0.63 higher)	⊕⊕OO LOW	
ean c	linician rated t	ypical depres	ssion scores at en	dpoint - Light b	ox vs low-den	sity ionisation (r	neasured with:	HAMD-17/H	RSD-21; Bet	ter indicated by lower	r values)	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	21	23	-	SMD 0.81 lower (1.43 to 0.19 lower)	⊕⊕⊕O MODERATE	
ean c lues)		ypical depres	ssion scores at en	dpoint - Low do	ose (<5000lux l	hours/day) light	box vs no light	box (measu	red with: HA	MD-17/HRSD-21; Bet	ter indicated l	by lo
	randomised	no serious	no serious	no serious	serious ⁴	none				SMD 0.26 higher	⊕⊕⊕О	
	trials	limitations	inconsistency	indirectness			9	12	-	(0.61 lower to 1.13 higher)	MODERATE	
					ose (<5000lux I	hours/day) light			sured with:	`	MODERATE	ed by
	linician rated t				ose (<5000lux l	nours/day) light			sured with:	higher)	MODERATE	ed by
wer v	clinician rated tralues) randomised trials	no serious limitations	no serious	no serious indirectness	serious ⁴	none	visor vs no ligh	nt visor (mea	-	higher) HAMD-17/HRSD-21; E SMD 0.2 higher (0.64 lower to 1.04	MODERATE Better indicate	ed by
wer v	clinician rated tralues) randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	visor vs no ligh	nt visor (mea	-	higher) HAMD-17/HRSD-21; E SMD 0.2 higher (0.64 lower to 1.04	MODERATE Better indicate	ed by
ean c	randomised trials linician rated a randomised trials	no serious limitations htypical depresentations	no serious inconsistency ession scores at e	no serious indirectness ndpoint (measu no serious indirectness	serious⁴ Ired with: SAD no serious imprecision	none subscale; Bette	visor vs no ligh	10 ower values	-	higher) HAMD-17/HRSD-21; E SMD 0.2 higher (0.64 lower to 1.04 higher) MD 1.25 lower (2.77 lower to 0.27	MODERATE Better indicate ⊕⊕⊕O MODERATE ⊕⊕⊕⊕	ed by

Mean clii values)	nician rated at	typical depres	sion scores at en	dpoint - Low do	se (<5000lux h	ours/day) light box	c vs no lig	ht box (measu	red with: SA	D subscale; Better	ndicated by lower
		no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	9	12	-	MD 1.2 higher (2.48 lower to 4.88 higher)	⊕⊕⊕O MODERATE
Mean clii /alues)	nician rated at	typical depres	sion scores at en	dpoint - Low do	se (<5000lux h	ours/day) light vis	or vs no li	ght visor (mea	sured with: \$	SAD subscale; Bett	er indicated by lower
I	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	12	10	-	MD 1.3 lower (3.84 lower to 1.24 higher)	⊕⊕⊕O MODERATE
Mean sel	f rated depres	ssion scores a	t endpoint - Light	box vs deactiv	ated negative id	on generator (mea	sured with	n: BDI; Better	ndicated by	lower values)	
1		no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	33	31	-	MD 2.6 lower (6.72 lower to 1.52 higher)	⊕⊕⊕O MODERATE
Non rem	ission (SIGH-	SAD or SIGH-	SAD-SR or HDRS)	(overall)							
6	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ³	none	99/176 (56.3%)	98/160 (61.3%)	RR 0.89 (0.66 to 1.2)	7 fewer per 100 (from 21 fewer to 12 more)	⊕⊕OO LOW
							(22272)	70.5%	(0000 00 00.2)	8 fewer per 100 (from 24 fewer to 14 more)	
Non remi	ission (SIGH-	SAD or SIGH-S	SAD-SR or HDRS)	- Low dose (<5	000lux hours/d	ay) LED light vs n	egative ior	n generator			
1		no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	7/15 (46.7%)	10/11 (90.9%)	RR 0.51 (0.29 to 0.91)	45 fewer per 100 (from 8 fewer to 65 fewer)	⊕⊕⊕O MODERATE
								90.9%	,	45 fewer per 100 (from 8 fewer to 65 fewer)	
Non rem	ission (SIGH-	SAD or SIGH-S	SAD-SR or HDRS)	- Light box vs	deactivated neg	gative ion generato	or				
1		no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	21/41 (51.2%)	30/40 (75%)	RR 0.68 (0.48 to 0.97)	24 fewer per 100 (from 2 fewer to 39 fewer)	⊕⊕⊕O MODERATE
	1	1	1	1	1	1	1	1		1	l

								75%		24 fewer per 100 (from 2 fewer to 39 fewer)	
n re	mission (SIGH-	SAD or SIGH	I-SAD-SR or HDRS	6) - Light visor v	s dim light viso	r					
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ⁴	none	33/64 (51.6%)	22/58 (37.9%)	(0.79 to	13 more per 100 (from 8 fewer to 48 more)	⊕⊕OO LOW
							, ,	38.7%	2.27)	13 more per 100 (from 8 fewer to 49 more)	2011
ı re	mission (SIGH-	SAD or SIGH	I-SAD-SR or HDRS	S) - Light box vs	high dose (>30	0lux) dim red	light box				
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	25/33 (75.8%)	19/26 (73.1%)	RR 1.04 (0.77 to 1.4)	3 more per 100 (from 17 fewer to 29 more)	⊕⊕OO LOW
					(1.0.070)	73.1%	(6)	3 more per 100 (from 17 fewer to 29 more)	2011		
on re	mission (SIGH-	SAD or SIGH	I-SAD-SR or HDRS	S) - Light box vs	low-density ior	nisation					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	13/23 (56.5%)	17/25 (68%)	RR 0.83 (0.53 to 1.3)		⊕⊕OO LOW
								68%		12 fewer per 100 (from 32 fewer to 20 more)	
on re	esponse (SIGH-S	SAD) (overall))			1					
on re		no serious limitations	serious ³	no serious indirectness	serious ¹	none	83/183 (45.4%)	92/171 (53.8%)	RR 0.86 (0.64 to 1.15)	8 fewer per 100 (from 19 fewer to 8 more)	⊕⊕OO LOW

1		no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	19/41 (46.3%)	25/40 (62.5%)	RR 0.74 (0.49 to 1.11)	16 fewer per 100 (from 32 fewer to 7 more)	⊕⊕⊕0 MODERATE
								62.5%		(from 32 fewer to 7 more)	
Non resp	onse (SIGH-S	SAD) - Light vi	sor vs dim light v	isor							
2		no serious limitations	serious ³	no serious indirectness	serious ⁴	none	30/64 (46.9%)	22/58 (37.9%)	(0.56 to	9 more per 100 (from 17 fewer to 66 more)	⊕⊕OO LOW
								37.2%	2.75)	9 more per 100 (from 16 fewer to 65 more)	
Non resp	onse (SIGH-S	SAD) - Light be	ox vs high dose (>	300lux) dim rec	l light box						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	13/33 (39.4%)		(0.42 to	15 fewer per 100 (from 31 fewer to 15 more)	⊕⊕⊕O MODERATE
							(001170)	53.9%	1.27)	15 fewer per 100 (from 31 fewer to 15 more)	
Non resp	onse (SIGH-S	SAD) - Light be	ox vs low-density	ionisation							
1		no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	9/23 (39.1%)	18/25 (72%)	RR 0.54 (0.31 to 0.96)	33 fewer per 100 (from 3 fewer to 50 fewer)	⊕⊕⊕O MODERATE
								72%	0.96)	33 fewer per 100 (from 3 fewer to 50 fewer)	
Non resp	onse (SIGH-S	SAD) - Low do	se (<5000lux hour	s/day) light box	vs no light box	x					
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	7/10 (70%)	7/12 (58.3%)	RR 1.2 (0.64 to 2.25)		⊕⊕⊕O MODERATE
								58.3%		12 more per 100 (from 21 fewer to 73 more)	

Non r	on response (SIGH-SAD) - Low dose (<5000lux hours/day) light visor vs no light visor														
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	5/12 (41.7%)	6/10 (60%)	RR 0.69 (0.3 to 1.61)	,	⊕⊕⊕O MODERATE				

¹ Inconclusive effect size

Is bright light effective for depression with a seasonal pattern/SAD compared with active treatments?

			Quality asse	eemant					Summary of	findings		
			Quanty asse	SSIIIEIIL			No o	f patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Active treatment control	Relative (95% CI)	Absolute	Quality	importanio
Leaving s	study early fo	or any reason -	Light box vs gro	up CBT								
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	2/25 (8%)	4/24 (16.7%)	RR 0.53 (0.12 to 2.31)	8 fewer per 100 (from 15 fewer to 22 more)	⊕⊕⊕O MODERATE	
							, ,	17.8%	Ì	8 fewer per 100 (from 16 fewer to 23 more)		
Leaving s	study early fo	or any reason -	Light box + place	ebo pill vs dim l	ight box + fluo	ketine						
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	12/68 (17.6%)	8/68 (11.8%)	RR 1.5 (0.65 to 3.44)	6 more per 100 (from 4 fewer to 29 more)	⊕⊕⊕O MODERATE	
							,	9.8%	,	5 more per 100 (from 3 fewer to 24 more)		
Leaving s	study early fo	or any reason -	Light box + hype	ericum vs dim li	ght + hypericur	n						

Single study; inconclusive effect size
 Significant heterogeneity; random effects model used

⁴ Single study

	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/10 (0%)	0/10 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH
								0%		not pooled	
eaving s	study early du	ue to side effe	ects - Light box +	placebo pill vs	dim light box +	fluoxetine					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	1/48 (2.1%)	2/48 (4.2%)	RR 0.5 (0.05 to 5.33)	2 fewer per 100 (from 4 fewer to 18 more)	⊕⊕OO LOW
								4.2%		2 fewer per 100 (from 4 fewer to 18 more)	
eaving	study early du	ue to side effe	ects - Light box ve	s group CBT							
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	0/16 (0%)	0/15 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
							, ,	0%		not pooled	
eaving s	study early du	ie to lack of e	efficacy - Light bo	x + placebo pill	l vs dim light bo	x + fluoxetine					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	2/43 (4.7%)	0/48 (0%)	(0.27 to more)		
								0%	112.00)	0 more per 100 (from 0 fewer to 0 more)	
eported	side effects	- Light box +	placebo pill vs di	m light box + fl	uoxetine						
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	37/48 (77.1%)	75%	RR 1.03 (0.82 to 1.29)	22 more per 1000 (from 135 fewer to 217 more)	⊕⊕⊕O MODERATE
ean clir	ician rated S	AD depression	on scores at endp	oint - Light box	vs group CBT	(measured with: \$	SIGH-SAD;	Better indicat	ed by lower v	alues)	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	16	15	-	MD 0.2 lower (6.5 lower to 6.1 higher)	⊕⊕OO LOW
ean clir	l ician rated S	AD depression	n scores at endp	oint - Light box	t + placebo pill v	 /s dim light box +	fluoxetine	(measured w	 ith: SIGH-SAD); Better indicated b	y lower values)
		no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	68	-	MD 0.49 lower (3.72 lower to 2.74 higher)	
an clir	ician rated ty	pical depress	sion scores at en	dpoint - Light b	ox vs group CB	T (measured with	: HAMD-17	/ //HRSD-21; Be	tter indicated	by lower values)	

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	16	15	-	SMD 0.13 lower (0.83 lower to 0.58 higher)	⊕⊕OO LOW	
Mean cl values)	inician rated ty	ypical depres	sion scores at en	dpoint - Light b	ox + placebo pi	ll vs dim light b	ox + fluoxetii	ne (measured	with: HAMD-	17/HRSD-21; Better	indicated by I	ower
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	68	-	SMD 0.04 lower (0.38 lower to 0.29 higher)	⊕⊕⊕⊕ HIGH	
Mean cl	inician rated ty	ypical depres	sion scores at en	dpoint - Light b	ox + hypericum	vs dim light +	hypericum (m	neasured with:	HAMD-17/HF	RSD-21; Better indic	ated by lowe	r values)
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	10	10	-	SMD 0.32 lower (1.2 lower to 0.57 higher)		
Mean cl	inician rated a	typical depre	ssion scores at e	ndpoint - Light I	box vs group C	BT (measured v	with: SAD sub	oscale; Better	indicated by	lower values)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	16	15	-	MD 0.4 higher (2.68 lower to 3.48 higher)		
Mean cl	inician rated a	typical depre	ssion scores at e	ndpoint - Light I	box + placebo p	oill vs dim light	box + fluoxet	ine (measured	d with: SAD s	ubscale; Better indi	cated by lowe	er values)
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	68	68	-	MD 0.3 lower (1.75 lower to 1.15 higher)		
Mean se	elf rated depre	ssion scores	at endpoint - Ligh	nt box vs group	CBT (measured	d with: BDI; Bet	ter indicated	by lower value	es)			
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	16	15	-	MD 0.7 lower (7.16 lower to 5.76 higher)	⊕⊕OO LOW	
Mean se	elf rated depre	ssion scores	at endpoint - Ligh	nt box + placebo	pill vs dim ligh	nt box + fluoxet	ine (measure	d with: BDI; B	etter indicate	d by lower values)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	48	48	-	MD 1.6 lower (5.68 lower to 2.48 higher)	⊕⊕OO LOW	
Non ren	nission - Light	box + placeb	o pill vs dim light	box + fluoxetin	ie		1		<u> </u>		<u> </u>	
2	randomised trials	no serious limitations	serious ⁴	no serious indirectness	serious ¹	none	34/68 (50%)	37/68 (54.4%)	RR 0.92 (0.67 to 1.27)	4 fewer per 100 (from 18 fewer to 15	⊕⊕OO LOW	

								60.4%		5 fewer per 100 (from 20 fewer to 16 more)		
lon rer	nission - Light	box vs group	СВТ									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/25 (48%)	15/24 (62.5%)	RR 0.77 (0.46 to 1.28)	14 fewer per 100 (from 34 fewer to 17 more)	⊕⊕⊕⊕ HIGH	
							(223)	63.3%	,	15 fewer per 100 (from 34 fewer to 18 more)		
on res	ponse - Light	box + placebo	pill vs dim light	box + fluoxetine	•							
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	22/68 (32.4%)	23/68 (33.8%)	RR 0.96 (0.59 to 1.54)	1 fewer per 100 (from 14 fewer to 18 more)	⊕⊕OO LOW	
								34.2%	,	1 fewer per 100 (from 14 fewer to 18 more)		

¹ Inconclusive effect size

Is bright light effective for depression with a seasonal pattern/SAD compared with a combination of bright light and CBT?

			Quality asse	ssment					Summary	of findings		
			•				No o	f patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Light + CBT combo	Relative (95% CI)	Absolute	Quality	
Leaving s	tudy early for	any reason										
		no serious limitations		no serious indirectness	serious ¹	none	2/25 (8%)	2/23 (8.7%)	RR 0.92 (0.17 to 4.91)	1 fewer per 100 (from 7 fewer to 34 more)	⊕⊕⊕O MODERATE	

² Inconclusive effect size/single study

Single study
 Significant heterogeneity; random effects model used

								9.6%		1 fewer per 100 (from 8 fewer to 38 more)	
Leaving s	study early du	ue to side effec	ets								
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	0/16 (0%)	1/15 (6.7%)	RR 0.31 (0.01 to	5 fewer per 100 (from 7 fewer to 41 more)	⊕⊕OO LOW
								6.7%	7.15)	5 fewer per 100 (from 7 fewer to 41 more)	
Mean clir	nician rated S	AD depression	n scores at endpo	int (measured w	ith: SIGH-SAD;	Better indicated b	y lower v	alues)			
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	16	15	-	MD 4.2 higher (0.52 lower to 8.92 higher)	
Mean clir	nician rated ty	pical depressi	ion scores at end	point (measured	with: HAMD-17	/HRSD-21; Better i	indicated	by lower va	lues)		<u>'</u>
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	16	15	-	SMD 0.46 higher (0.26 lower to 1.17 higher)	⊕⊕⊕O MODERATE
Mean clir	l nician rated at	typical depres	sion scores at end	dpoint (measure	d with: SAD sub	 scale; Better indi	cated by	lower values	5)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	16	15	-	MD 2 higher (0.12 lower to 4.12 higher)	⊕⊕⊕O MODERATE
Mean sel	f rated depres	ssion scores a	t endpoint (measu	ured with: BDI; E	Better indicated	by lower values)					
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	16	15	-	MD 2.3 higher (2.47 lower to 7.07 higher)	
Non remi	ssion (SIGH-	SAD)				•		•		•	. '
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/25 (48%)	5/23 (21.7%)	RR 2.22 (0.92 to	27 more per 100 (from 2 fewer to 94 more)	⊕⊕⊕⊕ HIGH
								19.6%	5.32)	24 more per 100 (from 2 fewer to 85 more)	

- ¹ Inconclusive effect size
 ² Inconclusive effect size; single study
 ³ Single study
- Does the time of day increase the effectiveness of bright light box therapy?

			Quality asses	sment				Sumn	nary of findi	ngs		
			quanty acces				N	No of patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Morning	Afternoon/evening bright light box	Relative (95% CI)	Absolute	Quality	
Leaving	study early fo	or any reason	(overall)	'	<u>'</u>		'					
			no serious inconsistency	no serious indirectness	serious ¹	none	8/66 (12.1%)	8/64 (12.5%)	RR 0.98 (0.41 to	0 fewer per 100 (from 7 fewer to 17 more)	⊕⊕⊕O MODERATE	
								0%	2.35)	0 fewer per 100 (from 0 fewer to 0 more)		
Leaving	study early fo	or any reason	- SAD									
		no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	8/50 (16%)	8/49 (16.3%)	RR 0.98 (0.41 to	0 fewer per 100 (from 10 fewer to 22 more)	⊕⊕⊕O MODERATE	
								10%	2.35)	0 fewer per 100 (from 6 fewer to 13 more)		
Leaving	study early fo	or any reason	- Subsyndromal	SAD								
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	0/16 (0%)	0/15 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE	
Leaving s	study early d	ue to side effe	ects - Subsyndro	mal SAD				0%		not pooled		
		T .	1		1	T	T T		T			
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	0/16 (0%)	0/15 (0%)	not pooled		⊕⊕⊕O MODERATE	
					L			0%		not pooled		
Reported	side effects	- Subsyndror	nai SAD									

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	1/16 (6.3%)	2/15 (13.3%)	RR 0.47 (0.05 to	7 fewer per 100 (from 13 fewer to 49 more)	⊕⊕OO LOW	
								13.3%	4.65)	7 fewer per 100 (from 13 fewer to 49 more)		
Mean cli	nician rated S	SAD depressi	on scores at end	point (overall)	(measured w	vith: SIGH-SAD;	Better indica	ated by lower values)				
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	35	33	-	MD 1.38 lower (5.49 lower to 2.73 higher)	⊕⊕OO LOW	
Mean cli	nician rated S	SAD depressi	on scores at end	point - Subsyn	dromal SAD	(measured with	: SIGH-SAD;	Better indicated by lov	wer values)			
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	16	14	-	MD 0.6 higher (3.89 lower to 5.09 higher)	⊕⊕OO LOW	
Mean cli	nician rated S	SAD depressi	on scores at end	point - SAD (m	easured with	n: SIGH-SAD; Be	tter indicate	d by lower values)				
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	19	19	-	MD 3.6 lower (8.5 lower to 1.3 higher)	⊕⊕OO LOW	
Mean cli	nician rated t	ypical depres	ssion scores at e	ndpoint (overa	II) (measured	with: HAMD-17	/HRSD-31; B	etter indicated by lowe	er values)		ļ	
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	25	22	-	SMD 0.05 lower (0.63 lower to 0.52 higher)	⊕⊕⊕O MODERATE	
Mean cli	nician rated t	ypical depres	ssion scores at e	ndpoint - Subs	yndromal SA	D (measured wi	th: HAMD-17	7/HRSD-21; Better indic	cated by low	ver values)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	16	14	-	SMD 0.15 lower (0.87 lower to 0.57 higher)	⊕⊕OO LOW	
Mean cli	nician rated t	ypical depres	ssion scores at e	ndpoint - SAD	(HRSD-31) (n	neasured with: H	IAMD-17/HR	SD-21; Better indicated	by lower v	alues)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	9	8	-	SMD 0.12 higher (0.83 lower to 1.07 higher)	⊕⊕OO LOW	

		no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	16	14	-	MD 1 higher (1.72 lower to 3.72 higher)	⊕⊕OO LOW
ean s	self rated depre	ession scores	s at endpoint - SA	AD (measured v	vith: BDI; Be	tter indicated	by lower values	s)	·		
		no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	33	32	-	MD 0.9 lower (4.66 lower to 2.86 higher)	⊕⊕OO LOW
on re	mission - SAD	L									
		no serious limitations	serious ⁴	no serious indirectness	serious ¹	none	27/50 (54%)	26/48 (54.2%)	RR 1.00 (0.69 to	0 fewer per 100 (from 17 fewer to 24 more)	⊕⊕OO LOW
								42.5%	1.45)	0 fewer per 100 (from 13 fewer to 19 more)	
on re	sponse (overal	II)				•					
		no serious limitations	serious ¹	no serious indirectness	serious ¹	none	29/66 (43.9%)	27/63 (42.9%)	RR 1 (0.51 to 1.98)	0 fewer per 100 (from 21 fewer to 42 more)	⊕⊕OO LOW
								40%		0 fewer per 100 (from 20 fewer to 39 more)	
on re	sponse - SAD										
		no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	24/50 (48%)	18/48 (37.5%)	RR 1.26 (0.78 to	10 more per 100 (from 8 fewer to 38 more)	⊕⊕⊕O MODERATE
								32.5%	2.01)	8 more per 100 (from 7 fewer to 33 more)	

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	5/16 (31.3%)	9/15 (60%)	RR 0.52 (0.23 to	29 fewer per 100 (from 46 fewer to 12 more)	
							(011070)	60%		29 fewer per 100 (from 46 fewer to 12 more)	

¹ Inconclusive effect size

Is dawn simulation effective for depression with a seasonal pattern/SAD? 5

			Quality asse	semant				Sı	ummary of f	indings		
			Quality asse	SSIIICIIL			No of p	patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dawn simulation	Attentional control	Relative (95% CI)	Absolute	Quality	
Leaving s	tudy early fo	or any reason		<u>l</u>	ļ.							1
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	2/70 (2.9%)	10/71 (14.1%)	RR 0.33 (0.05 to	9 fewer per 100 (from 13 fewer to 17 more)	⊕⊕OO LOW	
								19.4%	2.22)	13 fewer per 100 (from 18 fewer to 24 more)		
Leaving s	tudy early d	ue to side effe	ects									•
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	0/31 (0%)	1/31 (3.2%)	RR 0.33 (0.01 to	2 fewer per 100 (from 3 fewer to 22 more)	⊕⊕OO LOW	
								3.2%	7.88)	2 fewer per 100 (from 3 fewer to 22 more)	20	

² Single study

Inconclusive effect size; single study
 Significant heterogeneity; random effects model used

2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	0/45 (0%)	6/44 (13.6%)	RR 0.14 (0.02 to 1.1)	12 fewer per 100 (from 13 fewer to 1 more)	⊕⊕⊕O MODERATE
								11.9%		10 fewer per 100 (from 12 fewer to 1 more)	
Reported	I side effects										
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	6/14 (42.9%)	1/13 (7.7%)	RR 5.57 (0.77 to	35 more per 100 (from 2 fewer to 302 more)	⊕⊕OO LOW
								7.7%	40.26)	35 more per 100 (from 2 fewer to 302 more)	
Mean clir	nician rated t	ypical depres	sion scores at en	dpoint (measur	ed with: HAMD	-17/HRSD-21; Bet	ter indicated	by lower valu	es)		
2	randomised trials	no serious limitations	serious ³	no serious indirectness	no serious imprecision	none	37	36	-	SMD 0.53 lower (1.62 lower to 0.15 higher)	⊕⊕⊕O MODERATE
Mean clir	nician rated a	typical depre	ssion scores at e	endpoint (measu	red with: SAD	subscale; Better i	indicated by I	ower values)	ļ		<u> </u>
2	randomised trials	no serious limitations	serious ³	no serious indirectness	very serious ²	none	37	36	-	MD 2.20 lower (7.52 lower to 3.11 higher)	⊕000 VERY LOW
Non remi	ission (SIGH-	SAD)									
2		no serious limitations	serious ³	no serious indirectness	serious ¹	none	25/56 (44.6%)	29/58 (50%)	RR 0.9 (0.46 to 1.78)	5 fewer per 100 (from 27 fewer to 39 more)	⊕⊕OO LOW
								49.9%		5 fewer per 100 (from 27 fewer to 39 more)	
Non resp	onse (SIGH-	SAD)									<u> </u>
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	14/56 (25%)	21/58 (36.2%)	RR 0.71 (34 to 1.48)	11 fewer per 100 (from 17 more to 1195 more)	⊕⊕⊕O MODERATE

				36.3%	11 fewer per 100 (from 17 more to	
					1198 more)	

¹ Inconclusive effect size

Is dawn simulation more effective than bright light box therapy for depression with a seasonal pattern/SAD?

			Quality asse	ssment					Summary of	findings		
			4,				No of	patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light box	Dawn simulation	Relative (95% CI)	Absolute	Quality	
Leaving s	study early fo	r any reason					L					
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	5/56 (8.9%)	1/56 (1.8%)	RR 3.72 (0.62 to	5 more per 100 (from 1 fewer to 38 more)	⊕⊕⊕O MODERATE	
							(****)	2%	22.22)	5 more per 100 (from 1 fewer to 42 more)		
Leaving s	study early du	ue to side effec	cts									
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	2/33 (6.1%)	0%	RR 4.71 (0.23 to 94.31)	0 more per 1000 (from 0 fewer to 0 more)		
Leaving s	tudy early du	e to lack of ef	ficacy									
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/31 (0%)	0/31 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH	
Non remi	ssion (SIGH-	SAD)						0%		not pooled		
	randomised trials	no serious limitations	serious ³	no serious indirectness	very serious ¹	none	30/56 (53.6%)	25/56 (44.6%)	RR 1.19 (0.7 to 2)	8 more per 100 (from 13 fewer to 45 more)	⊕000 VERY LOW	

Inconclusive effect size; single study
 Significant heterogeneity; random effects model used

								46.1%		9 more per 100 (from 14 fewer to 46 more)		
Non resp	onse (SIGH-S	SAD)										
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	20/56 (35.7%)	14/56 (25%)	RR 1.45 (0.82 to	11 more per 100 (from 5 fewer to 39 more)	⊕⊕⊕O MODERATE	
								26.1%	2.58)	12 more per 100 (from 5 fewer to 41 more)		
Depressi	on: mean end	lpoint scores	(Better indicated	by lower values	5)							
l	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	21	24	-	MD 0.9 lower (4 lower to 2.2 higher)	⊕⊕OO LOW	
SAD: me	an endpoint s	cores (Better	indicated by low	er values)								
I	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	21	24	-	MD 1.8 lower (6.98 lower to 3.38 higher)	⊕⊕OO LOW	

¹ Inconclusive effect size

Non-light therapies for depression with a seasonal pattern/SAD

Are antidepressants effective in depression with a seasonal pattern/SAD? (Acute phase efficacy data)

			Quality asse	ssment				Summ	ary of findir	ngs		
			,				No of patient	s		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acute phase treatment :antidepressants	Control	Relative (95% CI)	Absolute	Quality	
Number r	not achieving	g =/> 50% red	uction in SIGH-S	AD score at en	dpoint (overall)						

Inconclusive effect size; single study
 Significant effect size - random effects model used

2		no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/129 (44.2%)	68/126 (54%)	RR 0.82 (0.63 to 1.05)	10 fewer per 100 (from 20 fewer to 3 more)	⊕⊕⊕⊕ HIGH
								57.8%	1.05)	10 fewer per 100 (from 21 fewer to 3 more)	
Number	not achieving	g =/> 50% red	uction SIGH-SAI) score							
1		no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	41/93 (44.1%)	47/94 (50%)	RR 0.88 (0.65 to	6 fewer per 100 (from 18 fewer to 10 more)	⊕⊕OO LOW
								50%	1.2)	6 fewer per 100 (from 18 fewer to 10 more)	
Number	not achieving	g =/> 50% red	uction in outcon	ne score at end	point - Fluoxet	ine vs Placebo					
1		no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	16/36 (44.4%)	21/32 (65.6%)	RR 0.68 (0.43 to	21 fewer per 100 (from 37 fewer to 3 more)	⊕⊕OO LOW
								65.6%	1.05)	21 fewer per 100 (from 37 fewer to 3 more)	2011
Mean en	dpoint SIGH-	SAD (clinicia	n rated) (antidep	ressants) (Bette	er indicated by	lower values)					
2		no serious limitations	serious ²	no serious indirectness	serious	none	52	47	-	SMD 0.11 lower (0.65 lower to 0.42 higher)	⊕⊕OO LOW
Mean en	dpoint (clinic	ian rated) (an	ntidepressants) -	Moclobemide v	vs Placebo (Be	tter indicated by	lower values)				
1		no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	16	15	-	SMD 0.23 higher (0.48 lower to 0.94 higher)	⊕⊕OO LOW
Mean en	dpoint (clinic	ian rated) (an	ntidepressants) -	Fluoxetine vs I	Placebo (Bette	r indicated by low	ver values)				
1		no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	36	32	-	SMD 0.33 lower (0.81 lower to 0.15 higher)	⊕⊕OO LOW

randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	36	32	-	MD 1.7 lower (6.53 lower to 3.13 higher)	⊕⊕OO LOW
n change (clinici	an rated) - Se	ertraline vs Place	bo (Better indic	ated by lower	values)	1				
randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	none	93	93	-	MD 4.51 lower (8.23 to 0.79 lower)	⊕⊕⊕O MODERATE
pse Prevention	Number of p	atients exprienc	ng a recurrence	9						
randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/542 (17%)	153/519 (29.5%)	RR 0.58 (0.46 to	12 fewer per 100 (from 8 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH
							31.9%	0.72)	13 fewer per 100 (from 9 fewer to 17 fewer)	

Are antidepressants effective in depression with a seasonal pattern/SAD? (Acute phase acceptability/tolerability data)

				Summary of findings								
	Quality assessment						No of patients Effe			ffect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acute phase acceptibility and tolerability (antidepressants)	Placebo	Relative (95% CI)	Absolute	Quality	·
Number	Number leaving the study early for any reason (overall)											
2	randomised trials	no serious limitations		no serious indirectness	very serious ²	none		20/109 (18.3%)	20/109 (18.3%) RR 0.7 (from 17 fewer to 42 more)	6 fewer per 100 (from 17 fewer to 42 more)	⊕OOO VERY LOW	
								19%	3.05)	6 fewer per 100 (from 16 fewer to 39 more)		

¹ Single study; inconclusive effect size ² Significant heterogeneity - random effects model used

³ Single study

Trandomised price	
Number leaving the study early for any reason - Moclobemide vs Placebo 1	
1 randomised trials limitations inconsistency limitations inconsistency limitations inconsistency limitations inconsistency limitations inconsistency limitations inconsistency limitations limitation	
trials limitations linconsistency lindirectness serious seriou	
Number leaving the study early due to side effects 3	
3 randomised trials no serious limitations no serious limitations no serious inconsistency no serious limitations no serious limitations no serious indirectness serious² none 12/145 (8.3%) 12/145 (8.3%) 8/144 (5.6%) RR 1.48 (0.63 to 3.47) 3 more per 100 (from 2 fewer to 14 more) 3 more per 100 (from 2 fewer to 13 more) Number leaving the study early due to side effects - Sertraline vs Placebo	
trials limitations inconsistency indirectness serious² 12/145 (8.3%) 12/145 (8.3%) RR 1.48 (0.63 to 3.47) 3 more per 100 (from 2 fewer to 14 more) Sometime to 14 more) Number leaving the study early due to side effects - Sertraline vs Placebo	
Number leaving the study early due to side effects - Sertraline vs Placebo 3 more per 100 (from 2 fewer to 13 more) Number leaving the study early due to side effects - Sertraline vs Placebo	
1 randomised trials no serious inconsistency indirectness regions indirectness regions randomised trials no serious indirectness regions no serious randomised trials no serious indirectness regions no serious randomised trials no serious indirectness regions no serious randomised trials no serious randomised for serious randomised trials no serious randomised for s	
5.69) 5 more per 100 (from 1 fewer to 25 more)	
Number leaving the study early due to side effects - Moclobemide vs Placebo	
1 randomised trials no serious limitations no serious inconsistency no serious indirectness regions no serious serious serious serious no seri	

N		4-4		Fl	Black			11.1%		9 fewer per 100 (from 11 fewer to 37 more)		
Number i	eaving the s	tuay eariy al	ue to side effects	- Fluoxetine v	s Placebo							
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	2/36 (5.6%)	1/32 (3.1%)	RR 1.78 (0.17 to	2 more per 100 (from 3 fewer to 55 more)	⊕⊕OO LOW	
								3.1%	18.69)	2 more per 100 (from 3 fewer to 55 more)		
lumber i	reporting sid	le effects - Se	ertraline vs Place	bo								
	randomised no trials lin	no serious no serious inconsistency		no serious indirectness	serious ⁴	none	76/93 (81.7%)	47/94 (50%)	RR 1.63 (1.31 to	31 more per 100 (from 15 more to 52 more)		
							50%	2.04)	31 more per 100 (from 15 more to 52 more)			
lumber i	reporting sid	le effects - FI	uoxetine vs Plac	ebo								
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	35/36 (97.2%)	29/32 (90.6%)	RR 1.07 (0.95 to 1.21)	6 more per 100 (from 5 fewer to 19 more)	⊕⊕⊕O MODERATE	
								90.6%		6 more per 100 (from 5 fewer to 19 more)		

¹ Significant heterogeneity - random effects model used ² Inconclusive effect size ³ Single study; inconclusive effect size

Which antidepressant is more effective in depression with a seasonal pattern/SAD?

Quality assessment	Summary of findings				
4, 6.000	No of patients	Effect	Quality	Importance	

⁴ Single study

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acute phase treatment: antidepressants	Active control	Relative (95% CI)	Absolute		
Number not achieving =/> 50% reduction in SIGH-SAD score at endpoint - High ion density v Low ion density												
				no serious indirectness	serious ¹	none	5/12 (41.7%)	11/13 (84.6%)	RR 0.49 (0.24 to 1)	43 fewer per 100 (from 64 fewer to 0 more)	⊕⊕⊕O MODERATE	
								84.6%		43 fewer per 100 (from 64 fewer to 0 more)		
Mean endpoint SIGH-SAD (clinician rated) - Moclobemide vs Fluoxetine (Better indicated by lower values)												
					very serious ¹	none	11	18	-	MD 1.6 lower (7.01 lower to 3.81 higher)	⊕⊕OO LOW	

¹ Single study; inconclusive effect size

2 Is continuation treatment effective for depression with a seasonal pattern/SAD?

Quality assessment							Summary of findings					
								No of patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation treatment Control Relative (95% CI)		Absolute	Quality		
Mean end	lpoint HAMD-	21 (clinician-ra	ated) - Propanolol	vs Placebo (Bet	tter indicated	by lower values)		<u> </u>				
1	randomised trials	no serious limitations		no serious indirectness	serious ¹	none	12	11	-	MD 7 lower (11.24 to 2.76 lower)	⊕⊕⊕O MODERATE	
Number I	eaving the st	udy early for a	ny reason - Propa	nolol vs Placeb	0							
1	randomised trials	no serious limitations		no serious indirectness	very serious ²	none	1/13 (7.7%)	0/11 (0%)	RR 2.57 (0.12 to	0 more per 100 (from 0 fewer to 0 more)	⊕⊕OO LOW	
							0%	57.44)	0 more per 100 (from 0 fewer to 0 more)			

3 4

Further-line treatment (chapter 8)

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

			Quality as	sessment			No of	f patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of antidepressant	Continuing with the antidepressant at the same dose	Relative (95% CI)	Absolute		
Remission	on (follow-up	5-8 wee	ks; assessed wit	h: ≤7 on HAMD))							
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	137/470 (29.1%)	141/483 (29.2%)		0 fewer per 1000 (from 53 fewer to 64 more)		
								29.8%		0 fewer per 1000 (from 54 fewer to 66 more)		
Respons	e (follow-up	5-8 week	s; assessed wit	h: ≥50% improv	ement on HA	MD)						
	randomised trials		no serious inconsistency		no serious imprecision	reporting bias ³	193/468 (41.2%)	220/487 (45.2%)	RR 0.89 (0.78 to 1.02)	50 fewer per 1000 (from 99 fewer to 9 more)	⊕⊕OO LOW	
								44.3%		49 fewer per 1000 (from 97 fewer to 9 more)		
Respons	e (follow-up	mean 5 v	weeks; assessed	l with: Much/ve	ry much impr	oved on CGI-I)						
	randomised trials	serious ¹	very serious ⁴	no serious indirectness	very serious⁵	reporting bias ³	96/135 (71.1%)	105/135 (77.8%)	RR 1.03 (0.59 to 1.8)	23 more per 1000 (from 319 fewer to 622 more)	⊕OOO VERY LOW	

¹ Single study ² Single study; inconclusive effect size

Donroes	ion symptom	atology	(follow up 5 8 w	ooke: moasuro	d with: HAMD	change score: R	etter indicated by lov	71.2%		21 more per 1000 (from 292 fewer to 570 more)		
Depiess								, 	1	T		
3	randomised trials	serious ¹	serious ⁶	no serious indirectness	no serious imprecision	reporting bias ³	328	346	-	MD 0.18 lower (1.71 lower to 1.36 higher)	⊕OOO VERY LOW	
Disconti	nuation for a	ny reaso	n (follow-up 5-8	weeks; assess	ed with: Numl	per of people lost	to follow-up (for any	y reason including adv	erse events	5))		
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	99/471 (21%)	97/487 (19.9%)	RR 1.08 (0.72 to 1.61)	16 more per 1000 (from 56 fewer to 121 more)	⊕000 VERY LOW	
								19.9%		16 more per 1000 (from 56 fewer to 121 more)		
Disconti	nuation due	to advers	se events (follow	v-up 5-8 weeks;	assessed wit	h: Number of peo	ple lost to follow-up	due to adverse events	5)			
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	34/371 (9.2%)	22/392 (5.6%)	RR 1.61 (0.7 to 3.71)	34 more per 1000 (from 17 fewer to 152 more)	⊕OOO VERY LOW	
								5.1%		31 more per 1000 (from 15 fewer to 138 more)		

¹ Risk of bias is high or unclear across multiple domains
² OIS not met (events<300)
³ Funding from pharmaceutical company

⁴ I2>80%

⁵ 95% CI crosses two clinical decision thresholds

⁶ I2>50%

Increasing the dose of antidepressant versus switching to another antidepressant

IIICIEas	ing the ut	JSE OI al	itiuepiessaiit	. versus swii	terning to an	nother antider	JIESSAIIL		ı		ı	ı
			Quality ass	essment			No of p	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of antidepressant	Switching to another antidepressant	Relative (95% CI)	Absolute	,	
Remissio	on (follow-up	mean 8 w	veeks; assessed	with: ≤10 on M	IADRS)	1						
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	124/229 (54.1%)	102/243 (42%)	RR 1.29 (1.07 to 1.56)	122 more per 1000 (from 29 more to 235 more)	⊕OOO VERY LOW	
								42%		122 more per 1000 (from 29 more to 235 more)		
Respons	e (follow-up	mean 8 w	eeks; assessed	with: ≥50% imp	provement on	MADRS)						
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	167/229 (72.9%)	170/243 (70%)	RR 1.04 (0.93 to 1.17)	28 more per 1000 (from 49 fewer to 119 more)	⊕⊕OO LOW	
								70%		28 more per 1000 (from 49 fewer to 119 more)		
Respons	e (follow-up	mean 8 w	eeks; assessed	with: Much/ver	y much impro	ved on CGI-I)			•			,
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	176/229 (76.9%)	182/243 (74.9%)	RR 1.03 (0.93 to 1.14)	22 more per 1000 (from 52 fewer to 105 more)	⊕⊕OO LOW	
								74.9%		22 more per 1000 (from 52 fewer to 105 more)		

press	ion sympton	natology (fo	ollow-up mean	8 weeks; meas	ured with: QID	S change score;	Better indicated by	lower values)			
		no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	229	243	-	MD 0.9 lower (1.88 lower to 0.08 higher)	⊕⊕⊕O MODERATE
conti	nuation for a	ny reason	(follow-up mea	n 8 weeks; ass	essed with: No	imber of people	lost to follow-up (for	r any reason includ	ing adverse	e events))	
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	56/238 (23.5%)	53/246 (21.5%)	RR 1.09 (0.78 to 1.52)	19 more per 1000 (from 47 fewer to 112 more)	⊕⊕OO LOW
							21.5%		19 more per 1000 (from 47 fewer to 112 more)		
sconti	inuation due	to adverse	events (follow-	up mean 8 wee	eks; assessed	with: Number of	people lost to follow	v-up due to adverse	e events)		•
		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	13/238 (5.5%)	13/246 (5.3%)	RR 1.03 (0.49 to 2.18)	2 more per 1000 (from 27 fewer to 62 more)	⊕OOO VERY LOW
								5.3%		2 more per 1000 (from 27 fewer to 63 more)	

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4 5

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

Quality assessment	No of patients	Effect	Quality	Importance

Blinding of outcome assessment unclear
OIS not met (events<300)
Study funded by pharmaceutical company
OS% CI crosses one clinical decision threshold

⁵ 95% CI crosses two clinical decision thresholds

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of antidepressant	Augmenting with another antidepressant/non-antidepressant agent	Relative (95% CI)	Absolute		
Remission	on - Increasi	ng dose o	f SSRI versus T	CA augmentati	on (follow-u	p mean 4 weeks;	assessed with: ≤7	on HAMD)			<u> </u>	
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	22/48 (45.8%)	13/46 (28.3%)	RR 1.6 (0.91 to 2.81)	170 more per 1000 (from 25 fewer to 512 more)	⊕OOO VERY LOW	
								27.2%		163 more per 1000 (from 24 fewer to 492 more)		
Remission	on - Increasi	ng dose o	f SSRI versus lit	hium augment	tation (follow	/-up mean 4 week	s; assessed with:	≤7 on HAMD)				
2	randomised trials	serious ¹		no serious indirectness	serious ⁴	reporting bias ³	22/48 (45.8%)	12/48 (25%)	RR 1.83 (1.03 to 3.25)	208 more per 1000 (from 7 more to 562 more)	⊕OOO VERY LOW	
								26.1%		217 more per 1000 (from 8 more to 587 more)		
Remission	on - Increasi	ng dose o	f SSRI versus To	eCA (mianserin	n) augmenta	tion (follow-up m	ean 5 weeks; asse	ssed with: ≤7 on HAMD)				
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	28/97 (28.9%)	43/98 (43.9%)	RR 0.66 (0.45 to 0.97)	149 fewer per 1000 (from 13 fewer to 241 fewer)	⊕OOO VERY LOW	
								43.9%		149 fewer per 1000 (from 13 fewer to 241 fewer)		
Remission	on - Increasi	ng dose o	f SSRI versus ar	ntipsychotic au	ugmentation	(follow-up mean	13 weeks; assesse	ed with: ≤7 on HAMD)				
1	randomised trials	very serious ⁶		no serious indirectness	very serious ⁷	none	9/28 (32.1%)	14/32 (43.8%)	RR 0.73 (0.38 to 1.43)	118 fewer per 1000 (from 271 fewer to 188 more)	⊕OOO VERY LOW	

								43.8%		118 fewer per 1000 (from 272 fewer to 188 more)	
spons	se (follow-up	5-13 wee	ks; assessed w	ith: ≥50% impr	rovement or	n HAMD)					
	randomised trials	serious⁵	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	69/125 (55.2%)	84/130 (64.6%)	RR 0.85 (0.69 to 1.04)	97 fewer per 1000 (from 200 fewer to 26 more)	⊕OOO VERY LOW
								61.8%		93 fewer per 1000 (from 192 fewer to 25 more)	
spons	se (follow-up	mean 5 v	veeks; assesse	d with: Much/v	ery much in	nproved on CGI-I)					
	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	66/97 (68%)	76/98 (77.6%)	RR 0.88 (0.74 to 1.04)	93 fewer per 1000 (from 202 fewer to 31 more)	⊕000 VERY LOW
								77.6%		93 fewer per 1000 (from 202 fewer to 31 more)	
press	ion sympton	natology -	Increasing dos	e of SSRI vers	sus TCA aug	gmentation (follow-	up mean 4 weeks; r	neasured with: HAMD c	hange score;	Better indicated	by lower va
	randomised trials	serious ¹	serious ⁸	no serious indirectness	serious ²	reporting bias ³	48	46	-	SMD 0.56 lower (1.23 lower to 0.11 higher)	⊕000 VERY LOW
press	ion symptor	natology -	Increasing dos	e of SSRI vers	us lithium a	augmentation (follo	w-up mean 4 weeks	s; measured with: HAMI	change scor	e; Better indica	ed by lower
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	48	48	-	SMD 0.34 lower (0.74 lower to 0.07 higher)	⊕000 VERY LOW

1		serious ⁶	no serious inconsistency	no serious indirectness	serious ²	none	28	32	-	SMD 0.07 higher (0.43 lower to 0.58 higher)	⊕OOO VERY LOW	
	tinuation for a	-	n - Increasing d	ose of SSRI ve	ersus TCA a	ugmentation (follo	w-up mean 4 weeks	s; assessed with: Number	of people lo	st to follow-up (for any r	eason
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁷	none	5/48 (10.4%)	8/46 (17.4%)	RR 0.58 (0.21 to 1.64)	73 fewer per 1000 (from 137 fewer to 111 more)	⊕OOO VERY LOW	
								19.9%		84 fewer per 1000 (from 157 fewer to 127 more)		
	tinuation for a		n - Increasing d	ose of SSRI ve	ersus lithiun	n augmentation (fo	llow-up mean 4 wee	eks; assessed with: Numb	er of people	lost to follow-u	p (for an	y reaso
ncludin	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁷	none	5/48 (10.4%)	7/48 (14.6%)	RR 0.72 (0.24 to 2.11)	41 fewer per 1000 (from 111 fewer to 162 more)	⊕OOO VERY LOW	
								14.5%		41 fewer per 1000 (from 110 fewer to 161 more)		
	tinuation for a			ose of SSRI ve	ersus TeCA	(mianserin) augme	entation (follow-up r	nean 5 weeks; assessed v	with: Numbe	r of people lost	to follow	-up (fo
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁷	reporting bias ³	15/98 (15.3%)	17/98 (17.3%)	RR 0.88 (0.47 to 1.67)	21 fewer per 1000 (from 92 fewer to 116 more)	⊕OOO VERY LOW	
								17.4%		21 fewer per 1000 (from 92 fewer to 117		

1	randomised trials	very serious ⁶	no serious inconsistency	no serious indirectness	very serious ⁷	none	4/28 (14.3%)	5/32 (15.6%)	RR 0.91 (0.27 to 3.08)	14 fewer per 1000 (from 114 fewer to 325 more)	⊕OOO VERY LOW	
								15.6%		14 fewer per 1000 (from 114 fewer to 324 more)		
Disconti adverse		to advers	e events - Incre	asing dose of	SSRI versus	TCA augmentation	n (follow-up mean 4	weeks; assessed with:	: Number of pe	eople lost to foll	ow-up du	e to
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁷	reporting bias ³	0/15 (0%)	2/12 (16.7%)	RR 0.16 (0.01 to 3.09)	140 fewer per 1000 (from 165 fewer to 348 more)	⊕OOO VERY LOW	
								16.7%		140 fewer per 1000 (from 165 fewer to 349 more)		
Disconti adverse		to advers	e events - Incre	asing dose of	SSRI versus	lithium augmenta	ition (follow-up mear	n 4 weeks; assessed wi	ith: Number of	f people lost to f	ollow-up	due to
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁷	reporting bias ³	0/15 (0%)	1/14 (7.1%)	RR 0.31 (0.01 to 7.09)	49 fewer per 1000 (from 71 fewer to 435 more)	⊕OOO VERY LOW	
										49 fewer per		
								7.1%		1000 (from 70 fewer to 432 more)		
	inuation due dverse even		se events - Incre	easing dose of	SSRI versus	antipsychotic au	gmentation (follow-u	7.1% p mean 13 weeks; asse	essed with: Nu	fewer to 432 more)	lost to fol	low-up
	randomised	ts)	no serious inconsistency	no serious indirectness	very serious ⁷	none	gmentation (follow-u 2/28 (7.1%)		RR 1.14 (0.17 to 7.59)	fewer to 432 more)	⊕OOO VERY LOW	llow-up

					fewer to 415	
					more)	

¹ Risk of bias is high or unclear across multiple domains

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8

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

	Quality assessment						No of patients		1	Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with another antidepressant or a non- antidepressant agent	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Remissi	on - Atypical	antidepre	ssant (follow-up	mean 4 weeks	; assessed wi	th: ≤7 on HAMD)						
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	23/41 (56.1%)	9/45 (20%)	RR 2.72 (1.44 to 5.14)	344 more per 1000 (from 88 more to 828 more)	⊕OOO VERY LOW	
								18.3%		315 more per 1000 (from 81 more to 758 more)		
Remissi	on - TCA (int	ravenous)	(follow-up mear	n 5 days; asses	sed with: ≤7 o	n HAMD)						
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	9/18 (50%)	0/18 (0%)	RR 19 (1.19 to 303.76)	-	⊕OOO VERY LOW	
Remissi	on - Antipsvo	chotic (foll	ow-up 4-12 weel	ks; assessed w	/ith: <10/11 on	MADRS/≤7 on H	AMD)	0%		-		

² 95% CI crosses one clinical decision threshold

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ OIS not met (events<300)

⁵ Blinding of outcome assessment unclear

⁶ Open-label

⁷ 95% CI crosses two clinical decision thresholds

⁸ I2>50%

	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	690/1961 (35.2%)	313/1526 (20.5%)	RR 1.53 (1.36 to 1.71)	109 more per 1000 (from 74 more to 146 more)	⊕⊕OO LOW	
								19.7%		104 more per 1000 (from 71 more to 140 more)		
Remission	on - Lithium	(follow-up	2-6 weeks; asse	essed with: ≤7/	<10 on HAMD)							
-	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	24/54 (44.4%)	12/56 (21.4%)	RR 2.07 (1.16 to 3.69)	229 more per 1000 (from 34 more to 576 more)	⊕000 VERY LOW	
								25%		267 more per 1000 (from 40 more to 673 more)		
Remissio	on - Thyroid	hormone (T3) (follow-up m	ean 2 weeks; a	assessed with	: <7 on HAMD)						
	trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	7/17 (41.2%)	2/16 (12.5%)	RR 3.29 (0.8 to 13.57)	286 more per 1000 (from 25 fewer to 1000 more)	⊕⊕⊕O MODERATE	
								12.5%		286 more per 1000 (from 25 fewer to 1000 more)		
Remission	on - Stimular	nt (methylp	henidate) (follo	w-up mean 4 w	eeks; assesse	ed with: ≤7 on HA	MD)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	4/30 (13.3%)	1/30 (3.3%)	RR 4 (0.47 to 33.73)	100 more per 1000 (from 18 fewer to 1000 more)	⊕000 VERY LOW	
								3.3%		99 more per 1000 (from 17 fewer to 1000 more)		
Respons	se - any AD/n	on-AD age	ent (follow-up 0.	3-12 weeks; as	sessed with: 2	250% improveme	nt on MADRS/HAMD)					

23	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	954/2169 (44%)	485/1702 (28.5%)	RR 1.38 (1.26 to 1.52)	108 more per 1000 (from 74 more to 148 more)	⊕⊕OO LOW	
								23.9%		91 more per 1000 (from 62 more to 124 more)		
Respons	se - Atypical a	antidepres	ssant (follow-up	mean 4 weeks	; assessed wit	th: ≥50% improve	ement on HAMD)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	7/11 (63.6%)	3/15 (20%)	RR 3.18 (1.05 to 9.62)	436 more per 1000 (from 10 more to 1000 more)	⊕OOO VERY LOW	
								20%		436 more per 1000 (from 10 more to 1000 more)		
Respons	se - TCA (intr	avenous)	(follow-up mean	5 days; asses	sed with: ≥50%	% improvement o	n HAMD)					
1	trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	11/18 (61.1%)	0/18 (0%)	RR 23 (1.46 to 363.07)	-	⊕⊕OO LOW	
Pasnans	eo - Antinevo	hotic (follo		e: accessed w	ith: >50% imp	rovement on MAI	DRS/HAMD)	0%		-		
					1til. 230 /6 illipi							
12	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	844/1882 (44.8%)	413/1447 (28.5%)	RR 1.4 (1.27 to 1.53)	114 more per 1000 (from 77 more to 151 more)	⊕⊕OO LOW	
								27.9%		112 more per 1000 (from 75 more to 148 more)		
Respons	se - Lithium (follow-up	0.3-6 weeks; ass	sessed with: ≥5	50% improvem	ent on HAMD)						
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	9/38 (23.7%)	6/38 (15.8%)	RR 1.55 (0.61 to 3.91)	87 more per 1000 (from 62 fewer to 459 more)	⊕OOO VERY LOW	

								15.1%		83 more per 1000 (from 59 fewer to 439 more)		
Respons	se - Anticonv	ulsant (lar	notrigine) (follo	w-up 8-10 weel	ks; assessed v	vith: ≥50% impro	vement on MADRS)					
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	21/65 (32.3%)	22/65 (33.8%)	RR 0.96 (0.59 to 1.56)	14 fewer per 1000 (from 139 fewer to 190 more)	⊕000 VERY LOW	
								34.3%		14 fewer per 1000 (from 141 fewer to 192 more)		
Respons	se - Omega-3	fatty acid	(follow-up mea	n 12 weeks; as	sessed with: ≥	50% improveme	nt on MADRS)					
1	randomised trials	serious ⁶	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	16/52 (30.8%)	4/17 (23.5%)	RR 1.31 (0.51 to 3.38)	73 more per 1000 (from 115 fewer to 560 more)	⊕OOO VERY LOW	
								23.5%		73 more per 1000 (from 115 fewer to 559 more)		
Respons	se - Stimulan	t (methylp	henidate) (follov	w-up 4-5 weeks	s; assessed wi	th: ≥50% improve	ement on MADRS/HAMD)					
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	46/103 (44.7%)	37/102 (36.3%)	RR 1.21 (0.87 to 1.68)	76 more per 1000 (from 47 fewer to 247 more)	⊕OOO VERY LOW	
								32.5%		68 more per 1000 (from 42 fewer to 221 more)		
Respons	se - Any AD/r	non-AD ag	ent (follow-up 4	-8 weeks; asse	essed with: Mu	ch/very much im	proved on CGI-I)					
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	46/127 (36.2%)	37/130 (28.5%)	RR 1.29 (0.85 to 1.97)	83 more per 1000 (from 43 fewer to 276 more)	⊕OOO VERY LOW	

								26.7%		77 more per 1000 (from 40 fewer to 259 more)		
Respons	se - Atypical	antidepres	ssant (follow-up	mean 4 weeks	; assessed wit	h: Much/very mu	ich improved on CGI-I)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	7/11 (63.6%)	3/15 (20%)	RR 3.18 (1.05 to 9.62)	436 more per 1000 (from 10 more to 1000 more)	⊕OOO VERY LOW	
								20%		436 more per 1000 (from 10 more to 1000 more)		
Respons	se - Lithium (follow-up	mean 6 weeks;	assessed with:	Much/very mu	ich improved on	CGI-I)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	5/18 (27.8%)	4/17 (23.5%)	RR 1.18 (0.38 to 3.67)	42 more per 1000 (from 146 fewer to 628 more)	⊕OOO VERY LOW	
								23.5%		42 more per 1000 (from 146 fewer to 627 more)		
Respons	se - Anticonv	ulsant (lar	notrigine) (follow	w-up mean 8 w	eeks; assesse	d with: much/ve	ry much improved on CGI-I)					
1	randomised trials	serious ⁶	no serious inconsistency	no serious indirectness	very serious ⁵	none	4/17 (23.5%)	6/17 (35.3%)	RR 0.67 (0.23 to 1.95)	116 fewer per 1000 (from 272 fewer to 335 more)	⊕OOO VERY LOW	
								35.3%		116 fewer per 1000 (from 272 fewer to 335 more)		
Respons	se - Anxiolyti	c (follow-ເ	ıp mean 6 week	s; assessed wi	th: Much/very	much improved	on CGI-I)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	17/51 (33.3%)	16/51 (31.4%)	RR 1.06 (0.61 to 1.86)	19 more per 1000 (from 122 fewer to 270 more)	⊕OOO VERY LOW	

								31.4%		19 more per 1000 (from 122 fewer to 270 more)	
espons	se - Stimulan	t (methylp	henidate) (follo	w-up mean 4 w	eeks; assesse	ed with: much/ver	y much improved on CGI-I)				
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	13/30 (43.3%)	8/30 (26.7%)	RR 1.62 (0.79 to 3.34)	165 more per 1000 (from 56 fewer to 624 more)	⊕000 VERY LOW
								26.7%		166 more per 1000 (from 56 fewer to 625 more)	
epress	ion sympton	natology -	Atypical antide	pressant (follow	v-up mean 4 w	veeks; measured	with: HAMD change score; B	etter indic	ated by lov	ver values)	
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	reporting bias ³	11	15	-	SMD 1.12 lower (1.96 to 0.27 lower)	⊕OOO VERY LOW
press	ion sympton	natology - A	Antipsychotic (follow-up 4-8 w	eeks; measur	ed with: MADRS/I	l HAMD change score; Better i	indicated b	y lower va	lues)	
	randomised trials	no serious risk of bias	serious ⁸	no serious indirectness	no serious imprecision	reporting bias ³	634	553	-	SMD 0.39 lower (0.6 to 0.18 lower)	⊕⊕OO LOW
press	ion sympton	natology -	Lithium (follow-	-up 2-3 weeks;	measured wit	h: MADRS/HAMD	change score; Better indicat	ed by lowe	er values)	<u>'</u>	!
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	41	42	-	SMD 0.23 lower (0.86 lower to 0.39 higher)	⊕⊕OO LOW
epress	ion sympton	natology -	Thyroid hormoi	ne (T3) (follow-	up mean 2 we	eks; measured wi	th: HAMD change score; Bet	ter indicat	ed by lowe	r values)	
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁷	none	17	16	-	SMD 0.78 lower (1.5 to 0.07 lower)	⊕⊕⊕O MODERATE
epress	ion sympton	l natology - <i>i</i>	 Anticonvulsant	(lamotrigine) (f	 follow-up 8-10	weeks; measure	 d with: MADRS change score	e; Better in	dicated by	lower values)	

2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	65	65	-	SMD 0.13 lower (0.54 lower to 0.27 higher)	⊕000 VERY LOW	
Depress	ion sympton	natology -	Omega-3 fatty a	cid (follow-up i	mean 12 week	s; measured with	: HAMD change score; Better	indicated	by lower	values)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	reporting bias ³	41	21	-	SMD 0.94 lower (1.5 to 0.39 lower)	⊕000 VERY LOW	
Depress	sion sympton	natology -	Stimulant (meth	ylphenidate) (f	ollow-up mear	า 5 weeks; measเ	red with: MADRS change sco	ore; Better	rindicated	by lower values)	
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	reporting bias ³	72	72	-	SMD 0.06 higher (0.27 lower to 0.38 higher)	⊕000 VERY LOW	
Discont	inuation for a	iny reason	- Atypical antid	epressant (foll	ow-up mean 4	weeks; assessed	d with: Number of people lost	to follow	-up (for any	reason includir	ng adverse ev	vents))
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	1/41 (2.4%)	2/45 (4.4%)	RR 0.68 (0.07 to 6.61)	14 fewer per 1000 (from 41 fewer to 249 more)	⊕OOO VERY LOW	
								6.7%		21 fewer per 1000 (from 62 fewer to 376 more)		
Discont	inuation for a	iny reason	- Antipsychotic	(follow-up 4-1	2 weeks; asse	ssed with: Numb	er of people lost to follow-up	(for any r	eason incl	uding adverse ev	vents))	
13	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	325/2033 (16%)	199/1579 (12.6%)	RR 1.26 (1.06 to 1.49)	33 more per 1000 (from 8 more to 62 more)	⊕⊕OO LOW	
								13.4%		35 more per 1000 (from 8 more to 66 more)		
Discont	inuation for a	iny reason	- Lithium (follow	w-up 2-6 weeks	s; assessed wi	th: Number of pe	ople lost to follow-up (for any	/ reason ii	ncluding a	dverse events))		
6	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	10/99 (10.1%)	12/101 (11.9%)		15 fewer per 1000 (from 70		

Discount			Thursid house	ana (T2) (fallay			with. Number of months located	5.6%	RR 0.87 (0.41 to 1.84)	fewer to 100 more) 7 fewer per 1000 (from 33 fewer to 47 more)	⊕OOO VERY LOW	W
2	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	0/27 (0%)		not pooled	not pooled	⊕⊕OO LOW	"
Disconti	nuation for a	ny reason	- Anticonvulsar	nt (lamotrigine)	(follow-up 8-1	0 weeks; assess	ed with: Number of people lo	st to follo	w-up (for a	ny reason includ	ling adverse eve	ents))
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	17/65 (26.2%)	21/65 (32.3%)	RR 0.81 (0.48 to 1.38)	61 fewer per 1000 (from 168 fewer to 123 more)	⊕OOO VERY LOW	
								29.5%		56 fewer per 1000 (from 153 fewer to 112 more)		
Disconti	nuation for a	ny reason	- Anxiolytic (fol	low-up mean 6	weeks; asses	sed with: Numbe	er of people lost to follow-up (for any re	ason inclu	ding adverse ev	ents))	
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	6/51 (11.8%)	10/51 (19.6%)	RR 0.6 (0.24 to 1.53)	78 fewer per 1000 (from 149 fewer to 104 more)	⊕OOO VERY LOW	
								19.6%		78 fewer per 1000 (from 149 fewer to 104 more)		
Disconti	nuation for a	ny reason	- Omega-3 fatty	acid (follow-u	p mean 12 wee	eks; assessed wi	th: Number of people lost to f	follow-up	(for any rea	son including a	dverse events))	
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	19/106 (17.9%)	10/45 (22.2%)	RR 0.83 (0.42 to 1.66)	38 fewer per 1000 (from 129 fewer to 147 more)	⊕OOO VERY LOW	

								22.2%		38 fewer per 1000 (from 129 fewer to 147 more)		
	nuation for a g adverse ev		(including adve	erse events) - S	Stimulant (met	hylphenidate) (fol	low-up mean 5 weeks; asse	ssed with:	Number of	people lost to fo	ollow-up (for a	iny reas
	randomised trials		no serious inconsistency	no serious indirectness	serious⁴	reporting bias ³	11/73 (15.1%)	4/72 (5.6%)	RR 2.71 (0.91 to 8.12)	95 more per 1000 (from 5 fewer to 396 more)	⊕000 VERY LOW	
								5.6%		96 more per 1000 (from 5 fewer to 399 more)		
isconti	nuation due	to adverse	events - Atypic	al antidepress	ant (follow-up	mean 4 weeks; a	ssessed with: Number of pe	ople lost t	o follow-up	due to adverse	events)	
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	0/30 (0%)	0/30 (0%)	not pooled	not pooled	⊕OOO VERY LOW	
								0%	-	not pooled		
sconti	nuation due	to adverse	e events - TCA (i	ntravenous) (f	ollow-up mear	n 5 days; assesse	d with: Number of people lo	st to follow	/-up due to	adverse events)		
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	0/18 (0%)	0/18 (0%)	not pooled	not pooled	⊕OOO VERY LOW	
								0%		not pooled		
sconti	nuation due	to adverse	events - Antips	sychotic (follow	v-up 4-12 wee	ks; assessed with	: Number of people lost to f	ollow-up d	ue to advers	se events)		
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	147/2033 (7.2%)	25/1579 (1.6%)	RR 3.16 (2.05 to 4.87)	34 more per 1000 (from 17 more to 61 more)	⊕⊕OO LOW	
								1.7%		37 more per 1000 (from 18 more to 66		

				 				0.00	55.46	4.4	Г
5	randomised	serious'	no serious	no serious	very serious ⁵	reporting bias ³	4/81	3/84	RR 1.3	11 more per	⊕000
	trials		inconsistency	indirectness			(4.9%)	(3.6%)	(0.33 to	1000 (from 24	VERY LOW
									5.14)	fewer to 148	
										more)	
								0%			
										-	
Disconti	inuation due	to adverse	e events - Thyro	id hormone (T3	3) (follow-up m	ean 2 weeks; ass	sessed with: Number of peopl	e lost to t	follow-up di	ue to adverse ev	ents)
2	randomised	serious1	no serious	no serious	serious ²	none	0/27	0/24	not pooled	not pooled	⊕⊕00
	trials		inconsistency	indirectness			(0%)	(0%)			LOW
								0%		not pooled	
Disconti	nuation due	to adverse	e events - Antico	onvulsant (lamo	otrigine) (follow	w-up 8-10 weeks:	assessed with: Number of pe	eople lost	to follow-u	p due to advers	e events)
								-			
2	randomised	serious1	no serious	no serious	very serious⁵	reporting bias ³	9/65	10/65	RR 1.12	18 more per	\oplus OOO
	trials		inconsistency	indirectness			(13.8%)	(15.4%)	(0.21 to	1000 (from 122	VERY LOW
									5.94)	fewer to 760	
										more)	
										12 more per	
								10.4%		1000 (from 82	
								10.4%		fewer to 514	
										more)	
Disconti	inuation due	to adverse	e events - Anxio	lytic (follow-up	mean 6 weeks	s; assessed with:	Number of people lost to foll	low-up du	e to advers	e events)	,
1	randomised	serious ¹	no serious	no serious	serious ²	reporting bias ³	0/51	0/51	not pooled	not pooled	⊕000
	trials		inconsistency	indirectness		3	(0%)	(0%)			VERY LOW
							(***)	(***)			
								0%		not pooled	
Disconti	nuation due	to adverse	e events - Omeg	a-3 fatty acid (f	ollow-up mear	n 12 weeks; asse	ssed with: Number of people		llow-up due	'	nts)
		1 . 1		1 .			0400	l =/	DD 0	40.6	
2	randomised	serious'	no serious	no serious	very serious ⁵	reporting bias ³	6/106	5/45	RR 0.57	48 fewer per	⊕000
	trials		inconsistency	indirectness			(5.7%)	(11.1%)	(0.18 to	1000 (from 91	VERY LOW
									1.73)	fewer to 81	
										more)	
				1		1				44 fewer per	
								10.2%		1000 (from 84	
								10.270		fewer to 74	
										more)	
Disconti	nuation due	to adverse	e events - Stimu	lant (methylph	enidate) (follov	v-up 4-5 weeks: a	assessed with: Number of peo	pple lost t	o follow-un	due to adverse	events)
				(, (101101		The state of the s				

2	randomised	serious ¹	serious ⁸	no serious	very serious ⁵	reporting bias3	8/103	2/102	RR 2.92	38 more per	⊕OOO	
	trials			indirectness			(7.8%)	(2%)	(0.21 to 40.65)	1000 (from 15 fewer to 777 more)	VERY LOW	
										•		
								3.3%		63 more per 1000 (from 26 fewer to 1000 more)		

¹ Risk of bias is unclear or high across multiple domains

8

9

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

			Quality as	sessment			No of patien	ts	E	Effect	Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with another antidepressant/non-antidepressant agent	Continuing with the antidepressant- only	Relative (95% CI)	Absolute	Quanty	importance		
Remissi	emission - TeCA (mianserin) + SSRI versus SSRI-only (follow-up 5-6 weeks; assessed with: HAMD≤7/8)													
	randomised trials	serious ¹	serious ²	no serious indirectness	serious ³	reporting bias ⁴	57/130 (43.8%)	44/136 (32.4%)	RR 1.52 (0.77 to 3.01)	168 more per 1000 (from 74 fewer to 650 more)				
								28.1%		146 more per 1000 (from 65 fewer to 565 more)				

² OIS not met (events<300)

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ 95% CI crosses one clinical decision threshold

⁵ 95% CI crosses two clinical decision thresholds

⁶ Unclear blinding of outcome assessment

⁷ OIS not met (N<400)

⁸ I2>50%

randomise trials	ed serious ¹	serious ²	no serious indirectness	very serious ⁵	reporting bias ⁴	71/283 (25.1%)	56/268 (20.9%)	RR 1.12 (0.46 to 2.75)	25 more per 1000 (from 113 fewer to 366 more)	⊕OOO VERY LOW	
							16.8%		20 more per 1000 (from 91 fewer to 294 more)		
emission - Antic	onvulsant	+ SSRI versus S	SRI-only (folio	ow-up mean 8	weeks; assesse	d with: HAMD≤7)					
randomise trials	ed serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias⁴	19/39 (48.7%)	21/45 (46.7%)	RR 1.04 (0.67 to 1.63)	19 more per 1000 (from 154 fewer to 294 more)	⊕OOO VERY LOW	
							46.7%		19 more per 1000 (from 154 fewer to 294 more)		
emission - Anxio	lytic + SSI	RI versus SSRI-	only (follow-up	mean 8 week	s; assessed with	n: HAMD≤7)					
randomise trials	ed serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	15/46 (32.6%)	21/45 (46.7%)	RR 0.7 (0.42 to 1.18)	140 fewer per 1000 (from 271 fewer to 84 more)	⊕OOO VERY LOW	
							46.7%		140 fewer per 1000 (from 271 fewer to 84 more)		
emission - SARI	+ SSRI vei	sus SSRI-only (follow-up mea	ın 8 weeks; as	sessed with: HA	MD≤7)					
randomise trials	ed serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ⁴	20/47 (42.6%)	21/45 (46.7%)	RR 0.91 (0.58 to 1.44)	42 fewer per 1000 (from 196 fewer to 205 more)	⊕OOO VERY LOW	
							46.7%		42 fewer per 1000 (from 196 fewer to 205 more)		
emission - Thyro	id hormon	e + SSRI versus	SSRI-only (fo	ollow-up mean	8 weeks; assess	sed with: HAMD≤7)					

	andomised rials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	18/48 (37.5%)	12/45 (26.7%)	RR 1.41 (0.77 to 2.58)	109 more per 1000 (from 61 fewer to 421 more)	⊕OOO VERY LOW	
								26.7%		109 more per 1000 (from 61 fewer to 422 more)		
Response	e - TeCA (m	ianserin) + SSRI versus	SSRI-only (fol	low-up 5-6 we	eks; assessed v	vith: ≥50% improvement on H	AMD)	_			
	andomised rials	serious ¹	serious ²	no serious indirectness	very serious ⁵	reporting bias ⁴	86/130 (66.2%)	83/136 (61%)	RR 1.22 (0.69 to 2.15)	134 more per 1000 (from 189 fewer to 702 more)	⊕OOO VERY LOW	
								53.6%		118 more per 1000 (from 166 fewer to 616 more)		
Response	e - Lithium +	+ SSRI v	ersus SSRI-only	/ (follow-up m	ean 1 weeks;	assessed with: ≥	50% improvement on HAMD)					
	andomised rials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ⁴	6/10 (60%)	2/14 (14.3%)	RR 4.2 (1.06 to 16.68)	457 more per 1000 (from 9 more to 1000 more)	⊕OOO VERY LOW	
								14.3%		458 more per 1000 (from 9 more to 1000 more)		
esponse	e - Antipsyc	hotic + \$	SSRI versus SS	RI-only (follow	-up mean 8 w	eeks; assessed	with: ≥50% improvement on N	MADRS/HAMD)				
	andomised rials	serious ¹	serious ²	no serious indirectness	very serious ⁵	reporting bias ⁴	111/283 (39.2%)	92/268 (34.3%)	RR 1.12 (0.61 to 2.07)	41 more per 1000 (from 134 fewer to 367 more)	⊕OOO VERY LOW	
								29.6%		36 more per 1000 (from 115 fewer to 317 more)		
Response	e - Anticonv	ulsant +	SSRI versus S	SRI-only (follo	w-up mean 8	weeks; assessed	l with: ≥50% improvement on	HAMD)				

randor trials	mised serious	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ⁴	24/39 (61.5%)	30/45 (66.7%)	RR 0.92 (0.67 to 1.27)	53 fewer per 1000 (from 220 fewer to 180 more)	⊕OOO VERY LOW	
							66.7%		53 fewer per 1000 (from 220 fewer to 180 more)		
esponse - An	nxiolytic + SS	RI versus SSRI-c	only (follow-up	mean 8 week	s; assessed with	: ≥50% improvement on HAM	D)	•		•	
randor trials	mised serious	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	26/46 (56.5%)	30/45 (66.7%)	RR 0.85 (0.61 to 1.18)	100 fewer per 1000 (from 260 fewer to 120 more)	⊕OOO VERY LOW	
							66.7%		100 fewer per 1000 (from 260 fewer to 120 more)		
esponse - SA	ARI + SSRI ve	rsus SSRI-only (follow-up meai	n 8 weeks; as:	sessed with: ≥50	% improvement on HAMD)					
randor trials	mised serious	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ⁴	29/47 (61.7%)	30/45 (66.7%)	RR 0.93 (0.68 to 1.26)	47 fewer per 1000 (from 213 fewer to 173 more)	⊕OOO VERY LOW	
							66.7%		47 fewer per 1000 (from 213 fewer to 173 more)		
sponse - Th	yroid hormo	ne + SSRI versus	SSRI-only (fol	llow-up mean	8 weeks; assess	ed with: ≥50% improvement o	on HAMD)				
randor trials	mised serious	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	28/48 (58.3%)	21/45 (46.7%)	RR 1.25 (0.84 to 1.85)	117 more per 1000 (from 75 fewer to 397 more)	⊕OOO VERY LOW	
							46.7%		117 more per 1000 (from 75 fewer to 397 more)		
esponse - Te	CA (mianseri	n) + SSRI versus	SSRI-only (fo	llow-up 5-6 we	eeks; assessed v	vith: Much/very much improve	ed on CGI-I)				

2	randomised trials	serious ¹	very serious ⁷	no serious indirectness	very serious ⁵	reporting bias⁴	99/130 (76.2%)	101/136 (74.3%)	RR 1.17 (0.65 to 2.12)	126 more per 1000 (from 260 fewer to 832 more)	⊕OOO VERY LOW
								65.2%		111 more per 1000 (from 228 fewer to 730 more)	
Depress	ion symptor	natology	- Any AD/non-	AD agent (folio	w-up 6-52 we	eks; measured w	vith: MADRS/HAMD/QIDS char	nge score; Better in	dicated by	lower values)	
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁴	297	283	-	SMD 0.35 lower (0.52 to 0.19 lower)	⊕⊕OO LOW
Depress	ion symptor	natology	- TeCA (mians	erin) + SSRI ve	rsus SSRI-on	ly (follow-up mea	an 6 weeks; measured with: H	AMD change score	Better ind	icated by lowe	er values)
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁸	reporting bias ⁴	32	38	-	SMD 0.66 lower (1.14 to 0.17 lower)	⊕OOO VERY LOW
Depress	ion symptor	natology	- Antipsychoti	+ SSRI versu	s SSRI-only (f	ollow-up mean 8	weeks; measured with: MAD	RS change score; E	etter indic	ated by lower	values)
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁴	238	223	-	SMD 0.33 lower (0.52 to 0.15 lower)	⊕⊕OO LOW
Depress	ion symptor	natology	- Lithium + any	AD versus ar	y AD (follow-	up mean 52 week	s; measured with: QIDS chan	ge score; Better ind	dicated by	lower values)	
1	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	27	22	-	SMD 0.12 lower (0.69 lower to 0.44 higher)	©OOO VERY LOW
Disconti	inuation for	any reas	on - Any AD/no	n-AD agent (fo	llow-up 5-52 v	veeks; assessed	with: Number of people lost t	o follow-up (for any	reason inc	cluding advers	e events))
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias⁴	98/400 (24.5%)	67/390 (17.2%)	RR 1.37 (1 to 1.88)	64 more per 1000 (from 0 more to 151 more)	⊕OOO VERY LOW
								18.5%		68 more per 1000 (from 0	

										more to 163		
										more)		
	inuation for a events))	any reaso	on - TeCA (miai	nserin) + SSRI	versus SSRI-	only (follow-up 5	-6 weeks; assessed with: Nur	nber of people los	t to follow-u	o (for any reaso	on includi	ng
	randomised trials		no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	23/130 (17.7%)	17/137 (12.4%)	RR 1.43 (0.79 to 2.56)	53 more per 1000 (from 26 fewer to 194 more)	⊕OOO VERY LOW	
	ontinuation for any reas							14.3%		61 more per 1000 (from 30 fewer to 223 more)		
				dverse events)	- Antipsycho	tic + SSRI versus	s SSRI-only (follow-up mean 8	weeks; assessed	with: Numb	er of people lo	st to follo	w-up
	randomised serior trials		no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ⁴	73/241 (30.3%)	45/226 (19.9%)	RR 1.44 (1.03 to 2)	88 more per 1000 (from 6 more to 199 more)	⊕OOO VERY LOW	
								22.2%		98 more per 1000 (from 7 more to 222 more)		
iscont /ents))		any reaso	on - Lithium + a	ny AD versus	any AD (follov	w-up mean 52 we	eeks; assessed with: Number	of people lost to f	ollow-up (fo	any reason ind	cluding ad	dvers
	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	none	2/29 (6.9%)	5/27 (18.5%)	RR 0.37 (0.08 to 1.76)	117 fewer per 1000 (from 170 fewer to 141 more)	⊕OOO VERY LOW	
								18.5%		117 fewer per 1000 (from 170 fewer to 141 more)		
iscont	inuation due	to adver	se events - Any	/ AD/non-AD a	gent (follow-u	p 6-8 weeks; ass	sessed with: Number of peopl	e lost to follow-up	due to adve	rse events)		
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ⁴	45/273 (16.5%)	5/264 (1.9%)		98 more per 1000 (from 31		

Disconti events)	nuation due	to adver	rse events - TeC	A (mianserin)	+ SSRI versus	s SSRI-only (folio	ow-up mean 6 weeks; assesse	0% ed with: Number of	RR 6.19 (2.65 to 14.47)	more to 255 more) - to follow-up d	⊕OOO VERY LOW	verse
	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias⁴	2/32 (6.3%)	0/38 (0%)	RR 5.91 (0.29 to 118.78)	-	⊕OOO VERY LOW	
Disconti	nuation due	to adve	rse events - Anti	psychotic + S	SRI versus SS	RI-only (follow-	up mean 8 weeks; assessed w	vith: Number of peo	ple lost to	follow-up due	to advers	se events)
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ⁴	43/241 (17.8%)	5/226 (2.2%)	RR 6.22 (2.57 to 15.07)	115 more per 1000 (from 35 more to 311 more)		
								1.2%		63 more per 1000 (from 19 more to 169 more)		

¹ Risk of bias is unclear or high across multiple domains

8 9

² I2>50%

³ 95% CI crosses one clinical decision threshold

⁴ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes ⁵ 95% CI crosses two clinical decision thresholds

⁶ OIS not met (events<300)

⁷ I2>80%

⁸ OIS not met (N<400)

⁹ Open-label trial

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

			Quality as	sessment			No of pat	ients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with lithium	'Other' augmentation agents	Relative (95% CI)	Absolute		
Remission	on - Lithium v	ersus an	y other agent (fo	ollow-up 2-14 w	eeks; assesse	d with: <8/10 on l	MADRS/HAMD)					
8	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	97/392 (24.7%)	126/412 (30.6%)		61 fewer per 1000 (from 110 fewer to 0 more)	⊕OOO VERY LOW	
					ssessed with: ≤7 o			27.2%		54 fewer per 1000 (from 98 fewer to 0 more)		
Remission	on - Lithium v	ersus TC	CA (follow-up me	an 4 weeks; as	sessed with: ≤	7 on HAMD)						
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious⁴	reporting bias ³	12/48 (25%)	13/46 (28.3%)	RR 0.88 (0.45 to 1.74)	34 fewer per 1000 (from 155 fewer to 209 more)	⊕OOO VERY LOW	
								27.2%	=	33 fewer per 1000 (from 150 fewer to 201 more)		
Remission	on - Lithium v	ersus an	tipsychotic (foll	ow-up 4-8 week	s; assessed w	vith: <8/10 on MAI	DRS/≤7 on HAMD)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	65/241 (27%)	84/259 (32.4%)	RR 0.75 (0.44 to 1.26)	81 fewer per 1000 (from 182 fewer to 84 more)	⊕OOO VERY LOW	
								31.9%		80 fewer per 1000 (from 179 fewer to 83 more)		
Remission	on - Lithium v	ersus th	yroid hormone (T3) (follow-up 2	2-14 weeks; as	sessed with: ≤7 o	n HAMD)					
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	17/86 (19.8%)	25/90 (27.8%)	RR 0.72 (0.42 to 1.22)	78 fewer per 1000 (from 161 fewer to 61 more)		

								32.9%		92 fewer per 1000 (from 191 fewer to 72 more)	⊕OOO VERY LOW
emissi	on - Lithium	versus ar	nticonvulsant (la	amotrigine) (fol	low-up mean 8	weeks; assessed	with: ≤7 on HAMD)				<u>, </u>
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	3/17 (17.6%)	4/17 (23.5%)	RR 0.75 (0.2 to 2.86)	59 fewer per 1000 (from 188 fewer to 438 more)	⊕OOO VERY LOW
								23.5%		59 fewer per 1000 (from 188 fewer to 437 more)	
Respons	se - Lithium v	ersus an	y other agent (f	ollow-up 4-14 w	eeks; assesse	d with: ≥50% impr	ovement on HAMD/N	MADRS/QIDS)			
5	randomised se trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	139/327 (42.5%)	161/349 (46.1%)	RR 0.92 (0.78 to 1.08)	37 fewer per 1000 (from 101 fewer to 37 more)	
								52.4%		42 fewer per 1000 (from 115 fewer to 42 more)	
Respons	se - Lithium v	ersus an	tipsychotic (foll	low-up 4-8 weel	ks; assessed w	ith: ≥50% improve	ment on HAMD/MAD	DRS)			
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	121/241 (50.2%)	135/259 (52.1%)	RR 0.95 (0.8 to 1.12)	26 fewer per 1000 (from 104 fewer to 63 more)	
								52.4%		26 fewer per 1000 (from 105 fewer to 63 more)	
Respons	se - Lithium v	ersus th	yroid hormone ((T3) (follow-up	mean 14 weeks	; assessed with: ≥	50% improvement o	n QIDS)			
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	11/69 (15.9%)	17/73 (23.3%)	RR 0.68 (0.35 to 1.36)	75 fewer per 1000 (from 151 fewer to 84 more)	
								23.3%		75 fewer per 1000 (from 151 fewer to 84 more)	

ranc trials	domised s	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	7/17 (41.2%)	9/17 (52.9%)	RR 0.78 (0.38 to 1.6)	116 fewer per 1000 (from 328 fewer to 318	⊕OOO VERY LOW	
									-	more) 116 fewer per		
								52.9%		1000 (from 328 fewer to 317 more)		
lesponse - L	Lithium ve	ersus an	tipsychotic (follo	w-up mean 6 w	veeks; assesse	ed with: Much/ver	y much improved on C	CGI-I)	ļ	/		
ranc trials		serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	133/221 (60.2%)	153/229 (66.8%)	RR 0.9 (0.78 to 1.04)	67 fewer per 1000 (from 147 fewer to 27 more)	⊕OOO VERY LOW	
								66.8%		67 fewer per 1000 (from 147 fewer to 27 more)		
epression s	symptoma	atology -	Lithium versus	any other agen	t (follow-up 2-	14 weeks; measu	red with: HAMD/QIDS	change score; Be	tter indicate	ed by lower values)	
ranc trials	domised s	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ³	151	153	-	SMD 0.14 higher (0.14 lower to 0.42 higher)	⊕OOO VERY LOW	
epression s	symptoma	atology -	Lithium versus	TCA (follow-up	mean 4 weeks	s; measured with:	HAMD change score;	Better indicated	by lower va	lues)	L	
ranc trials		serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ³	48	46	-	SMD 0.09 lower (0.49 lower to 0.32 higher)	⊕OOO VERY LOW	
epression s	symptoma	atology -	Lithium versus	thyroid hormor	ne (T3) (follow-	up 2-14 weeks; m	easured with: HAMD/0	QIDS change sco	re; Better in	dicated by lower v	alues)	
ranc trials		serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ³	86	90	-	SMD 0.15 higher (0.14 lower to 0.45 higher)	⊕OOO VERY LOW	
epression s	symptoma	atology -	Lithium versus	anticonvulsant	(lamotrigine)	(follow-up mean 8	weeks; measured wit	h: HAMD change	score; Bett	er indicated by low	ver values)	
ranc trials		serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	17	17	-	SMD 0.81 higher (0.11 to 1.51 higher)	⊕⊕OO LOW	
scontinuat	tion for an	ıy reasor	n - Lithium versu	s any other ag	ent (follow-up	 2-14 weeks; asse	ssed with: Number of	people lost to foll	ow-up (for a	 any reason includi	ng adverse	even

8	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	61/341 (17.9%)	46/351 (13.1%)	RR 1.3 (0.92 to 1.85)	39 more per 1000 (from 10 fewer to 111 more)	⊕OOO VERY LOW	
								8.4%		25 more per 1000 (from 7 fewer to 71 more)		
Disconti	nuation for a	ny reaso	n - Lithium versı	is TCA (follow-	up mean 4 wee	eks; assessed wit	h: Number of people lo	ost to follow-up (for any reaso	on including adver	se event	s))
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	7/48 (14.6%)	8/46 (17.4%)	RR 0.83 (0.33 to 2.11)	30 fewer per 1000 (from 117 fewer to 193 more)	⊕OOO VERY LOW	
								19.9%		34 fewer per 1000 (from 133 fewer to 221 more)		
Disconti	nuation for a	ny reaso	n - Lithium versu	is antipsychoti	c (follow-up 4-	8 weeks; assesse	d with: Number of peo	ple lost to follow	-up (for any	reason including a	adverse e	events))
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	51/249 (20.5%)	36/261 (13.8%)	RR 1.41 (0.95 to 2.08)	57 more per 1000 (from 7 fewer to 149 more)	⊕OOO VERY LOW	
								5%		20 more per 1000 (from 3 fewer to 54 more)		
Disconti events))	nuation for a	ny reaso	n - Lithium versu	is thyroid horm	none (T3) (follo	w-up mean 2 wee	ks; assessed with: Nu	mber of people lo	ost to follow	up (for any reaso	n includii	ng adverse
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/27 (3.7%)	0/27 (0%)	RR 2.84 (0.12 to 65.34)	-	⊕OOO VERY LOW	
D!			1 141-1	4'1-		\ (f = 11	. 0	0%				! !!!
adverse		ny reaso	n - Litnium versi	is anticonvuisa	int (iamotrigin	e) (follow-up mea	n 8 weeks; assessed w	itn: Number of p	eopie iost to	tollow-up (for any	reason	including
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	2/17 (11.8%)	2/17 (11.8%)	RR 1 (0.16 to 6.3)	0 fewer per 1000 (from 99 fewer to 624 more)	⊕000 VERY LOW	
								11.8%		0 fewer per 1000 (from 99 fewer to 625 more)		

	randomised	serious ¹	no serious	no serious	very serious4	reporting bias3	38/376	33/390	RR 1.27	23 more per 1000	⊕000
	trials	Serious	inconsistency	indirectness	very serious	reporting bias	(10.1%)	(8.5%)	(0.69 to	(from 26 fewer to	VERY
	triais		linconsistency	in idir coti icos			(10.170)	(0.570)	2.36)	115 more)	LOW
									2.50)	110111010)	LOW
									-	7 more per 1000	
								2.5%		(from 8 fewer to	
								2.070		34 more)	
iscont	inuation due	to advers	e events - Lithiu	ım versus TCA	(follow-up mea	n 4 weeks: assess	ed with: Number of	people lost to fol	llow-up due te	,	
					(,		poop.o	пр ппо г		
	randomised	serious1	no serious	no serious	very serious4	reporting bias3	1/14	2/12	RR 0.43	95 fewer per 1000	⊕OOO
	trials		inconsistency	indirectness			(7.1%)	(16.7%)	(0.04 to	(from 160 fewer to	
							,	, ,	`4.16)	` 527 more)	LOW
										95 fewer per 1000	
								16.7%		(from 160 fewer to	
										528 more)	
iscont			1		,		sessed with: Numb				
		serious1	no serious	no serious	very serious⁴	reporting bias ³	20/249	24/261	RR 0.86		
	trials		inconsistency	indirectness			(8%)	(9.2%)	(0.49 to	(from 47 fewer to	VERY
									1.52)	48 more)	LOW
						-				7 fewer per 1000	
								5%		(from 25 fewer to	
								070		26 more)	
										,	
scont	inuation due	to advers	o ovente - Lithiu	im vareue thur	aid harmana (T	3) /follow-up 2-1/1 v	nooke: seepeead wit	th: Number of no	ania last ta ta		
iscont	inuation due	to advers	e events - Lithiu	ım versus thyro		3) (follow-up 2-14 v		·		mow-up due to adv	erse events
iscont	randomised		no serious	no serious	serious ²	3) (follow-up 2-14 w	17/96	7/100	RR 2.44	101 more per	⊕000
			1					·			⊕000
	randomised		no serious	no serious			17/96	7/100	RR 2.44	101 more per	⊕000
	randomised		no serious	no serious			17/96	7/100 (7%)	RR 2.44 (1.1 to	101 more per 1000 (from 7 more	⊕OOO VERY
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	17/96 (17.7%)	7/100 (7%)	RR 2.44 (1.1 to 5.43)	101 more per 1000 (from 7 more to 310 more)	⊕OOO VERY LOW
iscont	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	17/96	7/100 (7%)	RR 2.44 (1.1 to 5.43)	101 more per 1000 (from 7 more to 310 more)	⊕OOO VERY LOW
iscont	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	17/96 (17.7%)	7/100 (7%)	RR 2.44 (1.1 to 5.43)	101 more per 1000 (from 7 more to 310 more)	⊕OOO VERY LOW
iscont	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	17/96 (17.7%)	7/100 (7%)	RR 2.44 (1.1 to 5.43)	101 more per 1000 (from 7 more to 310 more)	⊕OOO VERY LOW
iscont	randomised trials	serious ¹	no serious inconsistency e events - Lithiu	no serious indirectness um versus antid	serious²	reporting bias ³	17/96 (17.7%) o mean 8 weeks; as	7/100 (7%) 0% sessed with: Nun	RR 2.44 (1.1 to 5.43)	101 more per 1000 (from 7 more to 310 more) - e lost to follow-up	⊕OOO VERY LOW
	randomised trials	serious ¹	no serious inconsistency e events - Lithiu	no serious indirectness	serious²	reporting bias ³	17/96 (17.7%) o mean 8 weeks; as	7/100 (7%) 0% sessed with: Nun	RR 2.44 (1.1 to 5.43)	101 more per 1000 (from 7 more to 310 more) - e lost to follow-up	⊕OOO VERY LOW due to adve

Risk of bias is unclear or high across multiple domains

OIS not met (events<300)

Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

- 1 4 95% CI crosses two clinical decision thresholds
- 2 ⁵ 95% CI crosses one clinical decision threshold
- 3 6 OIS not met (N<400)

4

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

			Quality ass	essment			No of patie	ents		Effect	Quality	Importan
o of udies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with an antipsychotic	'Other' augmentation agents	Relative (95% CI)	Absolute		
nissic	on - Antipsyc	hotic ver	sus anticonvulsa	ant (follow-up r	nean 8 week	s; assessed with	: ≤7 on HAMD)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	12/45 (26.7%)	19/39 (48.7%)	RR 0.55 (0.31 to 0.98)	219 fewer per 1000 (from 10 fewer to 336 fewer)	⊕OOO VERY LOW	
		tipsychotic versus anxiolytic (follow-up mean 8 weeks; a				48.7%		219 fewer per 1000 (from 10 fewer to 336 fewer)				
nissio	on - Antipsyc	hotic ver	sus anxiolytic (fo	ollow-up mean	8 weeks; ass	sessed with: ≤7 o	n HAMD)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	12/45 (26.7%)	15/46 (32.6%)		59 fewer per 1000 (from 186 fewer to 179 more)	⊕OOO VERY LOW	
								32.6%		59 fewer per 1000 (from 186 fewer to 179 more)		
nissio	on - Antipsyc	hotic ver	sus thyroid horn	none (follow-up	mean 8 wee	ks; assessed wit	h: ≤7 on HAMD)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	12/45 (26.7%)	18/48 (37.5%)	RR 0.71 (0.39 to 1.3)	109 fewer per 1000 (from 229 fewer to 112 more)	⊕OOO VERY LOW	
								37.5%		109 fewer per 1000 (from 229 fewer to 112 more)		

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	12/45 (26.7%)	20/47 (42.6%)	RR 0.63 (0.35 to 1.13)	157 fewer per 1000 (from 277 fewer to 55 more)	⊕OOO VERY LOW
								42.6%		158 fewer per 1000 (from 277 fewer to 55 more)	
Respons	se - Antipsych	notic vers	sus anticonvuls	ant (follow-up i	mean 8 weel	ks; assessed with:	≥50% improvement on	HAMD)			
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	21/45 (46.7%)	24/39 (61.5%)	RR 0.76 (0.51 to 1.13)	148 fewer per 1000 (from 302 fewer to 80 more)	⊕OOO VERY LOW
								61.5%		148 fewer per 1000 (from 301 fewer to 80 more)	
Respons	se - Antipsych	notic vers	sus anxiolytic (f	ollow-up mean	8 weeks; as	ssessed with: ≥50%	improvement on HAM	ID)			
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	21/45 (46.7%)	26/46 (56.5%)	RR 0.83 (0.55 to 1.23)	96 fewer per 1000 (from 254 fewer to 130 more)	
								56.5%		96 fewer per 1000 (from 254 fewer to 130 more)	
Respons	se - Antipsych	notic vers	sus thyroid horn	none (follow-u	mean 8 we	eks; assessed wit	h: ≥50% improvement o	on HAMD)			
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	21/45 (46.7%)	28/48 (58.3%)	RR 0.8 (0.54 to 1.19)	117 fewer per 1000 (from 268 fewer to 111 more)	⊕OOO VERY LOW
								58.3%		117 fewer per 1000 (from 268 fewer to 111 more)	
Respons	se - Antipsych	notic vers	sus SARI (follow	v-up mean 8 we	eks; assess	sed with: ≥50% imp	provement on HAMD)	-	·		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	21/45 (46.7%)	29/47 (61.7%)	RR 0.76 (0.51 to 1.11)	148 fewer per 1000 (from 302 fewer to 68 more)	

					61.7%	148 fewer per 1000 (from 302 fewer to 68 more)	#000 VERY LOW	
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¹ Risk of bias is unclear or high across multiple domains

6

7

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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with an anticonvulsant	'Other' augmentation agents	Relative (95% CI)	Absolute		
Remission	on - Anticonv	ulsant ve	ersus anxiolytic (follow-up mea	n 8 weeks; as	ssessed with: ≤7	on HAMD)					
	randomised trials	serious ¹		no serious indirectness	serious ²	reporting bias ³	19/39 (48.7%)	15/46 (32.6%)	RR 1.49 (0.88 to 2.53)	160 more per 1000 (from 39 fewer to 499 more)	⊕OOO VERY LOW	
								32.6%		160 more per 1000 (from 39 fewer to 499 more)		
Remission	on - Anticonv	ulsant ve	ersus SARI (follo	w-up mean 8 w	eeks; assess	sed with: ≤7 on H	AMD)					
	randomised trials	serious ¹		no serious indirectness	very serious⁴	reporting bias ³	19/39 (48.7%)	20/47 (42.6%)	RR 1.14 (0.72 to 1.82)	60 more per 1000 (from 119 fewer to 349 more)	⊕000 VERY LOW	
								42.6%		60 more per 1000 (from 119 fewer to 349 more)		
Remission	on - Anticonv	ulsant ve	ersus thyroid ho	rmone (follow-u	ıp mean 8 we	eks; assessed w	rith: ≤7 on HAMD)					

² OIS not met (events<300)

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ 95% CI crosses two clinical decision thresholds

⁵ 95% CI crosses one clinical decision threshold

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	19/39 (48.7%)	18/48 (37.5%)	RR 1.3 (0.8 to 2.11)	112 more per 1000 (from 75 fewer to 416 more)	⊕OOO VERY LOW	
								37.5%		112 more per 1000 (from 75 fewer to 416 more)		
Respons	se - Anticonv	ulsant ve	rsus anxiolytic (follow-up mear	n 8 weeks; a	ssessed with: ≥50	% improvement on HAMI	D)				
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	24/39 (61.5%)	26/46 (56.5%)	RR 1.09 (0.76 to 1.55)	51 more per 1000 (from 136 fewer to 311 more)	⊕000 VERY LOW	
								56.5%		51 more per 1000 (from 136 fewer to 311 more)		
Respons	se - Anticonv	ulsant ve	rsus SARI (follo	w-up mean 8 w	eeks; asses	sed with: ≥50% im	provement on HAMD)					
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	24/39 (61.5%)	29/47 (61.7%)	RR 1 (0.71 to 1.39)	0 fewer per 1000 (from 179 fewer to 241 more)	⊕OOO VERY LOW	
								61.7%		0 fewer per 1000 (from 179 fewer to 241 more)		
Respons	se - Anticonv	ulsant ve	rsus thyroid ho	mone (follow-u	ip mean 8 w	eeks; assessed w	ith: ≥50% improvement o	n HAMD)				
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	24/39 (61.5%)	28/48 (58.3%)	RR 1.05 (0.75 to 1.49)	29 more per 1000 (from 146 fewer to 286 more)	⊕000 VERY LOW	
								58.3%		29 more per 1000 (from 146 fewer to 286 more)		

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses one clinical decision threshold

2

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes ⁴ 95% CI crosses two clinical decision thresholds

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

			Quality as	sessment		No of patients		Effect		Quality	Importan	
lo of udies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with an anxiolytic	'Other' augmentation agents	Relative (95% CI)	Absolute	Quanty	importan
missio	on - Anxiolyti	c versus	atypical antidep	ressant (follow	v-up mean 6 we	eeks; assessed w	ith: ≤7 on HAMD)					
	randomised trials	serious ¹		no serious indirectness	serious ²	reporting bias ³	86/286 (30.1%)	83/279 (29.7%)	RR 1.01 (0.79 to 1.3)	3 more per 1000 (from 62 fewer to 89 more)	⊕OOO VERY LOW	
								29.8%		3 more per 1000 (from 63 fewer to 89 more)		
missio	on - Anxiolyti	c versus	SARI (follow-up	mean 8 weeks	; assessed wit	h: ≤7 on HAMD)						
	randomised trials	serious ¹		no serious indirectness	very serious ⁴	reporting bias ³	15/46 (32.6%)	20/47 (42.6%)	RR 0.77 (0.45 to 1.3)	98 fewer per 1000 (from 234 fewer to 128 more)	⊕OOO VERY LOW	
								42.6%		98 fewer per 1000 (from 234 fewer to 128 more)		
missio	on - Anxiolyti	c versus	thyroid hormon	e (follow-up me	ean 8 weeks; a	ssessed with: ≤7	on HAMD)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	15/46 (32.6%)	18/48 (37.5%)	RR 0.87 (0.5 to 1.51)	49 fewer per 1000 (from 188 fewer to 191 more)	⊕OOO VERY LOW	
								37.5%		49 fewer per 1000 (from 188 fewer to 191 more)		

1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	77/286 (26.9%)	88/279 (31.5%)	RR 0.85 (0.66 to 1.1)	47 fewer per 1000 (from 107 fewer to 32 more)	⊕OOO VERY LOW
								31.5%		47 fewer per 1000 (from 107 fewer to 32 more)	
Respons	se - Anxiolytic	versus	SARI (follow-up	mean 8 weeks	; assessed with	h: ≥50% improven	nent on HAMD)			·	
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	26/46 (56.5%)	29/47 (61.7%)	RR 0.92 (0.65 to 1.29)	49 fewer per 1000 (from 216 fewer to 179 more)	⊕OOO VERY LOW
								61.7%		49 fewer per 1000 (from 216 fewer to 179 more)	
Respons	se - Anxiolytic	versus	thyroid hormon	e (follow-up me	ean 8 weeks; as	ssessed with: ≥50	% improvement on HA	AMD)		<u>'</u>	
I	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	26/46 (56.5%)	28/48 (58.3%)	RR 0.97 (0.68 to 1.37)	17 fewer per 1000 (from 187 fewer to 216 more)	⊕OOO VERY LOW
								58.3%	_	17 fewer per 1000 (from 187 fewer to 216 more)	
Depress	ion symptom	atology -	Anxiolytic vers	us atypical ant	tidepressant (fo	ollow-up mean 6 w	reeks; measured with:	QIDS change sco	ore; Better in	dicated by lower	values)
I	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	286	279	-	MD 8.2 higher (0.47 to 15.93 higher)	⊕⊕OO LOW
Disconti events)	l nuation due t	o advers	l se events - Anxi	l olytic versus at	ypical antidepr	l ressant (follow-up	mean 6 weeks; asses	ssed with: Number	r of people lo	l ost to follow-up du	ue to adverse
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	59/286 (20.6%)	35/279 (12.5%)	RR 1.64 (1.12 to 2.41)	80 more per 1000 (from 15 more to 177 more)	

¹ Risk of bias is unclear or high across multiple domains

6

7

10

Augmenting the antidepressant with a thyroid hormone compared to 'other' augmentation agents (head-to-head comparisons)

			Quality ass	essment			No of patie	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with a thyroid hormone	'Other' augmentation agents	Relative (95% CI)	Absolute		
Remissio	on - Thyroid I	hormone	versus SARI (fol	low-up mean 8	weeks; asse	essed with: ≤7 on	HAMD)					
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	18/48 (37.5%)	20/47 (42.6%)	RR 0.88 (0.54 to 1.44)	51 fewer per 1000 (from 196 fewer to 187 more)	⊕OOO VERY LOW	
								42.6%		51 fewer per 1000 (from 196 fewer to 187 more)		
Respons	e - Thyroid h	ormone	versus SARI (foll	ow-up mean 8	weeks; asse	ssed with: ≥50%	improvement on HAMD)					
1	randomised trials			no serious indirectness	very serious²	reporting bias ³	28/48 (58.3%)	29/47 (61.7%)	RR 0.95 (0.68 to 1.31)	31 fewer per 1000 (from 197 fewer to 191 more)	⊕OOO VERY LOW	
18: 1- (1			16:1					61.7%		31 fewer per 1000 (from 197 fewer to 191 more)		

¹ Risk of bias is unclear or high across multiple domains

² 95% CI crosses one clinical decision threshold

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ 95% CI crosses two clinical decision thresholds

⁵ OIS not met (events<300)

² 95% CI crosses two clinical decision thresholds

³ Funding from pharmaceutical company and/or data is not reported/cannot be extracted for all outcomes

Augmenting the antidepressant with a psychological intervention compared to attention-placebo

			Quality asse	essment			No of patients	5		Effect	Quality	Importan
No of tudies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with a psych intervention	Attention- placebo	Relative (95% CI)	Absolute		
missio	n - Mindfuln	ess-based	cognitive therap	py (MBCT) vers	us attention-	placebo (follow-ι	ıp mean 8 weeks; assess	ed with: ≤7 o	on HAMD)	<u> </u>		
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias²	19/87 (21.8%)	12/86 (14%)	RR 1.57 (0.81 to 3.02)	80 more per 1000 (from 27 fewer to 282 more)	⊕⊕OO LOW	
								14%		80 more per 1000 (from 27 fewer to 283 more)		
spons	e - Mindfulne	ess-based	cognitive therap	y (MBCT) vers	ا- us attention	placebo (follow-u	p mean 8 weeks; assess	ed with: ≥50%	% improver	ment on HAMD)		
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	27/87 (31%)	13/86 (15.1%)	RR 2.05 (1.14 to 3.71)	159 more per 1000 (from 21 more to 410 more)	⊕⊕OO LOW	
								15.1%		159 more per 1000 (from 21 more to 409 more)		
	on symptom by lower va		Mindfulness-base	ed cognitive th	erapy (MBCT) versus attention	n-placebo (follow-up mea	n 8 weeks; n	neasured w	vith: HAMD change	score; Bet	ter
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	23	20	-	MD 5.06 lower (7.78 to 2.34 lower)	⊕⊕⊕O MODERATE	

2	randomised	no serious	no serious	no serious	very	none	15/113	20/110	RR 0.73	49 fewer per	⊕⊕OO	
	trials	risk of	inconsistency	indirectness	serious ⁵		(13.3%)	(18.2%)	(0.39 to	1000 (from 111	LOW	
		bias							1.34)	fewer to 62 more)		
										56 fewer per		
								20.6%		1000 (from 126		
										fewer to 70 more)		

¹ 95% CI crosses one clinical decision threshold

6

Augmenting the antidepressant with a psychological intervention compared to continuing with the antidepressant-only

1.083			Quality ass		8.00.1.1.00.1		No of pat			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with a psychological intervention	Continuing with the antidepressant- only	Relative (95% CI)	Absolute	Quality	Importance
Remissi	on - CBASP	+ any AD	versus any AD (follow-up mea	n 12 weeks; a	issessed with: <	3 on HAMD)					
	randomised trials	serious ¹		no serious indirectness	very serious ²	reporting bias ³	67/174 (38.5%)	30/76 (39.5%)	RR 0.98 (0.7 to 1.36)	8 fewer per 1000 (from 118 fewer to 142 more)	⊕OOO VERY LOW	
								39.5%		8 fewer per 1000 (from 119 fewer to 142 more)		
Remission	on - CBT ind	ividual (o	ver 15 sessions)	+ TAU versus	TAU (follow-	up 20-27 weeks;	assessed with: ≤7 on H	AMD/<10 on BDI)				
	randomised trials	very serious ¹		no serious indirectness	serious ⁴	none	76/286 (26.6%)	41/291 (14.1%)	RR 1.89 (1.34 to 2.66)	125 more per 1000 (from 48 more to 234 more)	⊕OOO VERY LOW	

² Data is not reported/cannot be extracted for all outcomes

³ OIS not met (events<300)

⁴ OIS not met (N<400)

⁵ 95% CI crosses two clinical decision thresholds

Pomiosi	on CRT ind	ividual (u	ndor 15 accion	a) + TALLyara	IS TALL (2000)	sed with: ≤7 on	HAMD	13.3%		118 more per 1000 (from 45 more to 221 more)		
Veiiii33i	on - CBT ind	iviuuai (u	iluer 13 session	s) + IAU veisi	is TAU (asses	seu with. 27 on	HAMD)					
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	13/21 (61.9%)	4/21 (19%)	RR 3.25 (1.27 to 8.35)	429 more per 1000 (from 51 more to 1000 more)	⊕⊕⊕O MODERATE	
								19.1%		430 more per 1000 (from 52 more to 1000 more)		
Remissi	on - IPT + TA	AU versus	TAU (follow-up	mean 19 week	s; assessed v	vith: ≤7 on HAMI	0)					
l	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	5/16 (31.3%)	3/18 (16.7%)	RR 1.88 (0.53 to 6.63)	147 more per 1000 (from 78 fewer to 938 more)	⊕⊕OO LOW	
								16.7%		147 more per 1000 (from 78 fewer to 940 more)		
Remissi	on - Short-te	rm psych	odynamic psycl	notherapy indi	vidual + any A	D/TAU versus a	ny AD/TAU (follow-up n	nean 12 weeks; as	ssessed with	: <8 on HAMD)		
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	52/168 (31%)	30/76 (39.5%)	RR 0.78 (0.55 to 1.12)	87 fewer per 1000 (from 178 fewer to 47 more)	⊕OOO VERY LOW	
								39.5%		87 fewer per 1000 (from 178 fewer to 47 more)		
Remissi	on - Long-te	rm psycho	odynamic psych	notherapy + TA	U versus TAL	(follow-up mea	n 78 weeks; assessed v	vith: ≤8 on HAMD))			
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ⁶	6/67 (9%)	4/62 (6.5%)	RR 1.39 (0.41 to 4.69)	25 more per 1000 (from 38 fewer to 238 more)	⊕000 VERY LOW	

								6.5%		25 more per 1000 (from 38 fewer to 240 more)		
Remissi	on - Cognitiv	e and co	gnitive behaviou	iral therapies (combined) +	any AD/TAU vers	us any AD/TAU-only (fo	ollow-up 12-27 wee	eks; assess	ed with: ≤7/8 or	HAMD/<10 on Bi	DI)
4	randomised trials	serious ¹	serious ⁷	no serious indirectness	serious ⁴	none	156/481 (32.4%)	75/388 (19.3%)	RR 1.68 (1.02 to 2.78)	131 more per 1000 (from 4 more to 344 more)	⊕000 VERY LOW	
								17%		116 more per 1000 (from 3 more to 303 more)		
Respons	se - any psyd	ch interve	ntion (follow-up	19-27 weeks;	assessed wit	h: ≥50% improvei	ment on HAMD/BDI)					
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	118/243 (48.6%)	55/252 (21.8%)	RR 2.22 (1.7 to 2.9)	266 more per 1000 (from 153 more to 415 more)	⊕OOO VERY LOW	
								22.2%		271 more per 1000 (from 155 more to 422 more)		
Respons	e - CBT indi	vidual (ov	er 15 sessions)	+ TAU versus	TAU (follow-	up mean 27 week	s; assessed with: ≥50%	improvement on	BDI)			
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	95/206 (46.1%)	46/213 (21.6%)	RR 2.14 (1.59 to 2.87)	246 more per 1000 (from 127 more to 404 more)	⊕OOO VERY LOW	
								21.6%		246 more per 1000 (from 127 more to 404 more)		
Respons	se - CBT indi	vidual (ur	nder 15 sessions	s) + TAU versu	s TAU (asses	sed with: ≥50% i	mprovement on HAMD)					
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	17/21 (81%)	5/21 (23.8%)	RR 3.4 (1.54 to 7.51)	571 more per 1000 (from 129 more to 1000 more)	⊕⊕⊕O MODERATE	

								23.8%		571 more per 1000 (from 129 more to 1000 more)	
spons	se - IPT + TA	U versus	TAU (follow-up	mean 19 week	s; assessed w	vith: ≥50% impro	vement on HAMD)				
		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	6/16 (37.5%)	4/18 (22.2%)	RR 1.69 (0.58 to 4.92)	153 more per 1000 (from 93 fewer to 871 more)	⊕⊕OO LOW
								22.2%		153 more per 1000 (from 93 fewer to 870 more)	
espon	se - Cognitiv	e and cog	nitive behaviou	ıral therapies (combined) + T	AU versus TAU-	only (follow-up mean 2	27 weeks; assesse	d with: ≥50%	improvement	on HAMD/BDI)
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	112/227 (49.3%)	51/234 (21.8%)	RR 2.32 (1.64 to 3.27)	288 more per 1000 (from 139 more to 495 more)	⊕OOO VERY LOW
								22.7%		300 more per 1000 (from 145 more to 515 more)	
epress	ion symptor	natology	- CBASP + any	AD versus any	AD (follow-up	mean 12 weeks	measured with: HAM	D change score; B	etter indicat	ed by lower val	ues)
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁸	reporting bias ³	174	76	-	SMD 0.36 lower (0.64 to 0.09 lower)	⊕OOO VERY LOW
epress alues)	sion symptor	natology ·	- CBT individua	l (over 15 sess	ions) + TAU ve	ersus TAU (follo	ı v-up 20-27 weeks; mea	asured with: HAMD)/BDI change	score; Better i	ndicated by lowe
	randomised trials	very serious ¹	very serious ⁹	no serious indirectness	serious ⁵	none	286	291	-	SMD 0.41 lower (0.85 lower to 0.04 higher)	⊕OOO VERY LOW
epress	ion symptor	natology ·	- CBT individua	l (under 15 ses	sions) + TAU	versus TAU (mea	l asured with: HAMD cha	ange score; Better	indicated by	lower values)	

	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁸	none	21	21	-	SMD 1.29 lower (1.96 to 0.62 lower)	⊕⊕⊕O MODERATE
epress	sion symptor	natology	- IPT + TAU vers	sus TAU (follov	w-up mean 1	9 weeks; measured	d with: HAMD change s	score; Better indic	ated by low	er values)	
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁵	none	16	18	-	SMD 0.66 lower (1.35 lower to 0.04 higher)	⊕⊕⊕O MODERATE
	sion symptored by lower v		Short-term ps	ychodynamic p	osychotherap	oy individual + any	AD versus any AD (fol	llow-up mean 12 v	veeks; meas	sured with: HAM	D change sco
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁸	reporting bias ³	168	76	-	SMD 0.1 lower (0.37 lower to 0.17 higher)	⊕000 VERY LOW
annes.		natology .	- I ona-term nsv	<i>I</i> CNOOVNAMIC D	isvenomerac	IV + I AU Versus I A					
•	r values) randomised		no serious inconsistency	no serious indirectness	serious⁵	reporting bias ⁶	67	62	-	SMD 0.26 lower (0.61 lower to 0.09 higher)	⊕OOO VERY LOW
Jowe	r values) randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁶		62	-	SMD 0.26 lower (0.61 lower to 0.09 higher)	⊕OOO VERY LOW
y lowe	r values) randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁶	67	62	-	SMD 0.26 lower (0.61 lower to 0.09 higher) s; Better indicate	⊕OOO VERY LOW
y lowe	r values) randomised trials sion symptor randomised trials	very serious ¹ natology no serious risk of bias	no serious inconsistency - Cognitive bibli no serious inconsistency	no serious indirectness iotherapy + any no serious indirectness	serious ⁵ y AD versus serious ⁵	reporting bias ⁶ any AD (follow-up none	67 mean 6 weeks; measu	62 red with: HAMD c	hange score	SMD 0.26 lower (0.61 lower to 0.09 higher) e; Better indicate SMD 0.37 lower (0.79 lower to 0.05 higher)	⊕OOO VERY LOW ed by lower va ⊕⊕⊕O MODERATE

	randomised trials	very serious ¹	serious ⁷	no serious indirectness	no serious imprecision	none	481	388	-	SMD 0.52 lower (0.83 to 0.2 lower)	⊕OOO VERY LOW	
scont ents)		any reaso	n - CBASP + an	y AD versus a	ny AD (follow-	up mean 12 weel	ks; assessed with: Nui	mber of people los	t to follow-up	(for any reaso	n including ad	verse
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	25/200 (12.5%)	16/96 (16.7%)	RR 0.75 (0.42 to 1.34)	42 fewer per 1000 (from 97 fewer to 57 more)	⊕OOO VERY LOW	
								16.7%		42 fewer per 1000 (from 97 fewer to 57 more)		
	inuation for a		n - CBT individ	ual (over 15 se	ssions) + TAU	versus TAU (foll	ow-up 20-27 weeks; a	ssessed with: Num	ber of peopl	e lost to follow	-up (for any rea	ason
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	44/314 (14%)	34/313 (10.9%)	RR 1.29 (0.85 to 1.96)	32 more per 1000 (from 16 fewer to 104 more)	⊕OOO VERY LOW	
								12.4%		36 more per 1000 (from 19 fewer to 119 more)		
iscont /ents)		any reaso	n - CBT individ	ual (under 15 s	essions) + TA	U versus TAU (as	ssessed with: Number	of people lost to f	ollow-up (for	any reason inc	cluding advers	е
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	1/21 (4.8%)	2/21 (9.5%)	RR 0.5 (0.05 to 5.1)	48 fewer per 1000 (from 90 fewer to 390 more)	⊕⊕OO LOW	
								9.5%		47 fewer per 1000 (from 90 fewer to 389 more)		

	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	5/17 (29.4%)	2/23 (8.7%)	RR 3.38 (0.74 to 15.39)	207 more per 1000 (from 23 fewer to 1000 more)	⊕⊕OO LOW	
								8.7%		207 more per 1000 (from 23 fewer to 1000 more)		
			n - Short-term լ ny reason inclu			py individual + an	y AD/TAU versus any	AD/TAU (follow-u	p mean 12 w	eeks; assessed	d with: Number o	of
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	27/195 (13.8%)	16/96 (16.7%)	RR 0.83 (0.47 to 1.47)	28 fewer per 1000 (from 88 fewer to 78 more)	⊕OOO VERY LOW	
								16.7%		28 fewer per 1000 (from 89 fewer to 78		
										more)		
			n - Long-term p erse events))	esychodynamic	psychotherap	py + TAU versus T	「AU-only (follow-up m	nean 78 weeks; ass	sessed with:	more)	ple lost to follow	w-up
		uding adv		no serious indirectness		py + TAU versus T	10/67 (14.9%)	8/62 (12.9%)	RR 1.16 (0.49 to 2.74)	more)	⊕OOO VERY LOW	w-up
	randomised	very	no serious	no serious		·	10/67	8/62	RR 1.16 (0.49 to	Number of peo 21 more per 1000 (from 66 fewer to 225	⊕000	w-up
or any	reason inclu randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ⁶	10/67	8/62 (12.9%) 12.9%	RR 1.16 (0.49 to 2.74)	more) Number of peo 21 more per 1000 (from 66 fewer to 225 more) 21 more per 1000 (from 66 fewer to 224 more)	⊕000 VERY LOW	
for any	reason incluration inclured trials	very serious ¹ any reaso vents))	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ⁶ any AD (follow-u	10/67 (14.9%)	8/62 (12.9%) 12.9%	RR 1.16 (0.49 to 2.74)	more) Number of peo 21 more per 1000 (from 66 fewer to 225 more) 21 more per 1000 (from 66 fewer to 224 more)	⊕000 VERY LOW	

										fewer to 407		
										more)		
	nuation for a events))	ny reaso	n - Mutual peer	support + TAU	versus TAU (follow-up mean 2	24 weeks; assessed wi	ith: Number of peo	ple lost to fo	llow-up (for an	y reason incl	uding
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ¹⁰	15/144 (10.4%)	26/243 (10.7%)	RR 0.97 (0.53 to 1.78)	3 fewer per 1000 (from 50 fewer to 83 more)	⊕OOO VERY LOW	
								10.7%		3 fewer per 1000 (from 50 fewer to 83 more)		
			n - Cognitive an any reason inc			rapies (combined) + any AD/TAU versus	s any AD/TAU-only	(follow-up 1	l2-27 weeks; as	ssessed with:	Numbe
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	70/535 (13.1%)	52/430 (12.1%)	RR 1.06 (0.75 to 1.49)	7 more per 1000 (from 30 fewer to 59 more)	⊕⊕OO LOW	
								12.5%		7 more per 1000 (from 31 fewer to 61 more)		
sconti	nuation due	to advers	e events - CBA	SP + any AD vo	ersus any AD	(follow-up mean	12 weeks; assessed w	rith: Number of peo	ople lost to f	ollow-up due to	adverse eve	nts)
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	2/200 (1%)	2/96 (2.1%)	RR 0.48 (0.07 to 3.36)	11 fewer per 1000 (from 19 fewer to 49 more)	⊕000 VERY LOW	
								2.1%		11 fewer per 1000 (from 20 fewer to 50 more)		
	nuation due bllow-up due			t-term psychoo	dynamic psyc	hotherapy individ	lual + any AD versus a	nny AD (follow-up i	mean 12 wee	ks; assessed v	vith: Number	of peop
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	1/195 (0.5%)	2/96 (2.1%)		16 fewer per 1000 (from 20		

					RR 0.25 (0.02 to 2.68)	fewer to 35 more)	⊕OOO VERY LOW	
				2.1%		16 fewer per 1000 (from 21 fewer to 35 more)		

¹ Risk of bias is unclear or high across multiple domains

4

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11

Augmenting the antidepressant with a psychological intervention compared to augmenting with a non-antidepressant agent

			Quality ass	essment			No of patier	nts		Effect	Quality	Importano
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with a psychological intervention	Augmenting with a non-AD agent	Relative (95% CI)	Absolute	Quanty	Importanc
Remissio	on - CBT indi	vidual (u	nder 15 sessions	s) + AD versus	lithium + AD	(follow-up mean	8 weeks; assessed with: I	HAMD ≤7)				
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	6/23 (26.1%)	8/21 (38.1%)	RR 0.68 (0.28 to 1.65)	122 fewer per 1000 (from 274 fewer to 248 more)	⊕OOO VERY LOW	
								38.1%		122 fewer per 1000 (from 274 fewer to 248		

Depression symptomatology - CBT individual (under 15 sessions) + AD versus lithium + AD (follow-up mean 8 weeks; measured with: HAMD change score; Better indicated by lower values)

² 95% CI crosses two clinical decision thresholds

³ Authors have financial interests with pharmaceutical companies

⁴ OIS not met (events<300)

⁵ 95% CI crosses one clinical decision threshold

⁶ Study partially funded by the International Psychoanalytic Association

⁷ I2>50%

⁸ OIS not met (N<400)

⁹ I2>80%

¹⁰ Data is not reported/cannot be extracted for all outcomes

Augmenting the antidepressant with a psychological intervention compared to 'other' psychological intervention (head-to-head comparisons)

			Quality ass	essment			No of patier	nts		Effect	Quality	Importance
No of studies	Libeian	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant with a	'Other' psychological intervention	Relative (95% CI)	Absolute		

¹ Risk of bias is unclear or high across multiple domains

² 95% CI crosses two clinical decision thresholds

³ OIS not met (N<400)

							psychological intervention					
							[head-to-head]					
Remissi	ion - CBASP -	+ any AD	versus short-to	erm psychodyn	amic psych	notherapy individu	al + any AD (follow-up mean	12 weeks; assess	sed with: <8	3 on HAMD)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	67/174 (38.5%)	52/168 (31%)	RR 1.24 (0.93 to 1.67)	74 more per 1000 (from 22 fewer to 207 more)	⊕OOO VERY LOW	
								31%	_	74 more per 1000 (from 22 fewer to 208 more)		
	sion symptom Better indicate			AD versus sho	rt-term psy	chodynamic psycl	notherapy individual + any A	D (follow-up mea	n 12 weeks;	measured with:	HAMD ch	nange
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	174	168	-	MD 1.56 lower (2.81 to 0.31 lower)	⊕OOO VERY LOW	
			on (including ad				rt-term psychodynamic psyc	hotherapy indivi	dual + any A	D (follow-up me	an 12 wee	eks;
1	randomicod			()	eason men	during duverse eve	nis))					
	trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	25/200 (12.5%)	27/195 (13.8%)	RR 0.9 (0.54 to 1.5)	14 fewer per 1000 (from 64 fewer to 69 more)	⊕OOO VERY LOW	
	trials		inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	25/200 (12.5%)	(13.8%)	(0.54 to 1.5)	1000 (from 64 fewer to 69 more) 14 fewer per 1000 (from 64 fewer to 69 more)	VERY LOW	
	trials	to advers	inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	25/200	(13.8%)	(0.54 to 1.5)	1000 (from 64 fewer to 69 more) 14 fewer per 1000 (from 64 fewer to 69 more)	VERY LOW	Number
	trials	to advers	inconsistency se events - CBA e to adverse ev	no serious indirectness	very serious ⁵	reporting bias ³	25/200 (12.5%)	(13.8%)	(0.54 to 1.5)	1000 (from 64 fewer to 69 more) 14 fewer per 1000 (from 64 fewer to 69 more)	VERY LOW	Number

					fewer to 102	
					more)	1

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses one clinical decision threshold

6 7

Augmenting the antidepressant/standard treatment with exercise compared to control

Augine	nung une	antiuepi	essairt/stairt	and treatin	CITE WILLIE	exercise comp	Dared to control				1	1
			Quality asse	essment			No of patients		ı	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting the antidepressant/standard treatment with exercise	Control	Relative (95% CI)	Absolute		
Remission	on - any exer	rcise augm	entation compa	rison (follow-u	p 6-12 weeks	s; assessed with:	≤7/10 on HAMD/≤10 on MADRS	& ≥50%	improveme	ent)		
	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	55/99 (55.6%)	36/87 (41.4%)	RR 1.44 (0.94 to 2.2)	182 more per 1000 (from 25 fewer to 497 more)	⊕⊕⊕O MODERATE	
								20%		88 more per 1000 (from 12 fewer to 240 more)		
Remission	on - Exercise	e + SSRI/ar	y AD versus att	ention-placebo	+ SSRI/any	AD (follow-up 10	l-12 weeks; assessed with: ≤7/10	on HAN	ID)			
	randomised trials		no serious inconsistency		very serious ¹	none	39/55 (70.9%)	28/47 (59.6%)	RR 1.77 (0.37 to 8.41)	459 more per 1000 (from 375 fewer to 1000 more)	⊕⊕OO LOW	
								37.8%		291 more per 1000 (from 238 fewer to 1000 more)		

³ Authors have financial interests with pharmaceutical companies

⁴ OIS not met (N<400)

⁵ 95% CI crosses two clinical decision thresholds

randomi	ed serious ²	no serious	no serious	very	none	7/22	3/20	RR 2.12	168 more per	⊕000
trials	5511043	inconsistency	indirectness	serious ³		(31.8%)	(15%)	(0.63 to 7.11)	1000 (from 56 fewer to 917 more)	VERY LOW
							15%		168 more per 1000 (from 56 fewer to 917 more)	
sion - Exe	cise + TAU (100% CBT; 76%	AD) versus TA	U (follow-up	mean 6 weeks; as	sessed with: ≤10 on MADRS	5)			
randomi trials	ed very serious ²	no serious inconsistency	no serious indirectness	very serious ³	none	9/22 (40.9%)	5/20 (25%)	RR 1.64 (0.66 to 4.07)	160 more per 1000 (from 85 fewer to 768 more)	⊕OOO VERY LOW
							050/		160 more per 1000 (from 85	
							25%		fewer to 768 more)	
onse - any	xercise aug	mentation compa	arison (follow-u	ıp 6-12 weel	s; assessed with:	≥50% improvement on HAM				
randomi trials		no serious inconsistency	no serious indirectness	serious ⁴	none	≥50% improvement on HAM 27/63 (42.9%)		RR 1.99 (1.13 to 3.49)		⊕000 VERY LOW
randomi	ed very	no serious	no serious	<u>.</u>		27/63	D/MADRS) 11/50	(1.13 to	218 more per 1000 (from 29 more to 548	
randomi trials	ed very serious²	no serious inconsistency	no serious indirectness	serious ⁴	none	27/63	11/50 (22%) 25%	(1.13 to 3.49)	218 more per 1000 (from 29 more to 548 more) 248 more per 1000 (from 32 more to 623	
randomi trials	ed very serious²	no serious inconsistency	no serious indirectness	serious ⁴	none	27/63 (42.9%)	11/50 (22%) 25%	(1.13 to 3.49) n HAMD) RR 4.95 (0.29 to	218 more per 1000 (from 29 more to 548 more) 248 more per 1000 (from 32 more to 623	
randomi trials ponse - Exer randomi trials	ed very serious² ise + any Al ed very serious²	no serious inconsistency D versus attention no serious inconsistency	no serious indirectness n-placebo + an no serious indirectness	serious ⁴ y AD (follow very serious ³	none v-up mean 12 week reporting bias ⁵	27/63 (42.9%) (s; assessed with: ≥50% imp 4/19 (21.1%)	25% provement of (0%) 0%	(1.13 to 3.49) n HAMD) RR 4.95 (0.29 to 83.68)	218 more per 1000 (from 29 more to 548 more) 248 more per 1000 (from 32 more to 623 more)	VERY LOW
randomi trials ponse - Exer randomi trials	ed very serious² ise + any Al ed very serious²	no serious inconsistency D versus attention no serious inconsistency	no serious indirectness n-placebo + an no serious indirectness	serious ⁴ y AD (follow very serious ³	none v-up mean 12 week reporting bias ⁵	27/63 (42.9%) (s; assessed with: ≥50% imp	25% provement of (0%) 0%	(1.13 to 3.49) n HAMD) RR 4.95 (0.29 to 83.68)	218 more per 1000 (from 29 more to 548 more) 248 more per 1000 (from 32 more to 623 more)	VERY LOW

									RR 1.64 (0.66 to 4.07)	fewer to 768 more)	⊕OOO VERY LOW	
								25%		160 more per 1000 (from 85 fewer to 768 more)		
espo	nse - Exercise	+ TAU (10	00% CBT; 76% A	(D) versus TAU	(follow-up	mean 6 weeks; as	sessed with: ≥50% improvemen	t on MAD	RS)			
	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	serious ⁴	none	14/22 (63.6%)	6/20 (30%)	RR 2.12 (1.01 to 4.45)	336 more per 1000 (from 3 more to 1000 more)	⊕OOO VERY LOW	
								30%		336 more per 1000 (from 3 more to 1000 more)		
epres	ssion sympton	natology -	any exercise au	gmentation co	mparison (f	ollow-up 6-12 wee	ks; measured with: HAMD/MAD	RS chan	ge score; E	Better indicated b	y lower value	s)
	randomised trials	serious ²	very serious ⁶	no serious	serious ⁷	none	96	85	-	SMD 0.51 lower (0.83 to 0.2		
	liiais			indirectriess						lower)	VERY LOW	
		natology -	Exercise + SSR		s attention-	placebo + SSRI/ar	y AD (follow-up 10-12 weeks; m	neasured	with: HAM	lower)		ted by
	ssion sympton values)		Exercise + SSR svery serious ⁶		s attention-	placebo + SSRI/an	y AD (follow-up 10-12 weeks; m	neasured 45	with: HAM	lower)		ted by
ower v	ssion sympton values) randomised trials	no serious risk of bias	svery serious ⁶	no serious indirectness	serious ¹	none		45	-	D change score; SMD 0.4 lower (0.86 lower to 0.06 higher)	⊕OOO VERY LOW	
ower	ssion sympton values) randomised trials	no serious risk of bias natology -	svery serious ⁶	no serious indirectness	serious ¹	none	52	45	-	D change score; SMD 0.4 lower (0.86 lower to 0.06 higher)	⊕OOO VERY LOW	
epres	randomised trials randomised trials	no serious risk of bias natology -	Exercise + SSR no serious inconsistency	no serious indirectness I versus enhant no serious indirectness	serious ¹ aced TAU + S serious ⁷	none SSRI (follow-up management)	52 ean 10 weeks; measured with: M	45 MADRS cl	- hange scor -	SMD 0.4 lower (0.86 lower to 0.06 higher) re; Better indicate SMD 0.74 lower (1.37 to 0.11 lower)	⊕OOO VERY LOW ed by lower va	alues)

Disconti events))		ny reason	ı - any exercise a	augmentation (comparison	(follow-up 6-12 w	eeks; assessed with: Number o	f people	lost to follo	w-up (for any re	ason including	adverse
4	randomised trials	serious ²	no serious inconsistency	no serious indirectness	very serious ³	none	10/102 (9.8%)	7/88 (8%)	RR 1.15 (0.46 to 2.88)	12 more per 1000 (from 43 fewer to 150 more)	⊕OOO VERY LOW	
								7.3%		11 more per 1000 (from 39 fewer to 137 more)		
	nuation for a ncluding adv			RI/any AD vers	sus attention	-placebo + SSRI/a	any AD (follow-up 10-12 weeks	; assesse	d with: Nun	nber of people lo	ost to follow-up	(for any
2		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	6/58 (10.3%)	3/48 (6.3%)	RR 1.53 (0.4 to 5.86)	33 more per 1000 (from 38 fewer to 304 more)	⊕⊕OO LOW	
								7.3%		39 more per 1000 (from 44 fewer to 355 more)		
	nuation for a g adverse ev	-	ı - Exercise + SS	RI versus enha	anced TAU +	SSRI (follow-up	mean 10 weeks; assessed with	: Number	of people I	ost to follow-up	(for any reason	1
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	very serious ³	none	4/22 (18.2%)	4/20 (20%)	RR 0.91 (0.26 to 3.16)	18 fewer per 1000 (from 148 fewer to 432 more)	⊕OOO VERY LOW	
								20%		18 fewer per 1000 (from 148 fewer to 432 more)		
	nuation for a g adverse ev		ı - Exercise + TA	U (100% CBT;	76% AD) ver	sus TAU (follow-	up mean 6 weeks; assessed wi	th: Numb	er of people	e lost to follow-u	p (for any reaso	on
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ⁴	none	0/22 (0%)	0/20 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								0%		not pooled		

¹ 95% CI crosses one clinical decision threshold

² Risk of bias is unclear or high across multiple domains

³ 95% CI crosses two clinical decision thresholds

⁴ OIS not met (events<300)

⁵ Study partially funded by pharmaceutical company

6 I2>80%

⁷ OIS not met (N<400)

8

Augmenting the antidepressant with ECT compared to continuing with the antidepressant-only

			Quality ass	essment			No of p	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias Inconsistency Indirectness Imprecision Other considerations Augmenting the antidepressant with ECT Continuing with the antidepressant-only (95% CI) Absolute										
Depressi	on symptom	atology -	ECT + citalopran	n versus citalor	ram (follow-	up mean 4 weeks	s; measured with: HAN	ID change score; Bett	er indicat	ed by lower valu	es)	
1	randomised trials			no serious indirectness	serious ²	none	20	20	-	SMD 0.6 lower (1.23 lower to 0.04 higher)	⊕000 VERY LOW	
Discontine events))	nuation for a	ny reason	- ECT + citalopr	am versus cital	opram (follo	w-up mean 4 wee	ks; assessed with: Nu	imber of people lost to	follow-u	p (for any reasor	includin	g adverse
1	randomised trials			no serious indirectness	serious ³	none	0/20 (0%)	0/20 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								0%		not pooled		

¹ Risk of bias is unclear or high across multiple domains

13

14

10

12

Switching to another antidepressant of a different class compared to placebo

O =				
Quality assessment	No of patients	Effect	Quality	Importance

² 95% CI crosses one clinical decision threshold

³ OIS not met (events<300)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to another antidepressant of different class	Placebo	Relative (95% CI)	Absolute		
Remissio	n - SSRI to a	typical anti	depressant or pla	cebo (follow-up	mean 12 we	eks; assessed wit	th: ≤7 on HAMD)					
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	reporting bias ²	40/165 (24.2%)	39/157 (24.8%)	RR 0.98 (0.67 to 1.43)	5 fewer per 1000 (from 82 fewer to 107 more)	⊕OOO VERY LOW	
								24.8%		5 fewer per 1000 (from 82 fewer to 107 more)		
Respons	e - SSRI to at	ypical antid	lepressant or pla	cebo (follow-up	mean 12 we	eks; assessed wit	h: ≥50% improvement on	HAMD)				
1	randomised trials		no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	63/165 (38.2%)	58/157 (36.9%)	RR 1.03 (0.78 to 1.37)	11 more per 1000 (from 81 fewer to 137 more)	⊕⊕OO LOW	
								36.9%		11 more per 1000 (from 81 fewer to 137 more)		
Response	e - SSRI to at	ypical antid	lepressant or pla	cebo (follow-up	mean 12 we	eks; assessed wit	h: Much/very much impr	oved on C	GI-I)			
1	randomised trials		no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	79/165 (47.9%)	69/157 (43.9%)	RR 1.09 (0.86 to 1.38)	40 more per 1000 (from 62 fewer to 167 more)	⊕⊕OO LOW	
								44%		40 more per 1000 (from 62 fewer to 167 more)		
Depressi	on symptoma	atology - SS	SRI to atypical an	tidepressant or	placebo (foll	ow-up mean 12 we	eeks; measured with: HA	MD chang	e score; Be	etter indicated by lov	ver values)	
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	165	157	-	MD 0.2 higher (1.59 lower to 1.99 higher)	⊕⊕OO LOW	
Discontir adverse		l ny reason - S	l SSRI to atypical a	l antidepressant (or placebo (fe	ollow-up mean 12	weeks; assessed with: N	lumber of	people lost	to follow-up (for an	y reason inclu	uding
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ²	67/166 (40.4%)	47/159 (29.6%)	RR 1.37 (1.01 to 1.85)	109 more per 1000 (from 3 more to 251 more)	⊕⊕OO LOW	

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								29.6%		110 more per 1000 (from 3 more to 252 more)		
Discontine events)	nuation due to	o adverse e	vents - SSRI to a	typical antidepi	essant or pla	acebo (follow-up r	nean 12 weeks; assessed	with: Nur	nber of peo	ple lost to follow-up	due to a	dverse
·	T			1	Т .							
		no serious risk of bias		no serious indirectness	serious ³	reporting bias ²	39/166 (23.5%)	31/159 (19.5%)	RR 1.21 (0.79 to 1.83)	41 more per 1000 (from 41 fewer to 162 more)	⊕⊕OO LOW	
								19.5%		41 more per 1000 (from 41 fewer to 162 more)		

¹ 95% CI crosses two clinical decision thresholds

			Quality as	sessment			No of pa	tients		Effect	Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to another antidepressant of a different class	Continuing with the antidepressant	Relative (95% CI)	Absolute		
temissi	on - any swit	ch (follov	w-up 6-12 weeks	; assessed with	n: ≤8/10 on MA	DRS/≤7/8 on HAN	ID)					
,	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	82/336 (24.4%)	53/209 (25.4%)	RR 0.93 (0.65 to 1.34)	18 fewer per 1000 (from 89 fewer to 86 more)	⊕OOO VERY LOW	
								20.4%		14 fewer per 1000 (from 71		

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Switching to another antidepressant of a different class compared to continuing with the same antidepressant

² Study run and funded by pharmaceutical company ³ 95% CI crosses one clinical decision threshold

⁴ OIS not met (N<400)

⁵ OIS not met (events<300)

Remissi	on - Switch to	o SSRI v	ersus continuin	g TCA/SNRI (fo	ollow-up 8-12 w	eeks; assessed v	with: ≤8 on MADRS)				
2	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	29/198 (14.6%)	25/126 (19.8%)	RR 0.78 (0.47 to 1.27)	44 fewer per 1000 (from 105 fewer to 54 more)	⊕OOO VERY LOW
								20%		44 fewer per 1000 (from 106 fewer to 54 more)	
emissi	on - Switch to	o atypica	I AD/SNRI/TeC	A (mianserin) v	ersus continui	ng SSRI (follow-u	p 6-8 weeks; assessed	with: ≤7/8 on HAM	D)		
	randomised trials	very serious ¹	serious ⁴	no serious indirectness	very serious ²	reporting bias ³	53/138 (38.4%)	28/83 (33.7%)	RR 1.19 (0.52 to 2.77)	64 more per 1000 (from 162 fewer to 597 more)	⊕OOO VERY LOW
								32.5%		62 more per 1000 (from 156 fewer to 575 more)	
espons	se - any switc	ch (follow	v-up 6-12 weeks	; assessed wit	h: ≥50% improv	vement on MADR	S/HAMD)				
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	140/336 (41.7%)	94/209 (45%)	RR 0.91 (0.74 to 1.12)	40 fewer per 1000 (from 117 fewer to 54 more)	⊕OOO VERY LOW
								43.4%		39 fewer per 1000 (from 113 fewer to 52 more)	
espons	se - Switch to	SSRI ve	ersus continuino	TCA/SNRI (fo	llow-up 8-12 we	eeks; assessed v	vith: ≥50% improvement	on MADRS)			
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	60/198 (30.3%)	50/126 (39.7%)	RR 0.8 (0.58 to 1.09)	79 fewer per 1000 (from 167 fewer to 36 more)	⊕OOO VERY LOW
								40.4%		81 fewer per 1000 (from 170 fewer to 36 more)	

Respons	se - Switch to	atypical	AD/SNRI/TeCA	(mianserin) ve	ersus continuin	g SSRI (follow-u	6-8 weeks; assessed	with: ≥50% improve	ement on H	AMD)		
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	80/138 (58%)	44/83 (53%)	RR 1.01 (0.73 to 1.41)	5 more per 1000 (from 143 fewer to 217 more)	⊕OOO VERY LOW	
								51.8%		5 more per 1000 (from 140 fewer to 212 more)		
espons	se - Switch to	TeCA (r	nianserin) versı	us continuing S	SRI (follow-up	mean 6 weeks; a	ssessed with: Much/ve	ry much improved	on CGI-I)			
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	21/33 (63.6%)	17/38 (44.7%)	RR 1.42 (0.92 to 2.2)	188 more per 1000 (from 36 fewer to 537 more)	⊕OOO VERY LOW	
								44.7%		188 more per 1000 (from 36 fewer to 536 more)		
epress	ion symptom	natology	- any switch (fo	llow-up 6-12 w	eeks; measure	d with: MADRS/H	AMD change score; Be	tter indicated by lo	wer values)			
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	235	165	-	SMD 0.04 lower (0.3 lower to 0.23 higher)	⊕OOO VERY LOW	
epress	ion symptom	natology	- Switch to SSR	Il versus contin	uing TCA/SNR	I (follow-up 8-12	weeks; measured with:	MADRS change so	ore; Better	indicated by lowe	r values)	
		very serious ¹	serious ⁴	no serious indirectness	serious ⁶	reporting bias ³	202	127	-	SMD 0.03 higher (0.31 lower to 0.38 higher)	⊕OOO VERY LOW	
epress	ion symptom	natology	- Switch to TeC	A (mianserin) v	ersus continui	ng SSRI (follow-u	ip mean 6 weeks; meas	sured with: HAMD o	hange scor	e; Better indicate	d by lower v	value
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	33	38	-	SMD 0.24 lower (0.71 lower to 0.23 higher)	⊕OOO VERY LOW	
isconti	inuation for a	iny reaso	n - any switch (follow-up 6-12	weeks; assess	ed with: Number	of people lost to follow	-up (for any reasor	including a	adverse events))		
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	71/341 (20.8%)	38/210 (18.1%)		42 more per 1000 (from 34		

									RR 1.23 (0.81 to 1.86)	fewer to 156 more) 42 more per	⊕OOO VERY LOW	
								18.1%		1000 (from 34 fewer to 156 more)		
	nuation for a events))	ny reaso	n - Switch to SS	RI versus cont	inuing TCA/SN	IRI (follow-up 8-1	2 weeks; assessed with	n: Number of peopl	e lost to folle	ow-up (for any re	ason inc	luding
2	randomised trials	serious ¹	serious ⁴	no serious indirectness	very serious ²	reporting bias ³	40/202 (19.8%)	23/127 (18.1%)	RR 1.13 (0.54 to 2.38)	24 more per 1000 (from 83 fewer to 250 more)	⊕OOO VERY LOW	
								18.6%		24 more per 1000 (from 86 fewer to 257 more)		
	nuation for a on including			pical AD/SNRI/	/TeCA (mianse	rin) versus conti	nuing SSRI (follow-up 6	6-8 weeks; assesse	d with: Num	per of people los	t to follo	w-up (for
2	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	31/139 (22.3%)	15/83 (18.1%)	RR 1.37 (0.74 to 2.54)	67 more per 1000 (from 47 fewer to 278 more)	⊕OOO VERY LOW	
								18.1%		67 more per 1000 (from 47 fewer to 279 more)		
Disconti	nuation due	to advers	se events - any s	witch (follow-u	up 6-12 weeks;	assessed with: I	Number of people lost to	o follow-up due to	adverse eve	nts)		
4	randomised trials	serious ¹	serious ⁴	no serious indirectness	very serious ²	reporting bias ³	15/336 (4.5%)	4/210 (1.9%)	RR 1.74 (0.32 to 9.6)	14 more per 1000 (from 13 fewer to 164 more)	⊕OOO VERY LOW	
								2%		15 more per 1000 (from 14		

	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	7/202 (3.5%)	3/127 (2.4%)	RR 1.43 (0.38 to 5.47)	10 more per 1000 (from 15 fewer to 106 more)	⊕OOO VERY LOW
								2.3%		10 more per 1000 (from 14 fewer to 103 more)	
			se events - Swit	ch to atypical A	AD/SNRI/TeCA	(mianserin) versu	s continuing SSRI (fol	low-up 6-8 weeks;	assessed wi	th: Number of pe	ople lost to
p due 1	to adverse ev	ents)									
p due 1	randomised	,	very serious ⁷	no serious indirectness	very serious ²	reporting bias ³	8/134 (6%)	1/83 (1.2%)	RR 1.8 (0.01 to 222.73)	10 more per 1000 (from 12 fewer to 1000 more)	⊕OOO VERY LOW

¹ Risk of bias is unclear or high across multiple domains

8

Switching to a non-antidepressant agent compared to continuing with the antidepressant

			Quality ass	sessment			No of p	patients		Effect	Quality	Importance
No of studies	Libeian	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to non- antidepressant agent	Continuing with the antidepressant	Relative (95% CI)	Absolute		

² 95% CI crosses two clinical decision thresholds

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ I2>50%

⁵ 95% CI crosses one clinical decision threshold

⁶ OIS not met (N<400)

⁷ I2>80%

rando	lomised v	very	no serious	no serious	serious ²	reporting bias3	56/400	59/329	RR 0.79	38 fewer per 1000	⊕OOO
trials		serious ¹	inconsistency	indirectness	Scrious	reporting bias	(14%)	(17.9%)	(0.56 to 1.11)	(from 79 fewer to 20 more)	
								17.7%		37 fewer per 1000 (from 78 fewer to 19 more)	
nission - S	Switch to	combin	ed antipsychoti	ic + SSRI versu	s continuing	TCA/SNRI (follow-up	8-12 weeks; asses	ssed with: ≤8 on M	ADRS)	/	
rando trials		very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	94/376 (25%)	25/126 (19.8%)	RR 1.17 (0.79 to 1.75)	34 more per 1000 (from 42 fewer to 149 more)	
								20%		34 more per 1000 (from 42 fewer to 150 more)	
sponse - Sv	switch to a	antipsyc	hotic monothe	rapy versus co	ntinuing SSR	I/TCA/SNRI (follow-u	p 8-12 weeks; asse	essed with: ≥50% i	mprovement of	on MADRS)	
rando trials		very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	94/400 (23.5%)	110/329 (33.4%)	RR 0.69 (0.49 to 0.96)	104 fewer per 1000 (from 13 fewer to 171 fewer)	⊕OOO VERY LOW
		,			serious ⁴	reporting bias ³			(0.49 to	1000 (from 13 fewer to 171	VERY LOW
trials	s s	serious ¹	inconsistency	indirectness		reporting bias³ TCA/SNRI (follow-up	(23.5%)	(33.4%)	(0.49 to 0.96)	1000 (from 13 fewer to 171 fewer) 96 fewer per 1000 (from 12 fewer to 158 fewer)	VERY LOW
trials esponse - Sv	Switch to comised v	combine	inconsistency	indirectness		-	(23.5%)	(33.4%)	(0.49 to 0.96)	1000 (from 13 fewer to 171 fewer) 96 fewer per 1000 (from 12 fewer to 158 fewer)	VERY LOW
esponse - Sv rando trials	Switch to domised vs. s	combine very serious ¹	ed antipsychotic no serious inconsistency	indirectness c + SSRI versus no serious indirectness	s continuing 's serious ²	TCA/SNRI (follow-up reporting bias ³	(23.5%) 8-12 weeks; asses: 140/376 (37.2%)	(33.4%) 30.9% sed with: ≥50% im 50/126 (39.7%) 40.4%	(0.49 to 0.96) provement or RR 0.87 (0.68 to 1.12)	1000 (from 13 fewer to 171 fewer) 96 fewer per 1000 (from 12 fewer to 158 fewer) 1 MADRS) 52 fewer per 1000 (from 127 fewer to 48 more) 53 fewer per 1000 (from 129 fewer to 48 more)	⊕OOO VERY LOW
trials esponse - Sv rando trials	Switch to domised of s	combined very serious 1	ed antipsychotic no serious inconsistency	indirectness c + SSRI versus no serious indirectness	s continuing 's serious ²	TCA/SNRI (follow-up	(23.5%) 8-12 weeks; asses: 140/376 (37.2%)	(33.4%) 30.9% sed with: ≥50% im 50/126 (39.7%) 40.4%	(0.49 to 0.96) provement or RR 0.87 (0.68 to 1.12)	1000 (from 13 fewer to 171 fewer) 96 fewer per 1000 (from 12 fewer to 158 fewer) 1 MADRS) 52 fewer per 1000 (from 127 fewer to 48 more) 53 fewer per 1000 (from 129 fewer to 48 more)	⊕OOO VERY LOW

randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	389	127	-	MD 0.83 lower (2.56 lower to 0.91 higher)	⊕OOO VERY LOW
ntinuation for a ny reason inclu			tipsychotic mo	notherapy vers	us continuing SSF	RI/TCA/SNRI (follow	-up 8-12 weeks; as	ssessed with:	Number of people	e lost to fo
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	122/405 (30.1%)	63/333 (18.9%)	RR 1.67 (1.26 to 2.23)	127 more per 1000 (from 49 more to 233 more)	⊕OOO VERY LOW
							19.4%		130 more per 1000 (from 50 more to 239 more)	
ntinuation for a ny reason inclu			mbined antipsy	chotic + SSRI	versus continuing	TCA/SNRI (follow-u	ip 8-12 weeks; ass	essed with: I	Number of people	lost to follo
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁶	reporting bias ³	90/389 (23.1%)	23/127 (18.1%)	RR 1.22 (0.69 to 2.16)	40 more per 1000 (from 56 fewer to 210 more)	⊕OOO VERY LOW
							18.6%		41 more per 1000 (from 58 fewer to 216 more)	
ntinuation due -up due to adv			ch to antipsych	otic monothera	apy versus continu	ing SSRI/TCA/SNR	l (follow-up 8-12 w	eeks; assess	ed with: Number o	of people lo
	serious ¹	no serious	no serious indirectness	serious ⁴	reporting bias ³	51/405 (12.6%)	8/333 (2.4%)	RR 5.34 (2.57 to 11.09)	104 more per 1000 (from 38 more to 242	⊕OOO VERY LOW
randomised trials	Scrious	inconsistency							more)	

2	randomised s trials		no serious indirectness	serious ⁴	reporting bias ³	39/389 (10%)	3/127 (2.4%)	RR 3.48 (1.06 to 11.44)	59 more per 1000 (from 1 more to 247 more)	
							2.3%		57 more per 1000 (from 1 more to 240 more)	

¹ Risk of bias is unclear or high across multiple domains

7

8 9 Switching to another antidepressant or non-antidepressant agent compared to augmenting with another antidepressant or non-antidepressant agent

			Quality ass	sessment			No of p	patients	E	ffect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to another antidepressant/non-antidepressant agent	Augmentation with another antidepressant/non-antidepressant agent	Relative (95% CI)	Absolute	Quality	Importance
Remission	on - Switch t	to SNRI v	ersus switch to	SNRI augmen	ted with antip	osychotic (follow	r-up mean 8 weeks; asse	ssed with: ≤7 on HAMD)				
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	12/46 (26.1%)	19/49 (38.8%)	RR 0.67 (0.37 to 1.23)	128 fewer per 1000 (from 244 fewer to 89 more)	⊕OOO VERY LOW	
								38.8%		128 fewer per 1000 (from 244 fewer to 89 more)		

² 95% CI crosses one clinical decision threshold

³ Funding from pharmaceutical company

⁴ OIS not met (events<300)

⁵ I2=80%

⁶ 95% CI crosses two clinical decision thresholds

			no serious indirectness	very serious ³	reporting bias ⁴	12/33 (36.4%)	14/32 (43.8%)	RR 0.83 (0.46 to 1.51)	1000 (from 236 fewer to 223 more)	⊕OOO VERY LOW	
							43.8%		74 fewer per 1000 (from 237 fewer to 223 more)		
- Switch t	o antipsy	chotic versus a	augmentation	with antipsyc	hotic (follow-up	6-8 weeks; assessed wi	th: ≤10 on MADRS)				
als s	serious risk of		no serious indirectness	serious⁵	reporting bias ⁴	82/422 (19.4%)	127/427 (29.7%)	RR 0.65 (0.48 to 0.88)	104 fewer per 1000 (from 36 fewer to 155 fewer)	⊕⊕OO LOW	
							29.6%		104 fewer per 1000 (from 36 fewer to 154 fewer)		
- Switch t	o antipsy	chotic versus a	augmentation	with lithium (1	follow-up mean	6 weeks; assessed with:	: <10 on MADRS)				
als s	serious risk of		no serious indirectness	serious ²	reporting bias ⁴	53/225 (23.6%)	60/221 (27.1%)	RR 0.87 (0.63 to 1.19)	35 fewer per 1000 (from 100 fewer to 52 more)	⊕⊕OO LOW	
							27.2%		35 fewer per 1000 (from 101 fewer to 52 more)		
- Switch to	SNRI ve	rsus switch to	SNRI augmen	ted with antip	sychotic (follow	-up mean 8 weeks; asse	essed with: ≥50% improve	ement on HA	MD)		
			no serious indirectness	very serious ³	none	20/46 (43.5%)	24/49 (49%)	RR 0.89 (0.57 to 1.37)	54 fewer per 1000 (from 211 fewer to 181 more)	⊕OOO VERY LOW	
									54 fewer per 1000 (from		
a na na	- Switch to adomised in the state of the sta	- Switch to antipsy adomised no serious risk of bias - Switch to antipsy adomised no serious risk of bias - Switch to SNRI very	- Switch to antipsychotic versus andomised no serious risk of bias no serious inconsistency risk of bias no serious inconsistency risk of bias no serious no serious no serious no serious no serious	- Switch to antipsychotic versus augmentation Indomised Ino serious inconsistency indirectness - Switch to antipsychotic versus augmentation - Switch to antipsychotic versus augmentation Indomised Ino serious inconsistency indirectness - Switch to antipsychotic versus augmentation Indomised Ino serious inconsistency indirectness Indomised Ino serious inconsistency indirectness - Switch to SNRI versus switch to SNRI augmen Indomised Ino serious inconsistency indirectness - Switch to SNRI versus switch to SNRI augmen Indomised Ino serious inconsistency indirectness Indomised Ino serious inconsistency indirectness In o serious indirectn	- Switch to antipsychotic versus augmentation with antipsychodised no serious risk of bias no serious inconsistency indirectness no serious inconsistency indirectness no serious indirectness no serious indirectness no serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency indirectness no serious very serious no serious very serious very serious very serious very serious	- Switch to antipsychotic versus augmentation with antipsychotic (follow-up adomised no serious risk of bias - Switch to antipsychotic versus augmentation with lithium (follow-up mean of the bias are inconsistency inconsistency indirectness indirectness inconsistency risk of bias are inconsistency inconsistency indirectness ind	- Switch to antipsychotic versus augmentation with antipsychotic (follow-up 6-8 weeks; assessed with a serious risk of blas - Switch to antipsychotic versus augmentation with antipsychotic (follow-up 6-8 weeks; assessed with a serious risk of blas - Switch to antipsychotic versus augmentation with lithium (follow-up mean 6 weeks; assessed with a serious risk of blas - Switch to SNRI versus switch to SNRI augmented with antipsychotic (follow-up mean 8 weeks; assessed with a serious risk of blas - Switch to SNRI versus switch to SNRI augmented with antipsychotic (follow-up mean 8 weeks; assessed with a serious reporting blas 20/46	serious¹ inconsistency indirectness (36.4%) (43.8%) - Switch to antipsychotic versus augmentation with antipsychotic (follow-up 6-8 weeks; assessed with: ≤10 on MADRS) Indication No serious serious risk of bias No serious serious risk of bias No serious risk of bias risk of bias No serious risk of bias No serious risk of bias No seri	serious¹ inconsistency indirectness	Serious Inconsistency I	Serious

d no serious risk of bias	very serious ⁶	no serious indirectness	serious ²	reporting bias ⁴	6-8 weeks; assessed with 165/422 (39.1%)	62.5% ith: ≥50% improvement of 200/427 (46.8%) 46.4%	RR 0.8 (0.53 to 1.2)	312 fewer to 131 more) 138 fewer per 1000 (from 312 fewer to 131 more) 94 fewer per 1000 (from 220 fewer to 94 more) 93 fewer per 1000 (from 218 fewer to 93 more)	⊕OOO VERY LOW
d no serious risk of bias	very serious ⁶	no serious indirectness	serious ²	reporting bias ⁴	165/422 (39.1%)	200/427 (46.8%) 46.4%	RR 0.8 (0.53 to 1.2)	94 fewer per 1000 (from 312 fewer to 131 more) 94 fewer per 1000 (from 220 fewer to 94 more) 93 fewer per 1000 (from 218 fewer to	⊕OOO VERY
d no serious risk of bias	very serious ⁶	no serious indirectness	serious ²	reporting bias ⁴	165/422 (39.1%)	200/427 (46.8%) 46.4%	RR 0.8 (0.53 to 1.2)	1000 (from 220 fewer to 94 more) 93 fewer per 1000 (from 218 fewer to	VERY
serious risk of bias	rchotic versus a	indirectness			(39.1%)	(46.8%) 46.4%	(0.53 to 1.2)	1000 (from 220 fewer to 94 more) 93 fewer per 1000 (from 218 fewer to	VERY
			with lithium	ı (follow-up mean 6	weeks; assessed with		MADDS)	1000 (from 218 fewer to	
			with lithium	(follow-up mean 6	weeks; assessed with	: >E0% improvement on	MADDC		
d no	no serious				•	. 250 /6 improvement on i	IVIADKS)		
d no serious risk of bias	inconsistency	no serious indirectness	serious ⁵	reporting bias⁴	114/225 (50.7%)	112/221 (50.7%)	RR 1 (0.83 to 1.2)	0 fewer per 1000 (from 86 fewer to 101 more)	⊕⊕OO LOW
						50.7%		0 fewer per 1000 (from 86 fewer to 101 more)	
to TeCA v	ersus augment	tation with TeC	CA (mianser	rin) (follow-up mear	n 6 weeks; assessed w	ith: Much/very much imp	proved on CG	I-I)	
d very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁴	21/33 (63.6%)	23/32 (71.9%)	RR 0.89 (0.63 to 1.24)	79 fewer per 1000 (from 266 fewer to 173 more)	⊕OOO VERY LOW
						71.9%		79 fewer per 1000 (from 266 fewer to 173 more)	
	ed very serious ¹	ed very no serious inconsistency	ed very no serious no serious indirectness	ed very no serious no serious serious² inconsistency indirectness	ed very no serious inconsistency indirectness serious ² reporting bias ⁴	ed very serious inconsistency indirectness serious ² reporting bias ⁴ 21/33 (63.6%)	th to TeCA versus augmentation with TeCA (mianserin) (follow-up mean 6 weeks; assessed with: Much/very much important and very serious inconsistency inconsi	th to TeCA versus augmentation with TeCA (mianserin) (follow-up mean 6 weeks; assessed with: Much/very much improved on CG and very serious inconsistency i	to TeCA versus augmentation with TeCA (mianserin) (follow-up mean 6 weeks; assessed with: Much/very much improved on CGI-I) and very serious inconsistency inconsistency serious indirectness indirectn

	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁴	139/225 (61.8%)	153/229 (66.8%)	RR 0.92 (0.81 to 1.06)	53 fewer per 1000 (from 127 fewer to 40 more)	⊕⊕OO LOW	
								66.8%		53 fewer per 1000 (from 127 fewer to 40 more)		
Respon	se - Switch t	o antipsy	chotic versus a	augmentation	with lithium (follow-up mean 6	weeks; assessed with: N	Much/very much improved	on CGI-I)			
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁴	139/225 (61.8%)	133/221 (60.2%)	RR 1.03 (0.88 to 1.19)	18 more per 1000 (from 72 fewer to 114 more)	⊕⊕OO LOW	
								60.2%		18 more per 1000 (from 72 fewer to 114 more)		
Depress	sion sympto	matology	- any switch (fo	ollow-up 6-8 w	eeks; measu	red with: MADRS	/HAMD change score; Be	etter indicated by lower val	ues)			
	randomised trials	very serious ¹	very serious ⁶	no serious indirectness	no serious imprecision	reporting bias ⁴	276	279	-	SMD 0.73 higher (0.09 to 1.38 higher)	⊕OOO VERY LOW	
	sion sympto d by lower v		- Switch to SNI	RI versus swit	ch to SNRI αι	igmented with an	tipsychotic (follow-up m	ean 8 weeks; measured w	th: MADR	S/HAMD chan	ige score	e; Better
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	46	49	-	SMD 1.44 higher (0.99 to 1.89 higher)	⊕OOO VERY LOW	
Depress values)	sion sympto	matology	- Switch to TeC	A versus aug	mentation wi	th TeCA (mianser	rin) (follow-up mean 6 we	eks; measured with: HAM	D change	score; Better	indicate	d by lower
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁴	33	32	-	SMD 0.41 higher (0.08 lower to 0.91 higher)	⊕OOO VERY LOW	

randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	reporting bias⁴	197	198	-	SMD 0.38 higher (0.18 to 0.58 higher)	⊕OOO VERY LOW
		on - Switch to S verse events))	SNRI versus sv	vitch to SNR	I augmented with	antipsychotic (follow-up	mean 8 weeks; assessed	d with: Num	ber of people	lost to follo
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	0/46 (0%)	0/49 (0%)	not pooled	not pooled	⊕⊕OO LOW
							0%		not pooled	
trials		inconsistency	indirectness			(35.3%)	(18.8%)	(0.8 to 4.42)	1000 (from 37 fewer to 641 more)	VERY LOW
randomised trials	serious	no serious inconsistency	no serious indirectness	serious ²	reporting bias⁴	12/34 (35.3%)	6/32 (18.8%)	`	1000 (from 37 fewer to	
							18.8%		165 more per 1000 (from 38 fewer to 643 more)	
including ad			antipsychotic v	ersus augm	ientation with antip	sychotic (follow-up 6-8 v	weeks; assessed with: N	umber of pe	eople lost to to	ollow-up (foi
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁴	121/427 (28.3%)	87/431 (20.2%)	RR 1.4 (1.11 to 1.78)	81 more per 1000 (from 22 more to 157 more)	⊕000 VERY LOW
							20.6%		82 more per 1000 (from 23 more to	

randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ⁴	49/228 (21.5%)	47/229 (20.5%)	RR 1.05 (0.73 to 1.49)	10 more per 1000 (from 55 fewer to 101 more)	⊕OOO VERY LOW
							20.5%		10 more per 1000 (from 55 fewer to 100 more)	
tinuation due up due to adv			itch to SNRI ve	ersus switch t	o SNRI augment	ed with antipsychotic (fo	llow-up mean 8 weeks;	assessed with	th: Number of	people lost
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	0/46 (0%)	0/49 (0%)	not pooled	not pooled	⊕⊕OO LOW
							0%		not pooled	
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁴	8/34 (23.5%)	2/32 (6.3%)	RR 3.76 (0.86 to 16.41)	172 more per 1000 (from 9 fewer to 963	⊕OOO VERY LOW
							6.3%		more) 174 more per 1000 (from 9 fewer to 971 more)	
tinuation due adverse even		se events - Sw	itch to antipsy	chotic versus	augmentation w	ith antipsychotic (follow	l -up 6-8 weeks; assesse	ed with: Numb	,	ost to follow
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁴	60/427 (14.1%)	50/431 (11.6%)	RR 1.21 (0.85 to 1.72)	24 more per 1000 (from 17 fewer to 84 more)	⊕OOO VERY LOW
							11.7%		25 more per 1000 (from	

1	randomised trials	no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁴	28/228 (12.3%)		(0.89 to	44 more per 1000 (from 9 fewer to 137 more)	
							7.9%		44 more per 1000 (from 9 fewer to 137 more)	

¹ Risk of bias is unclear or high across multiple domains

8

Switching to another antidepressant of the same class compared to switching to another antidepressant of a different class

			Quality ass	sessment			No of p	patients	ı	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to another antidepressant of the same class	Switch to another antidepressant of a different class	Relative (95% CI)	Absolute		
Remission	on - Switch t	o another	SSRI versus sw	vitch to SNRI (f	ollow-up 12-1	4 weeks; assess	ed with: ≤4/7 on HAM	ID)				
			no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	75/440 (17%)	123/444 (27.7%)	RR 0.61 (0.45 to 0.83)	108 fewer per 1000 (from 47 fewer to 152 fewer)	⊕⊕OO LOW	
								28.1%		110 fewer per 1000 (from 48 fewer to 155 fewer)		

² 95% CI crosses one clinical decision threshold

³ 95% CI crosses two clinical decision thresholds

⁴ Funding from pharmaceutical company

⁵ OIS not met (events<300)

⁶ I2>80%

⁷ OIS not met (N<400)

ı		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	42/238 (17.6%)	51/239 (21.3%)	RR 0.83 (0.57 to 1.19)	36 fewer per 1000 (from 92 fewer to 41 more)	⊕⊕OO LOW	
								21.3%		36 fewer per 1000 (from 92 fewer to 40 more)		
Respons	se - Switch to	another	SSRI versus sw	ritch to SNRI (f	ollow-up meai	n 14 weeks; asses	ssed with: ≥50% imp	rovement on QIDS)				
I		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ²	63/238 (26.5%)	70/250 (28%)	RR 0.95 (0.71 to 1.26)	14 fewer per 1000 (from 81 fewer to 73 more)	⊕OOO VERY LOW	
								28%		14 fewer per 1000 (from 81 fewer to 73 more)		
Respons	se - Switch to	another	SSRI versus sw	vitch to an atyp	ical AD (follow	v-up mean 14 we	eks; assessed with:	≥50% improvement	on QIDS)			
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	63/238 (26.5%)	62/239 (25.9%)	RR 1.02 (0.76 to 1.38)	5 more per 1000 (from 62 fewer to 99 more)	⊕⊕OO LOW	
								25.9%		5 more per 1000 (from 62 fewer to 98 more)		
epress	ion sympton	natology -	Switch to anot	her SSRI versu	s switch to SI	NRI (follow-up me	an 14 weeks; measu	red with: QIDS char	nge score; B	etter indicated	by lower valu	ies)
			no serious	no serious	no serious	reporting bias ²	238	250	-	SMD 0.08	⊕⊕⊕О	
		no serious risk of bias	inconsistency	indirectness	imprecision					lower (0.26 lower to 0.09 higher)	MODERATE	
Depress values)	trials	serious risk of bias	inconsistency	indirectness	·	atypical AD (foll	ow-up mean 14 week	ks; measured with: (QIDS change	lower to 0.09 higher)		ower

		risk of bias								lower to 0.06 higher)		
	inuation for a		n - Switch to an	other SSRI vei	rsus switch to	SNRI (follow-up	mean 12 weeks; ass	essed with: Number	of people lo	st to follow-up	(for any reaso	on
	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	43/206 (20.9%)	49/200 (24.5%)	RR 0.85 (0.59 to 1.22)	37 fewer per 1000 (from 100 fewer to 54 more)	⊕OOO VERY LOW	
								24.5%		37 fewer per 1000 (from 100 fewer to 54 more)		
iscont vents)	inuation due	to advers	se events - Swit	ch to another S	SSRI versus sv	vitch to SNRI (fol	low-up 12-14 weeks	; assessed with: Nur	nber of peop	le lost to follov	v-up due to a	dverse
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ²	61/443 (13.8%)	64/448 (14.3%)	RR 0.99 (0.72 to 1.35)	1 fewer per 1000 (from 40 fewer to 50 more)	⊕OOO VERY LOW	
								13.4%		1 fewer per 1000 (from 38 fewer to 47 more)		
	inuation due events)	to advers	e events - Swit	ch to another S	SSRI versus sv	vitch to an atypic	al AD (follow-up me	an 14 weeks; assess	sed with: Nu	mber of people	lost to follow	-up du
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	50/238 (21%)	65/239 (27.2%)	RR 0.77 (0.56 to 1.07)	63 fewer per 1000 (from 120 fewer to 19 more)	⊕⊕OO LOW	
								27.2%		63 fewer per 1000 (from 120		

¹ OIS not met (events<300)
² Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes
³ 95% CI crosses one clinical decision threshold

 ⁴ 95% CI crosses two clinical decision thresholds
 ⁵ Risk of bias is unclear or high across multiple domains

2 Switching to another antidepressant or non-antidepressant agent (head-to-head comparisons)

	Quality assessment					No of pa	atients		Effect	Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to another antidepressant	Non- antidepressant agent	Relative (95% CI)	Absolute		
Remission	n - Switch to	SSRI vers	us switch to nor	ı-SSRI AD (folio	up 4-14 wee	l eks; assessed wit	l h: ≤4/7/9 on HAMD)					
4	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	102/587 (17.4%)	217/810 (26.8%)	RR 0.62 (0.5 to 0.77)	102 fewer per 1000 (from 62 fewer to 134 fewer)	⊕OOO VERY LOW	
								31.4%		119 fewer per 1000 (from 72 fewer to 157 fewer)		
										,		
Remission	on - Switch to	SSRI vers	sus switch to ant	ipsychotic (foll	ow-up 8-12 we	eks; assessed wi	th: ≤8 on MADRS)			1 /		
Remission 2		very serious ¹	no serious	no serious indirectness	very serious ³	reporting bias ²	th: ≤8 on MADRS) 29/198 (14.6%)	27/203 (13.3%)	RR 1.1 (0.68 to 1.8)	13 more per 1000 (from 43 fewer to 106 more)		
Remission 2	randomised	very	no serious	no serious		·	29/198		(0.68 to	13 more per 1000 (from 43 fewer to	VERY	
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	29/198	(13.3%)	(0.68 to	13 more per 1000 (from 43 fewer to 106 more) 13 more per 1000 (from 43 fewer to	VERY	
2	randomised trials on - Switch to	very serious ¹ D SNRI vers	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	29/198 (14.6%)	(13.3%)	(0.68 to	13 more per 1000 (from 43 fewer to 106 more) 13 more per 1000 (from 43 fewer to	VERY LOW	

2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	94/376 (25%)	27/203 (13.3%)	RR 1.63 (0.97 to 2.76)	84 more per 1000 (from 4 fewer to 234 more)	⊕OOO VERY LOW
								13.4%		84 more per 1000 (from 4 fewer to 236 more)	
Remissi	ion - Switch to	SSRI + an	tipsychotic vers	us switch to S	SRI-only (folio	ow-up 8-12 weeks;	assessed with: ≤8 c	on MADRS)		•	
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	94/376 (25%)	29/198 (14.6%)	RR 1.45 (0.97 to 2.17)	66 more per 1000 (from 4 fewer to 171 more)	⊕OOO VERY LOW
								15.6%		70 more per 1000 (from 5 fewer to 183 more)	
Respon	se - Switch to	SSRI vers	us switch to non	-SSRI AD (folio	w-up 4-14 we	eeks; assessed with	n: ≥50% improveme	nt on HAMD/QIDS	5)	•	
3	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	127/385 (33%)	196/616 (31.8%)	RR 0.91 (0.74 to 1.12)	29 fewer per 1000 (from 83 fewer to 38 more)	⊕OOO VERY LOW
								45%		40 fewer per 1000 (from 117 fewer to 54 more)	
Respon	se - Switch to	SSRI vers	us switch to anti	psychotic (follo	ow-up 8-12 w	eeks; assessed wit	h: ≥50% improveme	ent on MADRS)			
2	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ²	60/198 (30.3%)	43/203 (21.2%)	RR 1.43 (1.02 to 2.01)	91 more per 1000 (from 4 more to 214 more)	⊕OOO VERY LOW
								22.4%		96 more per 1000 (from 4 more to 226 more)	
Respon	se - Switch to	SNRI vers	us switch to aty	oical antidepre	ssant (follow-	up 8-14 weeks; ass	essed with: ≥50% i	mprovement on H	AMD)		
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	102/300 (34%)	94/294 (32%)	RR 1.09 (0.88 to 1.35)	29 more per 1000 (from 38 fewer to 112 more)	⊕⊕OO LOW
								42.1%		38 more per 1000 (from 51 fewer to 147 more)	

	randomised trials	very serious ¹		no serious indirectness	serious ⁵	reporting bias ²	140/376 (37.2%)	43/203 (21.2%)	RR 1.54 (1.13 to 2.1)	114 more per 1000 (from 28 more to 233 more)	⊕OOO VERY LOW
								22.4%		121 more per 1000 (from 29 more to 246 more)	
espo	nse - Switch to	SSRI + ar	ntipsychotic vers	sus switch to S	SRI-only (folio	ow-up 8-12 weeks; as	sessed with: ≥50%	% improvement o	n MADRS)		
!	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	140/376 (37.2%)	60/198 (30.3%)	RR 1.09 (0.82 to 1.47)	27 more per 1000 (from 55 fewer to 142 more)	⊕OOO VERY LOW
								31.4%		28 more per 1000 (from 57 fewer to 148 more)	
espo	nse - Switch to	SSRI vers	sus switch to SN	RI (follow-up n	nean 4 weeks;	assessed with: Muc	n/very much impre	oved on CGI-I)			
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	36/55 (65.5%)	33/52 (63.5%)	RR 1.03 (0.78 to 1.37)	19 more per 1000 (from 140 fewer to 235 more)	⊕OOO VERY LOW
								63.5%		19 more per 1000 (from 140 fewer to 235 more)	
	ssion symptom	atology -	Switch to SSRI v	ersus switch to	o non-SSRI AL) (follow-up 4-14 wee	ks; measured with	h: HAMD/QIDS cl	nange score;	Better indicated b	y lower valu
epre		very	serious ⁶	no serious indirectness	no serious imprecision	reporting bias ²	378	608	-	SMD 0.08 higher (0.18 lower to	⊕OOO VERY
Depre	randomised trials	serious ¹								0.34 higher)	LOW
<u> </u>	trials		Switch to SSRI v	ersus switch to	o antipsychoti	c (follow-up 8-12 wed	eks; measured wit	h: MADRS chang	je score; Bet	,	

		very serious ¹	very serious ⁷	no serious indirectness	serious ⁴	reporting bias ²	389	206	-	SMD 0.44 lower (0.91 lower to 0.03 higher)	⊕OOO VERY LOW
press ues)	sion symptom	atology - S	Switch to SSRI +	antipsychotic	versus switch	to SSRI-only (follow	v-up 8-12 weeks; n	neasured with: M	ADRS chang	e score; Better ind	licated by Ic
		very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	389	202	-	SMD 0.13 lower (0.35 lower to 0.1 higher)	⊕OOO VERY LOW
	inuation for a events))	ny reason	- Switch to SSRI	versus switch	to non-SSRI A	AD (follow-up 4-12 w	eeks; assessed w	ith: Number of po	eople lost to	follow-up (for any	reason inclu
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	70/373 (18.8%)	75/345 (21.7%)	RR 0.86 (0.65 to 1.16)	30 fewer per 1000 (from 76 fewer to 35 more)	⊕OOO VERY LOW
										28 fewer per 1000	
								20.2%		(from 71 fewer to 32 more)	
	inuation for a events))	ny reason	- Switch to SSRI	versus switch	to antipsycho	tic (follow-up 8-12 w	veeks; assessed w		eople lost to	32 more)	reason incl
	events))	ny reason	no serious inconsistency	no serious indirectness	to antipsycho	reporting bias ²	40/202 (19.8%)		RR 0.82 (0.56 to 1.18)	32 more)	⊕000
	randomised	_	no serious	no serious			40/202	vith: Number of p	RR 0.82 (0.56 to	32 more) follow-up (for any 44 fewer per 1000 (from 107 fewer to	⊕OOO VERY
scont	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴		40/202 (19.8%)	50/206 (24.3%) 25.6%	RR 0.82 (0.56 to 1.18)	32 more) follow-up (for any) 44 fewer per 1000 (from 107 fewer to 44 more) 46 fewer per 1000 (from 113 fewer to 46 more)	⊕OOO VERY LOW
dverse	randomised trials inuation for a including adv	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias²	40/202 (19.8%)	50/206 (24.3%) 25.6%	RR 0.82 (0.56 to 1.18)	32 more) follow-up (for any) 44 fewer per 1000 (from 107 fewer to 44 more) 46 fewer per 1000 (from 113 fewer to 46 more)	⊕OOO VERY LOW

2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious⁴	reporting bias ²	90/389 (23.1%)	50/206 (24.3%)	RR 0.89 (0.65 to 1.21)	27 fewer per 1000 (from 85 fewer to 51 more)	⊕000 VERY LOW	
								25.6%		28 fewer per 1000 (from 90 fewer to 54 more)		
	nuation for a g adverse eve		Switch to SSRI	+ antipsychoti	c versus swi	tch to SSRI-only (fol	low-up 8-12 weeks	; assessed with:	Number of po	eople lost to follow	/-up (for a	any reaso
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	90/389 (23.1%)	40/202 (19.8%)	RR 1.12 (0.78 to 1.59)	24 more per 1000 (from 44 fewer to 117 more)	⊕OOO VERY LOW	
								19.9%		24 more per 1000 (from 44 fewer to 117 more)		
Discontine events)	nuation due t	o adverse	events - Switch	to SSRI versus	switch to no	on-SSRI AD (follow-เ	ıp 4-12 weeks; asse	essed with: Numb	er of people	lost to follow-up o	lue to adv	/erse
3	randomised trials	ndomised serious no serious			serious ⁴	reporting bias ²	64/505 (12.7%)	134/748 (17.9%)	RR 0.87 (0.66 to 1.14)	23 fewer per 1000 (from 61 fewer to 25 more)		
								8.2%		11 fewer per 1000 (from 28 fewer to 11 more)		
Disconti events)	nuation due t	o adverse	events - Switch	to SSRI versus	switch to an	tipsychotic (follow-	up 8-12 weeks; ass	essed with: Num	ber of people	lost to follow-up	due to ad	verse
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ²	7/202 (3.5%)	19/206 (9.2%)	RR 0.39 (0.16 to 0.91)	56 fewer per 1000 (from 8 fewer to 77 fewer)	⊕OOO VERY LOW	
								8.9%		54 fewer per 1000 (from 8 fewer to 75 fewer)		
Disconting adverse		o adverse	events - Switch	to SNRI versus	switch to at	ypical antidepressai	nt (follow-up 8-14 w	veeks; assessed v	with: Numbe	of people lost to	follow-up	due to
2		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	53/300 (17.7%)	65/289 (22.5%)	RR 0.78 (0.57 to 1.07)	49 fewer per 1000 (from 97 fewer to 16 more)	⊕⊕OO LOW	

								13.6%		30 fewer per 1000 (from 58 fewer to 10 more)		
	nuation due to adverse ev		events - Switch t	to SSRI + antip	sychotic versu	s switch to antips	sychotic-only (follow	v-up 8-12 weeks; a	issessed wi	th: Number of peo	ple lost to	o follow-
!	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	39/389 (10%)	19/206 (9.2%)	RR 0.98 (0.48 to 2.03)	2 fewer per 1000 (from 48 fewer to 95 more)	⊕000 VERY LOW	
								8.9%		2 fewer per 1000 (from 46 fewer to 92 more)		
	nuation due t events)	to adverse	events - Switch t	to SSRI + antip	sychotic versu	s switch to SSRI-	only (follow-up 8-12	weeks; assessed	with: Numb	per of people lost t	o follow-	up due
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ²	39/389 (10%)	7/202 (3.5%)	RR 2.41 (1.07 to 5.42)	49 more per 1000 (from 2 more to 153 more)	⊕000 VERY LOW	
								3.9%		55 more per 1000 (from 3 more to 172 more)		

¹ Risk of bias is unclear or high across multiple domains

8

Switching to a combined psychological and pharmacological intervention versus switching to a psychological intervention-only

			Quality ass	essment			No of p	atients		Effect	Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to combined psych and pharm intervention	Switching to a psychological intervention-only	Relative (95% CI)	Absolute			

² Funding from pharmaceutical company and/or data is not reported/cannot be extracted for all outcomes

³ 95% CI crosses two clinical decision thresholds

⁴ 95% CI crosses one clinical decision threshold

⁵ OIS not met (events<300)

⁶ I2>50%

⁷ I2>80%

		•	n - CBT individu w-up (for any re	•	,		s CBT individual (und	er 15 sessions)-only	follow-up r	nean 12 weeks; as	ssessed	with:
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	1/11 (9.1%)	6/11 (54.5%)	RR 0.17 (0.02 to 1.17)	453 fewer per 1000 (from 535 fewer to 93 more)		
								54.6%		453 fewer per 1000 (from 535 fewer to 93 more)		

¹ Risk of bias is unclear or high across multiple domains

4

10

Chronic depressive symptoms (chapter 9)

Problem solving versus pill placebo for chronic depressive symptoms

			Quality assess	sment		No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Problem solving	Pill placebo	Relative (95% CI)	Absolute		
Remission	n (follow-up m	nean 11 weeks	s; assessed with: N	Number of people	e scoring <7	on Hamilton Ratin	g Scale for D	Depression	n (HAM-D))			
1	randomised trials			no serious indirectness	serious ¹	reporting bias ²	32/63 (50.8%)	25/62 (40.3%)	RR 1.26 (0.85 to 1.86)	105 more per 1000 (from 60 fewer to 347 more)	⊕⊕OO LOW	
								40.3%		105 more per 1000 (from 60 fewer to 347 more)		

¹ 95% CI crosses one clinical decision threshold

Problem solving versus antidepressant for dysthymia

Quality assessment	No of patients	Effect	Quality Importance

² 95% CI crosses one clinical decision threshold

³ Study funded by pharmaceutical company and data is not reported for all outcomes

² Authors have some financial interests in pharmaceutical companies

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Problem solving	Antidepressant	Relative (95% CI)	Absolute	
Remissio	n - Problem s	olving versu	s paroxetine (folio	w-up mean 11 w	veeks; asses	sed with: <7 on H	AM-D)				
1				no serious indirectness	serious ¹	reporting bias ²	32/63 (50.8%)	26/57 (45.6%)		50 more per 1000 (from 105 fewer to 283 more)	
								45.6%		50 more per 1000 (from 105 fewer to 283 more)	

¹ 95% CI crosses one clinical decision threshold

Cognitive and cognitive behavioural therapies versus pill placebo for chronic depressive symptoms

			Quality asse	essment			No of patients			Effect	Quality	Importan
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies (individual)	Pill placebo	Relative (95% CI)	Absolute		importan-
emissio	n - CBT indiv	idual (ov	er 15 sessions) v	ersus pill placel	bo (follow-up	mean 16 weeks;	assessed with: <7 on HAM	1-D)		<u> </u>		
		very serious ¹		no serious indirectness	very serious ²	reporting bias ³	6/16 (37.5%)	4/15 (26.7%)	RR 1.41 (0.49 to 4.02)	109 more per 1000 (from 136 fewer to 805 more)	⊕OOO VERY LOW	
								26.7%		109 more per 1000 (from 136 fewer to 806 more)		
epression	on symptoma	atology - (CBT individual (o	ver 15 sessions) versus pill	placebo (follow-u	p mean 16 weeks; measur	ed with: H	AM-D chan	ge score; Better indi	cated by	lower
		very serious ¹		no serious indirectness	very serious ²	reporting bias ³	16	15	-	SMD 0.2 lower (0.91 lower to 0.51 higher)	⊕OOO VERY LOW	

² Authors have some financial interests in pharmaceutical companies

1	randomised trials	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	0/16 (0%)	0/15 (0%)	not pooled	not pooled	⊕000 VERY LOW	
							0%		not pooled		

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses two clinical decision thresholds

Cognitive and cognitive hehavioural theranies versus antidenressant for chronic depressive symptoms

Cogniti	ve and co	gnitive b	ehavioural th	nerapies ver	sus antide	pressant for c	hronic depressiv	e symptoms				
			Quality ass	essment			No of pa	itients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies (individual)	Antidepressants	Relative (95% CI)	Absolute	Quality	Importance
						us any AD) (follow g Scale (MADRS)	v-up 8-16 weeks; ass)	sessed with: Num	ber of peop	ole scoring <7/≤8	on Hamiltor	Rating
	trials	no serious risk of bias	serious ¹	no serious indirectness	very serious ²	reporting bias ³	79/261 (30.3%)	78/264 (29.5%)	RR 0.76 (0.37 to 1.55)	71 fewer per 1000 (from 186 fewer to 162 more)	⊕000 VERY LOW	
								29.1%		70 fewer per 1000 (from 183 fewer to 160 more)		
Remission	on (CBASP v	ersus nefa	zodone) (follow-	up mean 12 we	eeks; assesse	d with: Number o	f people scoring ≤8	on Hamilton Ratin	g Scale for	Depression (HA	M-D))	
	trials		no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	72/216 (33.3%)	64/220 (29.1%)	RR 1.15 (0.87 to 1.52)	44 more per 1000 (from 38 fewer to 151 more)	⊕⊕OO LOW	
								29.1%		44 more per 1000 (from 38 fewer to 151 more)		

³ Data is not reported or cannot be extracted for all outcomes

⁴ OIS not met (events<300)

	randomised	serious ⁵	no serious	no serious	very serious ²	reporting bias3	1/29	5/30	RR 0.21	132 fewer per	⊕OOO	
	trials		inconsistency	indirectness		, , , , , , , , , , , , , , , , , , ,	(3.4%)	(16.7%)	(0.03 to 1.67)	1000 (from 162 fewer to 112 more)		
								16.7%		132 fewer per 1000 (from 162 fewer to 112 more)		
niss	sion (CBT vers	sus imipra	mine) (follow-up	mean 16 week	ks; assessed w	ith: Number of pe	eople scoring <7 on	HAM-D)		,		
	randomised trials	very serious ⁵	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	6/16 (37.5%)	9/14 (64.3%)	RR 0.58 (0.28 to 1.23)	270 fewer per 1000 (from 463 fewer to 148 more)	⊕OOO VERY LOW	
										270 fewer per 1000 (from 463		
								64.3%		fewer to 148 more)		
							r-up 8-12 weeks; ass n Montgomery Asbe	sessed with: Num		fewer to 148 more) le showing ≥50%	improvemen	t on
	on Rating Sca		ression (HAM-D)					sessed with: Num		fewer to 148 more) le showing ≥50%	⊕OOO VERY LOW	t on
milto	randomised trials	no serious risk of bias	ression (HAM-D	no serious indirectness	very serious²	reporting bias ³	33/245 (13.5%)	sessed with: Numrg Depression Ra 49/250 (19.6%)	RR 0.56 (0.21 to 1.49)	fewer to 148 more) le showing ≥50% MADRS)) 86 fewer per 1000 (from 155 fewer to 96 more) 100 fewer per 1000 (from 179 fewer to 111 more)	⊕OOO VERY LOW	
spor	randomised trials	no serious risk of bias	ression (HAM-D	no serious indirectness	very serious²	reporting bias ³	Montgomery Asbe	sessed with: Numrg Depression Ra 49/250 (19.6%)	RR 0.56 (0.21 to 1.49)	fewer to 148 more) le showing ≥50% MADRS)) 86 fewer per 1000 (from 155 fewer to 96 more) 100 fewer per 1000 (from 179 fewer to 111 more)	⊕OOO VERY LOW	
spor	randomised trials	no serious risk of bias ersus nefa	ression (HAM-D	no serious indirectness	very serious²	reporting bias ³	33/245 (13.5%)	sessed with: Numrg Depression Ra 49/250 (19.6%)	RR 0.56 (0.21 to 1.49)	fewer to 148 more) le showing ≥50% MADRS)) 86 fewer per 1000 (from 155 fewer to 96 more) 100 fewer per 1000 (from 179 fewer to 111 more)	⊕OOO VERY LOW	

										fewer to 33		
										more)		
pon: DRS		ersus esci	talopram) (follo	w-up mean 8 w	eeks; assesse	ed with: Number of	people showing ≥5	60% improvemen	t on Montgo	mery Asberg De	pression Ratin	g Sc
	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	2/29 (6.9%)	8/30 (26.7%)	RR 0.26 (0.06 to 1.12)	197 fewer per 1000 (from 251 fewer to 32 more)	⊕OOO VERY LOW	
								26.7%		198 fewer per 1000 (from 251 fewer to 32 more)		
	sion sympton d by lower va		any cognitive or	cognitive beh	avioural thera	py [individual] vers	us any AD) (follow-	-up 12-16 weeks;	measured v	vith: HAMD chan	ge score; Bette	er
	randomised trials	serious ⁵	serious ¹	no serious indirectness	serious ⁴	none	242	252	-	SMD 0.25 higher (0.4 lower to 0.91 higher)	⊕OOO VERY LOW	
	ion sympton r values)	natology (CBASP versus i	nefazodone) (fo	ollow-up mean	12 weeks; measure	ed with: Hamilton F	_ Rating Scale for [Depression (∐ (HAM-D; change∍	score); Better i	indic
	,							3	·			
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	216	220	-	SMD 0.11 higher (0.08 lower to 0.3 higher)	⊕⊕⊕O MODERATE	
epress	randomised trials	risk of bias	inconsistency	indirectness	imprecision	reporting bias ³ /eeks; measured wi	216	220	-	higher (0.08 lower to 0.3 higher)	MODERATE	ated
	randomised trials	risk of bias natology (inconsistency	indirectness	imprecision		216	220	-	higher (0.08 lower to 0.3 higher)	MODERATE	ated
epress ower va	randomised trials sion symptonalues) randomised trials	risk of bias natology (f	no serious inconsistency	no serious indirectness	-up mean 16 w	veeks; measured wi	216 Ith: Hamilton Rating	220 g Scale for Depre	ession (HAM	higher (0.08 lower to 0.3 higher) -D; change score SMD 1.3 higher (0.36 to 2.24 higher)	MODERATE a); Better indic aheron	ated

	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	63/291 (21.6%)	73/290 (25.2%)	RR 0.83 (0.45 to 1.52)	43 fewer per 1000 (from 138 fewer to 131 more)	⊕OOO VERY LOW
								24.6%		42 fewer per 1000 (from 135 fewer to 128 more)	
iscor vents		ıny reasor	(CBASP versus	s nefazodone)	(follow-up mea	n 12 weeks; asse	ssed with: Number o	of participants di	scontinuing	for any reason i	ncluding adve
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	55/228 (24.1%)	59/226 (26.1%)	RR 0.92 (0.67 to 1.27)	21 fewer per 1000 (from 86 fewer to 70 more)	⊕000 VERY LOW
								26.1%		21 fewer per 1000 (from 86 fewer to 70 more)	
Discor events		ıny reasor	ı (CBASP versus	s escitalopram)	(follow-up me	an 8 weeks; asse	ssed with: Number	of participants di	scontinuing	for any reason i	ncluding adve
l	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	2/29 (6.9%)	5/31 (16.1%)	RR 0.43 (0.09 to 2.03)	92 fewer per 1000 (from 147 fewer to 166 more)	⊕OOO VERY LOW
								16.1%		92 fewer per 1000 (from 147 fewer to 166 more)	
Discor	tinuation for a	ıny reasor	(CBT versus fl	uoxetine) (follo	w-up mean 16	weeks; assessed	with: Number of pa	rticipants discon	tinuing for a	ny reason inclu	ling adverse e
	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	very serious ²	none	6/18 (33.3%)	3/13 (23.1%)	RR 1.44 (0.44 to	102 more per 1000 (from 129	⊕000 VERY LOW

								23.1%		102 more per 1000 (from 129 fewer to 864 more)		
Disconti	nuation for a	ny reason	(CBT versus imi	pramine) (follo	w-up mean 16	S weeks; assesse	d with: Number of pa	rticipants discon	tinuing for	any reason inclu	uding advers	e events)
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	0/16 (0%)	6/20 (30%)	RR 0.1 (0.01 to 1.57)	270 fewer per 1000 (from 297 fewer to 171 more)	⊕000 VERY LOW	
								30%		270 fewer per 1000 (from 297 fewer to 171 more)		
Disconti	nuation due t	to adverse	events (CBASP	versus nefazo	done) (follow-	up mean 12 week	s; assessed with: Nเ	imber of participa	ınts discon	itinuing due to a	dverse event	s)
			no serious inconsistency	no serious indirectness	serious ⁷	reporting bias ³	3/228 (1.3%)	31/226 (13.7%)	RR 0.1 (0.03 to 0.31)	123 fewer per 1000 (from 95 fewer to 133 fewer)	⊕⊕OO LOW	
110 - 200								13.7%		123 fewer per 1000 (from 95 fewer to 133 fewer)		

¹ I2=>50%

8

5

Cognitive and cognitive behavioural therapies versus other psychological interventions for chronic depressive symptoms

Quality assessment	No of patients	Effect	Quality	Importance

² 95% CI crosses two clinical decision thresholds

³ Funding from pharmaceutical company and/or data is not reported/cannot be extracted for all outcomes ⁴ 95% CI crosses one clinical decision threshold

⁵ Risk of bias is unclear or high across multiple domains

⁶ OIS not met (N<400)

⁷ OIS not met (events<300)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies (individual)	Other psych intervention	Relative (95% CI)	Absolute		
Remission	on (any cogn	itive or cog	nitive behaviou	ral therapy vers	sus any other	r psych) (follow-	up mean 16 weeks; ass	sessed with: sc	ore ≤8 on H	AM-D)		
	randomised trials	,	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	14/30 (46.7%)	8/29 (27.6%)	RR 1.66 (0.62 to 4.43)	182 more per 1000 (from 105 fewer to 946 more)	⊕OOO VERY LOW	
								27.9%		184 more per 1000 (from 106 fewer to 957 more)		
Remission	on (CBASP v	ersus IPT)	(follow-up mean	16 weeks; ass	essed with: N	Number of people	e scoring ≤8 on Hamilt	on Rating Scale	for Depres	ssion (HAM-D))		
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	none	8/14 (57.1%)	3/15 (20%)	RR 2.86 (0.94 to 8.66)	372 more per 1000 (from 12 fewer to 1000 more)	⊕⊕⊕O MODERATE	
								20%		372 more per 1000 (from 12 fewer to 1000 more)		
Remission	on (CBT vers	us IPT) (fol	low-up mean 16	weeks; assess	ed with: sco	re ≤8 on HAM-D)					<u>'</u>	
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	6/16 (37.5%)	5/14 (35.7%)	RR 1.05 (0.41 to 2.7)	18 more per 1000 (from 211 fewer to 607 more)	⊕OOO VERY LOW	
								35.7%		18 more per 1000 (from 211 fewer to 607 more)		
Respons HAMD so		ersus IPT) (follow-up mean	16 weeks; asse	essed with: N	umber of people	showing ≥50% improv	ement on Ham	ilton Rating	Scale for Depres	ssion (HAM-D) AND
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	none	9/14 (64.3%)	4/15 (26.7%)	RR 2.41 (0.96 to 6.08)	376 more per 1000 (from 11 fewer to 1000 more)	⊕⊕⊕O MODERATE	

								26.7%		376 more per 1000 (from 11 fewer to 1000 more)		
	ion symptom d by lower va		ny cognitive or o	cognitive behav	vioural thera	py versus any oth	ner psych) (follow-up n	nean 16 weeks	measured v	with: HAMD chan	ge score; Bet	ter
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	30	29	-	SMD 0.58 lower (1.16 lower to 0 higher)	⊕OOO VERY LOW	
epress alues)	ion symptom	atology (C	BASP versus IP	T) (follow-up m	ean 16 weel	ks; measured with	n: Hamilton Rating Sca	le for Depressi	on (HAM-D;	change score); B	Setter indicate	d by low
	randomised trials		no serious inconsistency	no serious indirectness	serious ⁵	none	14	15	-	SMD 0.89 lower (1.66 to 0.12 lower)	⊕⊕⊕O MODERATE	
epress	ion symptom	atology (C	BT versus IPT) ((follow-up mea	n 16 weeks;	measured with: H	IAMD change score; Be	etter indicated	by lower val	lues)	<u> </u>	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	16	14	-	SMD 0.3 lower (1.02 lower to 0.43 higher)	⊕000 VERY LOW	
			(any cognitive o cluding adverse		avioural the	rapy versus any o	other psych) (follow-up	mean 16 week	(s; assessed	l d with: Number of	participants	
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	2/31 (6.5%)	2/29 (6.9%)	RR 1 (0.16 to 6.2)	0 fewer per 1000 (from 58 fewer to 359 more)	⊕⊕OO LOW	
								6.7%	-	0 fewer per 1000 (from 56 fewer to 348 more)		
isconti	nuation for a	ny reason	CBASP versus	IPT) (follow-up	mean 16 we	eks; assessed wi	ith: Number of particip	ants discontini	uing for any	reason including	adverse ever	nts)
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	2/15 (13.3%)	2/15 (13.3%)	RR 1 (0.16 to 6.2)	0 fewer per 1000 (from 112 fewer to 693 more)	⊕⊕OO LOW	
								13.3%		0 fewer per 1000 (from 112 fewer to 692 more)		

Discont	inuation for a	iny reason	(CBT versus IP)	Γ) (follow-up m	ean 16 week	s; assessed with:	Number of participant	s discontinuing	for any rea	son including ad	lverse events	3)
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ³	0/16 (0%)	0/14 (0%)	not pooled	not pooled	⊕OOO VERY LOW	
								0%		not pooled		

¹ Risk of bias is unclear or high across multiple domains

7 Cognitive and cognitive behavioural therapies + TAU/AD versus TAU/AD-only for chronic depressive symptoms

			Quality ass	sessment			No of patients			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies (individual) + TAU/AD	TAU/AD- only	Relative (95% CI)	Absolute		
	on (any cogn 13 on IDS)	itive or cog	gnitive behaviou	ral therapy [ind	ividual] + TAU	AD versus TAU/	AD-only) (follow-up 12-52	weeks; as	sessed wit	h: Number of peo	ple scoring	≤8 on
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	122/293 (41.6%)	72/291 (24.7%)	RR 1.66 (1.31 to 2.11)	163 more per 1000 (from 77 more to 275 more)	⊕⊕OO LOW	
								20.2%		133 more per 1000 (from 63 more to 224 more)		
Remission	on (CBASP +	nefazodor	ne versus nefazo	done) (follow-u	p mean 12 wee	eks; assessed wi	th: Number of people sco	ring ≤8 on	HAMD)			
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	109/226 (48.2%)	64/220 (29.1%)	RR 1.66 (1.3 to 2.12)	192 more per 1000 (from 87 more to 326 more)	⊕⊕OO LOW	
								29.1%		192 more per 1000 (from 87		

² 95% CI crosses two clinical decision thresholds

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ 95% CI crosses one clinical decision threshold

⁵ OIS not met (N<400)

⁶ OIS not met (events<300)

									more to 326 more)	
sion (CBASF	+ TAU versu	ıs TAU) (follow-	up mean 52 we	eks; assesse	ed with: Number of peo	pple scoring ≤13 on	Inventory of	Depressive	,	
		, ,	<u> </u>			<u> </u>		•		
randomise trials	d very serious ³	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	13/67 (19.4%)	8/71 (11.3%)	RR 1.72 (0.76 to 3.89)	81 more per 1000 (from 27 fewer to 326 more)	⊕OOO VERY LOW
							11.3%		81 more per 1000 (from 27 fewer to 327 more)	
					AU/AD versus TAU/AD- ≥50% improvement on		-52 weeks; as	sessed wit	h: Number of peo	ple showing ≥50
rement on m	WID GITANIE	7 30016 0-10 [16.	sponse without	remission _j ,	200 / Improvement on	150)				
randomise trials		no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	77/293 (26.3%)	57/292 (19.5%)	RR 1.35 (1 to 1.83)	68 more per 1000 (from 0 more to 162 more)	⊕⊕OO LOW
									71 more per 1000	
							20.4%		(from 0 more to 169 more)	
nse (CBASP	emission))		odone) (follow-	up mean 12 v	veeks; assessed with:	Number of people s		improvem	(from 0 more to 169 more)	AMD score 8-15
	emission))		no serious indirectness	up mean 12 v	veeks; assessed with:	Number of people s 56/226 (24.8%)		RR 1.33 (0.93 to 1.9)	(from 0 more to 169 more)	<u>, </u>
randomise trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	56/226 (24.8%)	41/220 (18.6%)	RR 1.33 (0.93 to 1.9)	(from 0 more to 169 more) nent on HAMD & H 61 more per 1000 (from 13 fewer to	⊕⊕OO
randomise trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴		56/226 (24.8%)	41/220 (18.6%)	RR 1.33 (0.93 to 1.9)	(from 0 more to 169 more) nent on HAMD & H 61 more per 1000 (from 13 fewer to 168 more) 61 more per 1000 (from 13 fewer to	⊕⊕OO
randomise trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	56/226 (24.8%)	41/220 (18.6%)	RR 1.33 (0.93 to 1.9) on IDS)	(from 0 more to 169 more) nent on HAMD & H 61 more per 1000 (from 13 fewer to 168 more) 61 more per 1000 (from 13 fewer to	⊕⊕00 LOW

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	277	273	-	SMD 0.7 lower (0.93 to 0.47 lower)	⊕⊕⊕O MODERATE	
Depress	ion symptom	atology (Cl	BASP + nefazoo	lone versus ne	fazodone) (foll	ow-up mean 12 w	eeks; measured with: I	HAMD chang	e score; Be	etter indicated by	lower values)
		no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	226	220	-	SMD 0.77 lower (0.97 to 0.58 lower)	⊕⊕⊕O MODERATE	
epress	ion symptom	atology (Cl	BASP + TAU ve	rsus TAU) (folio	ow-up mean 52	2 weeks; measured	d with: IDS change sco	ore; Better in	dicated by	lower values)		
	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ²	51	53	-	SMD 0.51 lower (0.9 to 0.12 lower)	⊕OOO VERY LOW	
			l (any cognitive only ny reason includ			py [individual] + T	AU/AD versus TAU/AD)-only) (follow	v-up 12-52	weeks; assessed	with: Numbe	r of
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	64/294 (21.8%)	78/298 (26.2%)	RR 0.83 (0.62 to 1.11)	44 fewer per 1000 (from 99 fewer to 29 more)	⊕⊕OO LOW	
								26.3%		45 fewer per 1000 (from 100 fewer to 29 more)		
	nuation for a events)	ny reason (CBASP + nefaz	odone versus i	nefazodone) (f	ollow-up mean 12	weeks; assessed with	: Number of _l	participant	s discontinuing fo	r any reason	includ
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	48/227 (21.1%)	59/226 (26.1%)	RR 0.81 (0.58 to 1.13)	50 fewer per 1000 (from 110 fewer to 34 more)	⊕⊕OO LOW	
								26.1%		50 fewer per 1000 (from 110 fewer to 34 more)		
isconti vents)	nuation for a	ny reason (CBASP + TAU	versus TAU) (fo	ollow-up mean	52 weeks; assess	ed with: Number of pa	rticipants dis	continuing	g for any reason ir	cluding adve	erse
	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁶	reporting bias ²	16/67 (23.9%)	19/72 (26.4%)	RR 0.9 (0.51 to 1.61)	26 fewer per 1000 (from 129 fewer to 161 more)	⊕OOO VERY LOW	

CBASP (maintenance treatment) versus assessment-only for relapse prevention in chronic depressive symptoms

			Quality ass	essment			No of pat	ients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBASP (maintenance treatment)	Assessment- only	Relative (95% CI)	Absolute		
Relapse (follow-up me	ean 52 we	eks; assessed wi	th: Number of p	eople scoring	g ≥16 on Hamiltor	Rating Scale for D	epression (HAN	1-D) on 2 cor	secutive visits AND	meeting	DSM-IV
	or a diagnosis	s of MDD)			·	-	· ·		·		ŭ	
	<u> </u>	very serious ¹	no serious	no serious indirectness	serious ²	reporting bias ³	1/42 (2.4%)	8/40 (20%)	RR 0.12 (0.02 to 0.91)	176 fewer per 1000 (from 18 fewer to 196 fewer)	⊕OOO VERY LOW	

² Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

³ Risk of bias is unclear or high across multiple domains

⁴ 95% CI crosses one clinical decision threshold

⁵ OIS not met (N<400)

⁶ 95% CI crosses two clinical decision thresholds

1			no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	42	40	-	SMD 0.91 lower (1.37 to 0.45 lower)	⊕OOO VERY LOW	
Disconti	nuation for ar	ny reason	(follow-up mean	52 weeks; asses	ssed with: N	umber of participa	nts discontinuing fo	or any reason i	ncluding adv	verse events)		
1			no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	10/42 (23.8%)	11/40 (27.5%)	RR 0.87 (0.41 to 1.81)	36 fewer per 1000 (from 162 fewer to 223 more)	⊕OOO VERY LOW	
								27.5%		36 fewer per 1000 (from 162 fewer to 223 more)		

¹ Risk of bias is unclear or high across multiple domains
² OIS not met (events<300)
³ Funding from pharmaceutical company
⁴ OIS not met (N<400)
⁵ 95% CI crosses two clinical decision thresholds

CBT+ fluoxetine (dose increase) versus fluoxetine (dose increase) for relapse prevention in chronic depressive symptoms

			Quality asse	essment			No of pa	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + fluoxetine (dose increase)		Relative (95% CI)	Absolute		
Relapse	(follow-up me	an 28 wee	eks; assessed wit	h: ≥15 on HAMI	on 2 conse	cutive visits or DS	SM-III-R MDD)				•	
1		very serious ¹	no serious inconsistency	no serious indirectness	very serious²	reporting bias ³	27/66 (40.9%)	29/66 (43.9%)	RR 0.93 (0.63 to 1.39)	31 fewer per 1000 (from 163 fewer to 171 more)	#000 VERY LOW	
								43.9%		31 fewer per 1000 (from 162 fewer to 171 more)		
Depressi	on symptoma	tology (fo	ollow-up mean 28	weeks; measur	ed with: HAN	ID change score;	Better indicated b	y lower values)			•	
1		very serious¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	66	66	-	SMD 0.18 lower (0.52 lower to 0.16 higher)	⊕000 VERY LOW	

Disconti	nuation for an	y reason	(follow-up mean	28 weeks; asses	sed with: N	umber of participa	nts discontinuing	for any reason i	including adv	verse events)		
1	randomised trials	- ,	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	23/66 (34.8%)	24/66 (36.4%)	RR 0.96 (0.61 to 1.52)	15 fewer per 1000 (from 142 fewer to 189 more)	⊕000 VERY LOW	
								36.4%		15 fewer per 1000 (from 142 fewer to 189 more)		
Disconti	nuation due to	adverse	events (follow-up	mean 28 week	s; assessed	with: Number of p	articipants discor	ntinuing due to a	dverse even	ts)		
1	randomised trials	- ,	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	3/66 (4.5%)	1/66 (1.5%)	RR 3 (0.32 to 28.1)	30 more per 1000 (from 10 fewer to 411 more)	⊕000 VERY LOW	
								1.5%		30 more per 1000 (from 10 fewer to 406 more)		

¹ Risk of bias is unclear or high across multiple domains

Behavioural, cognitive, or CBT groups + TAU/AD versus TAU/AD-only for chronic depressive symptoms

			Quality asso	essment			No of patients	1		Effect	Quality	Importance
No of studies	Design	ign Risk of bias Inconsistency Inconstruction		Indirectness	Imprecision	Other	Behavioural, cognitive, or CBT groups + TAU/AD	TAU/AD- only	Relative (95% CI)	Absolute		
Remissio	n (MBCT+TA	U versus	TAU) (follow-up r	nean 8 weeks; a	ssessed with	n: Number of part	icipants scoring ≤13 on	BDI-II & ≥5	0% improver	ment on BDI-II/<7 on	HAMD)	
				no serious indirectness	serious ²	none	12/52 (23.1%)	3/50 (6%)	RR 3.72 (1.1 to 12.54)	163 more per 1000 (from 6 more to 692 more)	⊕OOO VERY LOW	
								6.2%		169 more per 1000 (from 6 more to 715 more)		
Remissio	n (CBASP (g	roup) + T/	AU versus TAU) (follow-up mean	8 weeks; ass	sessed with: Num	ber of participants scori	ng <7 on H	HAMD)			

² 95% CI crosses two clinical decision thresholds

Study partially funded by pharmaceutical company
 95% CI crosses one clinical decision threshold

1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	9/35 (25.7%)	2/35 (5.7%) 5.7%	RR 4.5 (1.05 to 19.35)	(from 3 more to 1000 more) 199 more per 1000 (from 3 more to 1000	⊕OOO VERY LOW	
Depression	on symptoma	atology (N	/IBCT+TAU versu	s TAU) (follow-i	up 8-12 wee	ks: measured with	n: BDI-II/HAMD change	score: Bette	r indicated by	more)		
-								· ·				
4	randomised trials	very serious ¹	serious ³	no serious indirectness	serious ⁴	none	78	83	-	SMD 1.21 lower (1.93 to 0.5 lower)	⊕000 VERY LOW	
Depressi	on symptoma	atology (C	BT (group) + TA	U versus waitlis	t + TAU) (fo	llow-up mean 10 v	weeks; measured with:	BDI change	score; Better	indicated by lower v	alues)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	48	40	-	SMD 0.85 lower (1.29 to 0.41 lower)	⊕000 VERY LOW	
Depressi	on symptoma	atology (C	BASP (group) +	TAU versus TAI	J) (follow-u	mean 8 weeks; r	measured with: HAMD	change score	e; Better indic	cated by lower values	5)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	28	32	-	SMD 1.29 lower (1.85 to 0.73 lower)	⊕000 VERY LOW	
Discontin	uation for ar	ny reason	(MBCT+TAU ver	sus TAU) (follow	v-up 8-12 we	eeks; assessed wi	ith: Number of participa	ants disconti	l nuing for any	reason including ad	lverse eve	ents)
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	none	18/91 (19.8%)	7/89 (7.9%)	RR 2.01 (0.74 to 5.44)	79 more per 1000 (from 20 fewer to 349 more)	⊕000 VERY LOW	
								9.3%		94 more per 1000 (from 24 fewer to 413 more)		
Discontir adverse		ny reason	(CBT (group) + 1	AU versus wait	list + TAU) (follow-up mean 1	0 weeks; assessed with	n: Number of	participants	discontinuing for an	y reason	including
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	0/48 (0%)	8/48 (16.7%)	RR 0.06 (0 to 0.99)	157 fewer per 1000 (from 2 fewer to 167 fewer)	⊕⊕OO LOW	
								16.7%		157 fewer per 1000 (from 2 fewer to 167 fewer)		

Discontine events)	nuation for ar	y reason	(CBASP (group)	+ TAU versus T	AU) (follow-ı	up mean 8 weeks;	assessed with: Number	of particip	ants discont	inuing for any reaso	n includir	ng adverse
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	10/35 (28.6%)	1/35 (2.9%)	RR 10 (1.35 to 74)	257 more per 1000 (from 10 more to 1000 more)	⊕OOO VERY LOW	
								2.9%		261 more per 1000 (from 10 more to 1000 more)		

¹ Risk of bias was unclear or high across multiple domains ² OIS not met (events<300)

IPT versus pill placebo for chronic depressive symptoms

	· ·		Quality asse	essment			No of	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Pill placebo	Relative (95% CI)	Absolute		
Remission	(follow-up m	ean 16 wee	eks; assessed with	Number of partic	cipants scorir	ng <7 on HAM-D)						
1	randomised trials	· ,	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	5/14 (35.7%)	4/15 (26.7%)	RR 1.34 (0.45 to 4)	91 more per 1000 (from 147 fewer to 800 more)	⊕OOO VERY LOW	
								26.7%		91 more per 1000 (from 147 fewer to 801 more)		
Depressio	n symptomate	ology (follo	w-up mean 16 wee	ks; measured wit	h: HAM-D cha	ange score; Better	indicate	d by lower	r values)			
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	14	15	-	SMD 0.14 higher (0.59 lower to 0.87 higher)	⊕000 VERY LOW	
Discontinu	uation for any	reason (fo	llow-up mean 16 w	eeks; assessed w	ith: Number	of participants dis	continui	ng for any	reason inclu	ding adverse events)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	0/14 (0%)	0/15 (0%)	not pooled	not pooled	⊕OOO VERY LOW	
								0%		not pooled		

³ I2>50%

⁴ OIS not met (N<400) ⁵ 95% CI crosses two clinical decision thresholds

- ¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses two clinical decision thresholds
- ³ Data is not reported or cannot be extracted for all outcomes
- ⁴ OIS not met (events<300)

IPT versus antidepressant for chronic hypertension

			Quality as	sessment			No	of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Antidepressant	Relative (95% CI)	Absolute		
Remissio	n (IPT versus	any antid	epressant) (follow	-up mean 16 we	eks; assessed w	vith: score <7 on H	IAM-D &	>50% improven	nent on HAME	& GAF score>70/<7 H	AM-D only	/)
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	10/37 (27%)	19/38 (50%)	RR 0.54 (0.3 to 0.99)	230 fewer per 1000 (from 5 fewer to 350 fewer)	⊕000 VERY LOW	
								53%		244 fewer per 1000 (from 5 fewer to 371 fewer)		
	n (IPT versus AND GAF sc) (follow-up mean	16 weeks; asses	ssed with: Numb	per of people scori	ing <7 o	n Hamilton Ratir	ng Scale for D	epression (HAM-D) ANI	O >50% in	nprovement
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	5/23 (21.7%)	10/24 (41.7%)	RR 0.52 (0.21 to 1.29)	200 fewer per 1000 (from 329 fewer to 121 more)	⊕000 VERY LOW	
	trials	serious ¹	inconsistency	indirectness	,		(21.7%)	(41.7%) 41.7%	(0.21 to 1.29)	(from 329 fewer to 121 more) 200 fewer per 1000 (from 329 fewer to 121 more)	VERY	
	trials	serious ¹	inconsistency	indirectness	,		(21.7%)	(41.7%) 41.7%	(0.21 to 1.29)	(from 329 fewer to 121 more) 200 fewer per 1000 (from 329 fewer to 121	VERY	
Remission 1	trials	serious ¹	inconsistency ne) (follow-up mea	indirectness	,		(21.7%)	(41.7%) 41.7% on Hamilton Ra	(0.21 to 1.29)	(from 329 fewer to 121 more) 200 fewer per 1000 (from 329 fewer to 121 more)	VERY	

	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	91/201 (45.3%)	131/220 (59.5%)	RR 0.76 (0.63 to 0.92)	143 fewer per 1000 (from 48 fewer to 220 fewer)	⊕OOO VERY LOW
								59%		142 fewer per 1000 (from 47 fewer to 218 fewer)	
epressi	on symptoma	tology (IP	T versus any ant	depressant) (fol	low-up 16-26 we	eks; measured wi	th: MADRS	HAMD chang	ge score; Bette	r indicated by lower val	ues)
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	215	240	-	SMD 0.43 higher (0.12 to 0.74 higher)	⊕OOO VERY LOW
epressi	on symptoma	tology (IP	T versus sertralii	ne) (follow-up 16	-26 weeks; meas	sured with: MADR	S/HAMD ch	ange score;	Better indicated	d by lower values)	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	201	220	-	SMD 0.49 higher (0.24 to 0.74 higher)	⊕OOO VERY LOW
epressi	on symptoma	tology (IP	T versus imipran	nine) (follow-up i	mean 16 weeks;	measured with: H	AMD chang	e score; Bett	ter indicated by	lower values)	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	14	20	-	SMD 0.02 lower (0.7 lower to 0.67 higher)	⊕OOO VERY LOW
iscontir /ents)	nuation for an	y reason (IPT versus any a	ntidepressant) (1	follow-up mean '	16 weeks; assesse	ed with: Nu	mber of parti	cipants discon	inuing for any reason in	ncluding adve
Julio)											
· onto	randomised trials	very serious ¹	serious ⁶	no serious indirectness	very serious ⁴	reporting bias ³	4/37 (10.8%)	11/44 (25%)	RR 0.43 (0.06 to 3.27)	142 fewer per 1000 (from 235 fewer to 567 more)	⊕OOO VERY LOW
vonta)			serious ⁶		very serious ⁴	reporting bias ³				(from 235 fewer to 567	VERY
	trials	serious ¹		indirectness	·		(10.8%)	(25%) 25.4%	(0.06 to 3.27)	(from 235 fewer to 567 more) 145 fewer per 1000 (from 239 fewer to 577	VERY LOW
	trials	serious ¹		indirectness	·		(10.8%)	(25%) 25.4%	(0.06 to 3.27) scontinuing for RR 0.83	(from 235 fewer to 567 more) 145 fewer per 1000 (from 239 fewer to 577 more) any reason including a 35 fewer per 1000 (from	VERY LOW

1	randomised	serious ¹	no serious	no serious	very serious4	reporting bias3	0/14	6/20	RR 0.11	267 fewer per 1000	\oplus OOO	
	trials		inconsistency	indirectness			(0%)	(30%)	(0.01 to 1.77)	(from 297 fewer to 231	VERY	
										more)	LOW	
										267 fewer per 1000		
								30%		(from 297 fewer to 231		
										more)		

¹ Risk of bias is unclear or high across multiple domains

5

IPT versus brief supportive psychotherapy (BSP) for chronic depressive symptoms

			Quality asse	essment				No of patients		Effect	Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Brief supportive psychotherapy (BSP)	Relative (95% CI)	Absolute		
temissio core>70)	•	nean 16 w	eeks; assessed v	vith: Number of	people scori	ng <7 on Hamiltor	n Rating	Scale for Depression (H	IAM-D) AND	>50% improvement or	HAMD A	AND GAF
		very serious ¹	no serious inconsistency	no serious indirectness	very serious²	reporting bias ³	5/23 (21.7%)		RR 1.88 (0.5 to 7.03)	102 more per 1000 (from 58 fewer to 696 more)	⊕000 VERY LOW	
								11.5%		101 more per 1000 (from 58 fewer to 693 more)		
esponse	(follow-up m	nean 16 w	eeks; assessed w	ith: Number of p	eople showi	ng ≥50% improve	ment on	Hamilton Rating Scale	for Depression	on (HAM-D))		
		- ,	no serious inconsistency	no serious indirectness	very serious²	reporting bias ³	8/23 (34.8%)	8/26 (30.8%)	RR 1.13 (0.51 to 2.52)	40 more per 1000 (from 151 fewer to 468 more)	⊕OOO VERY LOW	
						Iton Rating Scale		30.8%		40 more per 1000 (from 151 fewer to 468 more)		

² OIS not met (events<300)

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ 95% CI crosses two clinical decision thresholds

⁵ 95% CI crosses one clinical decision threshold

⁶ I2>50%

1		very serious ¹	no serious inconsistency	no serious indirectness	very serious²	reporting bias ³	23	26	-	SMD 0.06 lower (0.63 lower to 0.5 higher)	⊕000 VERY LOW	
Discontin	nuation for an	y reason	(follow-up mean 1	6 weeks; assess	ed with: Nur	mber of participan	its disco	ntinuing for any reason	including ad	dverse events)		
1		very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	4/23 (17.4%)	11/26 (42.3%)	RR 0.41 (0.15 to 1.11)	250 fewer per 1000 (from 360 fewer to 47 more)	⊕OOO VERY LOW	
								42.3%		250 fewer per 1000 (from 360 fewer to 47 more)		

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses two clinical decision thresholds

IPT + TAU/AD versus TAU/AD-only for chronic depressive symptoms

			Quality as	sessment			No of p	oatients		Effect	Quality	Importa
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT + TAU/AD	TAU/AD- only	Relative (95% CI)	Absolute		
missio	n (IPT + any A	AD/TAU ve	rsus any AD/TAU)	(follow-up 5-16	weeks; assessed	d with: score ≤7 or	on HAM-D/score <7 on HAM-D & >50% impr				core>70)	
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	35/79 (44.3%)	20/75 (26.7%)	<u> </u>		⊕⊕OO LOW	
								28.6%		172 more per 1000 (from 9 more to 426 more)		
emissio	n (IPT + stand	lard pharn	nacotherapy versu	s standard phar	macotherapy + o	linical manageme	nt) (follow-	up mean 5	weeks; assess	sed with: score ≤7 on HA	M-D)	
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	12/24 (50%)	6/21 (28.6%)	RR 1.75 (0.8 to 3.84)	214 more per 1000 (from 57 fewer to 811 more)	⊕⊕OO LOW	
								28.6%		215 more per 1000 (from 57 fewer to 812 more)		

Funding from pharmaceutical company
 95% CI crosses one clinical decision threshold

	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias⁵	11/21 (52.4%)	10/24 (41.7%)	RR 1.26 (0.67 to 2.35)	108 more per 1000 (from 138 fewer to 562 more)	⊕OOO VERY LOW	
								41.7%		108 more per 1000 (from 138 fewer to 563 more)		
nissi	on (IPT group	+ medicat	ion management +	OT versus TAU) (follow-up mea	n 16 weeks; asses	ssed with: s	core ≤7 on	HAM-D)			
	randomised	serious ¹	no serious	no serious	serious ³	none	12/34	4/30	RR 2.65 (0.95	220 more per 1000 (from	⊕⊕00	
	trials		inconsistency	indirectness			(35.3%)	(13.3%)	to 7.34)	7 fewer to 845 more)	LOW	
								13.3%		219 more per 1000 (from 7 fewer to 843 more)		
spon	se (IPT + any A	D/TAU ve	rsus any AD/TAU)	(follow-up 5-26 v	weeks; assessed	d with: ≥50% impr	ovement on	HAM-D/≥4	0% improveme	nt on MADRS)	•	
	randomised	very	serious ⁶	no serious	serious ³	reporting bias ⁵	163/291	144/271	RR 1.21 (0.84	112 more per 1000 (from	⊕ООО	
	trials	serious ¹		indirectness			(56%)	(53.1%)	to 1.75)	85 fewer to 399 more)	VERY LOW	
								48.2%		101 more per 1000 (from		
								40.270		77 fewer to 361 more)		
spon	se (IPT + stand	ard pharm	acotherapy versu	s standard phar		clinical manageme				ed with: ≥50% improvem	ent on HA	AM-D
spon	randomised	ard pharm	no serious	no serious	serious ²	none	17/24	8/21	RR 1.86 (1.02	328 more per 1000 (from	⊕⊕00	AM-D
spon	,			·						328 more per 1000 (from 8 more to 914 more)		AM-D
spon	randomised		no serious	no serious			17/24	8/21	RR 1.86 (1.02	328 more per 1000 (from	⊕⊕00	AM-D
	randomised trials	serious ¹	no serious	no serious indirectness	serious ²	none	17/24 (70.8%)	8/21 (38.1%) 38.1%	RR 1.86 (1.02 to 3.4)	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more)	⊕⊕00	AM-D
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	17/24 (70.8%)	8/21 (38.1%) 38.1%	RR 1.86 (1.02 to 3.4)	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more)	⊕⊕OO LOW	AM-D
	randomised trials	serious ¹	no serious inconsistency s sertraline) (follo	no serious indirectness w-up 16-26 week	serious ²	none h: ≥50% improver	17/24 (70.8%)	8/21 (38.1%) 38.1% / I-D/≥40% i	RR 1.86 (1.02 to 3.4)	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS)	⊕⊕00	AM-D
	randomised trials se (IPT + sertra	serious ¹	no serious inconsistency s sertraline) (follo	no serious indirectness w-up 16-26 week	serious ²	none h: ≥50% improver	17/24 (70.8%)	8/21 (38.1%) 38.1% M-D/≥40% i 131/220 (59.5%)	RR 1.86 (1.02 to 3.4) mprovement o	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS) 18 fewer per 1000 (from 101 fewer to 77 more) 18 fewer per 1000 (from	⊕⊕OO LOW ⊕OOO VERY	AM-D
	randomised trials se (IPT + sertra	serious ¹	no serious inconsistency s sertraline) (follo	no serious indirectness w-up 16-26 week	serious ²	none h: ≥50% improver	17/24 (70.8%)	8/21 (38.1%) 38.1% M-D/≥40% i 131/220	RR 1.86 (1.02 to 3.4) mprovement o	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS) 18 fewer per 1000 (from 101 fewer to 77 more)	⊕⊕OO LOW ⊕OOO VERY	AM -C
espon	randomised trials se (IPT + sertral randomised trials	serious ¹ line versu very serious ¹	no serious inconsistency s sertraline) (follo	no serious indirectness w-up 16-26 week no serious indirectness	serious ² serious ² serious ²	none h: ≥50% improver reporting bias ⁵	17/24 (70.8%) ment on HAI 134/233 (57.5%)	8/21 (38.1%) 38.1% 3-D/≥40% ii 131/220 (59.5%) 59%	RR 1.86 (1.02 to 3.4) mprovement o RR 0.97 (0.83 to 1.13)	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS) 18 fewer per 1000 (from 101 fewer to 77 more) 18 fewer per 1000 (from 100 fewer to 77 more)	⊕⊕OO LOW ⊕OOO VERY	AM-D
spon	randomised trials se (IPT + sertral randomised trials	serious ¹ line versu very serious ¹	no serious inconsistency s sertraline) (follo no serious inconsistency	no serious indirectness w-up 16-26 week no serious indirectness	serious ² serious ² serious ²	none h: ≥50% improver reporting bias ⁵	17/24 (70.8%) ment on HAI 134/233 (57.5%)	8/21 (38.1%) 38.1% 3-D/≥40% ii 131/220 (59.5%) 59%	RR 1.86 (1.02 to 3.4) mprovement o RR 0.97 (0.83 to 1.13) vement on HAI	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS) 18 fewer per 1000 (from 101 fewer to 77 more) 18 fewer per 1000 (from 100 fewer to 77 more)	⊕⊕OO LOW ⊕OOO VERY LOW	AM -C
espon	randomised trials se (IPT + sertral randomised trials se (IPT group +	serious¹ line versu very serious¹ medication	no serious inconsistency s sertraline) (follo no serious inconsistency on management +	no serious indirectness w-up 16-26 week no serious indirectness OT versus TAU)	serious ² serious ² serious ² (follow-up mean	none h: ≥50% improver reporting bias ⁵ n 16 weeks; asses	17/24 (70.8%) ment on HAI 134/233 (57.5%)	8/21 (38.1%) 38.1% 38.1% 38.1% 131/220 (59.5%) 59% 59% improve	RR 1.86 (1.02 to 3.4) mprovement o RR 0.97 (0.83 to 1.13)	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS) 18 fewer per 1000 (from 101 fewer to 77 more) 18 fewer per 1000 (from 100 fewer to 77 more)	⊕⊕OO LOW ⊕OOO VERY	AM-C
espon	randomised trials se (IPT + sertral randomised trials se (IPT group + randomised	serious¹ line versu very serious¹ medication	no serious inconsistency s sertraline) (follo no serious inconsistency on management +	no serious indirectness w-up 16-26 week no serious indirectness OT versus TAU)	serious ² serious ² serious ² (follow-up mean	none h: ≥50% improver reporting bias ⁵ n 16 weeks; asses	17/24 (70.8%) ment on HAII 134/233 (57.5%) seed with: ≥8	8/21 (38.1%) 38.1% 4-D/≥40% ii 131/220 (59.5%) 59% 50% improv	RR 1.86 (1.02 to 3.4) mprovement o RR 0.97 (0.83 to 1.13) rement on HAI	328 more per 1000 (from 8 more to 914 more) 328 more per 1000 (from 8 more to 914 more) n MADRS) 18 fewer per 1000 (from 101 fewer to 77 more) 18 fewer per 1000 (from 100 fewer to 77 more) 7-D) 187 more per 1000 (from 100 from 100 fewer to 77 more)	⊕⊕00 LOW ⊕000 VERY LOW	AM-D

5	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁵	296	282	-	SMD 0.14 lower (0.33 lower to 0.05 higher)	⊕000 VERY LOW	
	on symptomatetter indicated			rmacotherapy ve	rsus standard ph	narmacotherapy +	clinical ma	nagement)	(follow-up mea	an 5 weeks; measured w	ith: HAME) change
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	24	21	-	SMD 0.71 lower (1.32 to 0.1 lower)	⊕⊕OO LOW	
Depression lower value		ology (IP	T + moclobemide	versus moclobe	mide + clinical m	nanagement) (follo	w-up mean	12 weeks;	measured with	n: MADRS change score	Better in	dicated by
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	11	13	-	SMD 0.03 lower (0.83 lower to 0.77 higher)	⊕OOO VERY LOW	
Depression	on symptomat	ology (IP	T + sertraline ver	sus sertraline) (fo	ollow-up 16-26 w	eeks; measured w	ith: HAMD/I	MADRS cha	ange score; Be	tter indicated by lower v	alues)	
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁵	233	220	-	SMD 0.06 lower (0.24 lower to 0.12 higher)	⊕000 VERY LOW	
Depression values)	on symptomat	tology (IP	I Г group + medica	tion managemen	t + OT versus TA	AU) (follow-up mea	ın 16 weeks	; measure	d with: HAMD o	change score; Better ind	icated by	lower
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	28	28	-	SMD 0.24 lower (0.76 lower to 0.29 higher)	⊕⊕OO LOW	
Discontine events)	uation for any	reason (l	 PT + any AD/TAL	J versus any AD/	TAU) (follow-up	5-16 weeks; asses	sed with: N	umber of p	articipants dis	continuing for any reaso	on includi	ng adverse
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	23/95 (24.2%)	21/94 (22.3%)	RR 1.12 (0.57 to 2.2)	96 fewer to 268 more)	⊕OOO VERY LOW	
								15.4%		18 more per 1000 (from 66 fewer to 185 more)		
			PT + standard ph y reason includir			pharmacotherapy	+ clinical m	anagemen	t) (follow-up m	ean 5 weeks; assessed	with: Num	nber of
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	6/24 (25%)	2/21 (9.5%)	RR 2.62 (0.59 to 11.64)	154 more per 1000 (from 39 fewer to 1000 more)		

								9.5%		154 more per 1000 (from 39 fewer to 1000 more)	⊕000 VERY LOW	
	nuation for an on including a	•		de versus moclo	bemide + clinica	nl management) (fo	ollow-up me	an 12 week	s; assessed w	ith: Number of participar	its discor	itinuing fo
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	6/16 (37.5%)	11/19 (57.9%)	RR 0.65 (0.31 to 1.36)	203 fewer per 1000 (from 399 fewer to 208 more)	⊕OOO VERY LOW	
								57.9%		203 fewer per 1000 (from 400 fewer to 208 more)		
events)	Ţ			<u></u>						continuing for any reasor		g adverse
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias⁵	4/21 (19%)	5/24 (20.8%)	RR 0.91 (0.28 to 2.97)	19 fewer per 1000 (from 150 fewer to 410 more)	⊕000 VERY LOW	
								20.8%		19 fewer per 1000 (from 150 fewer to 410 more)		
	nuation for an	•	•	cation managem	ent + OT versus	TAU) (follow-up r	nean 16 wee	ks; assess	sed with: Numb	per of participants discor	tinuing fo	or any
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	7/34 (20.6%)	3/30 (10%)	RR 2.06 (0.58 to 7.26)	106 more per 1000 (from 42 fewer to 626 more)	⊕000 VERY LOW	
								10%		106 more per 1000 (from 42 fewer to 626 more)		

¹ Risk of bias is unclear or high across multiple domains ² OIS not met (events<300) ³ 95% CI crosses one clinical decision threshold

8

Brief supportive psychotherapy (BSP) versus sertraline for dysthymia

Quality assessment	No of patients	Effect	Quality Importance

⁴ 95% CI crosses two clinical decision thresholds

⁵ Funding from pharmaceutical company

⁶ I2>50%

⁷ OIS not met (N<400)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brief supportive psychotherapy (BSP)	Sertraline	Relative (95% CI)	Absolute		
Remissio score>70	•	mean 16 v	veeks; assessed v	with: Number of	people scor	ing <7 on Hamilto	n Rating Scale for Dep	ression (H	AM-D) AND	>50% improvement or	HAMD A	AND GAF
1	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	3/26 (11.5%)	10/24 (41.7%)	RR 0.28 (0.09 to 0.89)	300 fewer per 1000 (from 46 fewer to 379 fewer)	⊕000 VERY LOW	
								41.7%		300 fewer per 1000 (from 46 fewer to 379 fewer)		
Response	e (follow-up r	nean 16 w	reeks; assessed v	vith: Number of	people show	ring ≥50% improv	ement on Hamilton Rat	ing Scale f	or Depression	on (HAM-D))		
1	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	8/26 (30.8%)	14/24 (58.3%)	RR 0.53 (0.27 to 1.03)	274 fewer per 1000 (from 426 fewer to 17 more)	⊕000 VERY LOW	
								58.3%		274 fewer per 1000 (from 426 fewer to 17 more)		
Depression	on symptoma	tology (fo	ollow-up mean 16	weeks; measure	ed with: Ham	ilton Rating Scale	e for Depression (HAM-	D; change	score); Bett	er indicated by lower	values)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	26	24	-	SMD 0.77 higher (0.19 to 1.34 higher)	⊕000 VERY LOW	
Discontin	uation for an	y reason	(follow-up mean 1	16 weeks; asses	sed with: Nu	mber of participa	nts discontinuing for a	ny reason	including ad	verse events)		
1	randomised trials	very serious ¹		no serious indirectness	serious ⁴	reporting bias ³	11/26 (42.3%)	5/24 (20.8%)	RR 2.03 (0.83 to 4.99)	215 more per 1000 (from 35 fewer to 831 more)	⊕OOO VERY LOW	
								20.8%		214 more per 1000 (from 35 fewer to 830 more)		

¹ Risk of bias is unclear or high across multiple domains
² OIS not met (events<300)
³ Funding from pharmaceutical company
⁴ 95% CI crosses one clinical decision threshold
⁵ OIS not met (N<400)

1 Body Psychotherapy (BPT) + TAU versus TAU for chronic depressive symptoms

			Quality asses	ssment			·			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Body Psychotherapy (BPT) + TAU	TAU	Relative (95% CI)	Absolute		
Depression	on symptoma	tology (follo	w-up mean 10 we	eks; measured v	with: HAMD o	change score; Bet	ter indicated by lower	values	5)			
1		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	11	12	-	- SMD 1.53 lower (2.48 to 0.58 lower)		
Discontin	uation for an	y reason (fo	llow-up mean 10 v	veeks; assessed	d with: Numb	er of participants	discontinuing for any	reasor	including a	dverse events)		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	5/16 (31.3%)	3/15 (20%)	RR 1.56		⊕OOO VERY LOW	
								20%		112 more per 1000 (from 110 fewer to 886 more)		

¹ OIS not met (N<400)

Cognitive-Interpersonal Group Psychotherapy for Chronic Depression (CIGP-CD) + fluoxetine versus fluoxetine for maintenance treatment for

6 relapse prevention of dysthymia

			Quality ass	essment			No of patients			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Cognitive-Interpersonal Group Psychotherapy for Chronic Depression (CIGP-CD) + fluoxetine	Fluoxetine	Relative (95% CI)	Absolute	Quanty	importance
Relapse	(follow-up m	ean 16 w	eeks; assessed v	with: Number o	f people sco	ring >0 on item #	1 (depressed mood) on Hamilto	n Rating Sc	ale for Dep	ression (HAM-D)	OR meet	ing DSM-IV

Relapse (follow-up mean 16 weeks; assessed with: Number of people scoring >0 on item #1 (depressed mood) on Hamilton Rating Scale for Depression (HAM-D) OR meeting DSM-I\
criteria for a diagnosis of dysthymia)

² Data is not reported or cannot be extracted for all outcomes

³ 95% CI crosses two clinical decision thresholds

		very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	3/17 (17.6%)	6/16 (37.5%)	RR 0.47 (0.14 to 1.57)	199 fewer per 1000 (from 322 fewer to 214 more)	⊕OOO VERY LOW	
								37.5%		199 fewer per 1000 (from 322 fewer to 214 more)		
	e (follow-up d on CGI-I (so			d with: Numbe	r of people s	showing ≥50% imp	provement on Hamilton Rating S	cale for De	oression (H	AM-D) AND much	n/very mu	ıch
•	· ·			T .	1			T			ı	
		- ,	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	16/18 (88.9%)	13/17 (76.5%)	RR 1.16 (0.85 to 1.59)	122 more per 1000 (from 115 fewer to 451 more)	⊕OOO VERY LOW	
								76.5%		122 more per 1000 (from 115 fewer to 451 more)		
Disconti	nuation for a	ny reaso	n (follow-up mea	n 16 weeks; as	sessed with	: Number of parti	cipants discontinuing for any re	ason includ	ling advers	e events)		
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	2/20 (10%)	3/20 (15%)	RR 0.67 (0.12 to 3.57)	49 fewer per 1000 (from 132 fewer to 386 more)	⊕OOO VERY LOW	
	iaa ia waalaa							15%		49 fewer per 1000 (from 132 fewer to 386 more)		

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses two clinical decision thresholds

5 6

1 2 3

SSRIs versus placebo for chronic depressive symptoms

Quality assessment	No of patients	Effect	Quality	Importance
				į.

³ Funding from pharmaceutical company ⁴ 95% CI crosses one clinical decision threshold

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Placebo	Relative (95% CI)	Absolute		
Remissio	n (any SSRI) (follow-up 11-1	13 weeks; assesse	ed with: Number	of people scorin	ng <7/≤4/7/8 on Har	nilton Ra	ting Sca	le for Depress	ion (HAM-D))		
5	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	137/301 (45.5%)	85/277 (30.7%)	RR 1.47 (1.15 to 1.87)	144 more per 1000 (from 46 more to 267 more)	⊕OOO VERY LOW	
								25.6%		120 more per 1000 (from 38 more to 223 more)		
Remission	n (sertraline) ((follow-up me	an 12 weeks; asse	essed with: Numb	per of people sc	oring ≤4 on Hamilt	on Ratin	g Scale f	or Depression	(HAM-D))		
I	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	63/134 (47%)	45/140 (32.1%)	RR 1.46 (1.08 to 1.98)	148 more per 1000 (from 26 more to 315 more)	⊕000 VERY LOW	
								32.1%		148 more per 1000 (from 26 more to 315 more)		
Remissio	n (fluoxetine)	(follow-up me	an 13 weeks; ass	essed with: Num	ber of people sc	oring ≤7 on Hamil	ton Ratin	g Scale	for Depression	(HAM-D))		
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	32/72 (44.4%)	10/39 (25.6%)	RR 1.73 (0.96 to 3.14)	187 more per 1000 (from 10 fewer to 549 more)	⊕OOO VERY LOW	
								25.6%		187 more per 1000 (from 10 fewer to 548 more)		
Remission nood) sco		m) (follow-up	mean 12 weeks; a	ssessed with: N	umber of people	scoring ≤4 on Ha	milton Ra	ating Sca	le for Depress	ion (HAM-D) AND HAMD	item # 1 (d	epress
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	4/17 (23.5%)	1/17 (5.9%)	RR 4 (0.5 to 32.2)	176 more per 1000 (from 29 fewer to 1000 more)	⊕OOO VERY LOW	
								5.9%		177 more per 1000 (from 30 fewer to 1000 more)		
Remissio	n (paroxetine)	(follow-up 11	-12 weeks; assess	sed with: Numbe	r of people scor	ing <7/≤8 on Hami	Iton Ratii	ng Scale	for Depression	n (HAM-D))		
2	randomised trials	serious ¹	serious ⁶	no serious indirectness	very serious ⁵	reporting bias ³	38/78 (48.7%)	29/81 (35.8%)		208 more per 1000 (from 115 fewer to 952 more)	⊕000 VERY LOW	
								30.7%		178 more per 1000 (from 98 fewer to 817 more)	2011	

	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³		152/462 (32.9%)	RR 1.5 (1.29 to 1.75)	165 more per 1000 (from 95 more to 247 more)	⊕000 VERY LOW
								29.9%		149 more per 1000 (from 87 more to 224 more)	LOW
spoi I-I)	nse (sertraline)	(follow-up mea	an 12 weeks; ass	sessed with: ≥50°	% improvement o	on HAMD & HAMD	score≤10/	⁄≥50% im	provement on	MADRS/much or very mu	ıch impr
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³		115/325 (35.4%)	RR 1.47 (1.17 to 1.83)	166 more per 1000 (from 60 more to 294 more)	⊕OOO VERY LOW
								30.3%		142 more per 1000 (from 52 more to 251 more)	LOW
spo	nse (fluoxetine)	(follow-up 8-1	3 weeks; assess	ed with: ≥50% in	nprovement on H	AMD & much/very	much im	proved o	n CGI-I)		
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³		26/101 (25.7%)	RR 1.7 (1.17 to 2.47)	180 more per 1000 (from 44 more to 378 more)	⊕000 VERY LOW
								19.6%		137 more per 1000 (from 33 more to 288 more)	
	nse (escitalopra ery much impro			assessed with:	Number of people	e showing ≥50% ir	nproveme	nt on Ha	milton Rating	Scale for Depression (HA	M-D) AN
	randomised	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	7/17 (41.2%)	5/17 (29.4%)	RR 1.4 (0.55 to 3.55)	118 more per 1000 (from 132 fewer to 750 more)	⊕000 VERY
	trials		1				,	29.4%	,	118 more per 1000 (from	LOW
								29.4%			
	trials			sessed with: Nu	mber of people s	showing ≥50% imp	rovement		Iton Rating Sc	132 fewer to 750 more) ale for Depression (HAM-	D) AND/0
	trials			no serious indirectness	mber of people s	showing ≥50% imp	14/21	on Hami	RR 2.11 (1.02	,	⊕OOO VERY LOW

8	randomised trials	very serious ¹		no serious indirectness	no serious imprecision	reporting bias ³	495	461	-	SMD 0.56 lower (0.83 to 0.29 lower)	⊕OOO VERY LOW	
Depression	on symptomat	ology (sertra	ine) (follow-up me	ean 12 weeks; me	easured with: HA	AMD/MADRS chang	ge score	; Better i	ndicated by lov	wer values)		
3	randomised trials	very serious ¹	very serious ⁷	no serious indirectness	serious ⁴	reporting bias ³	325	324	-	SMD 0.39 lower (0.79 lower to 0.01 higher)	⊕OOO VERY LOW	
Depression	on symptomat	ology (fluoxe	tine) (follow-up 8-	13 weeks; meası	red with: HAMD	change score; Be	tter indic	cated by	lower values)			
3	randomised trials	very serious ¹	serious ⁶	no serious indirectness	serious ⁸	reporting bias ³	132	101	-	SMD 0.66 lower (1.13 to 0.18 lower)	⊕OOO VERY LOW	
Depression values)	on symptomat	ology (escita	lopram) (follow-up	mean 12 weeks	; measured with	: Hamilton Rating	Scale for	Depress	sion (HAM-D; c	hange score); Better indi	cated by	lower
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁸	reporting bias ³	17	17	-	SMD 0.9 lower (1.61 to 0.19 lower)	⊕000 VERY LOW	
Depression	on symptomat	ology (parox	etine) (follow-up m	iean 12 weeks; m	neasured with: H	lamilton Rating Sc	ale for D	epressio	n (HAM-D; cha	nge score); Better indica	ted by lov	wer values)
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁸	none	21	19	-	SMD 0.77 lower (1.41 to 0.12 lower)	⊕OOO VERY LOW	
Discontin	uation for any	reason (any	SSRI) (follow-up 8	I-13 weeks; asse	ssed with: Numb	per of participants	disconti	nuing fo	any reason in	cluding adverse events)		
8	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	95/520 (18.3%)		RR 0.83 (0.57 to 1.21)	37 fewer per 1000 (from 95 fewer to 46 more)	⊕OOO VERY LOW	
								22.3%		38 fewer per 1000 (from 96 fewer to 47 more)		
Discontin	uation for any	reason (sert	raline) (follow-up r	mean 12 weeks;	assessed with: N	Number of participa	ants disc	ontinuin	g for any reas	on including adverse eve	nts)	
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³		80/326 (24.5%)	RR 0.78 (0.58 to 1.05)	54 fewer per 1000 (from 103 fewer to 12 more)	⊕OOO VERY LOW	
								24.3%		53 fewer per 1000 (from 102 fewer to 12 more)	-	

	randomised trials	serious ¹	serious ⁶	no serious indirectness	very serious ⁵	reporting bias ³	27/154 (17.5%)		RR 1.18 (0.35 to 3.94)	32 more per 1000 (from 117 fewer to 530 more)	⊕000 VERY
								45.00/		27 more per 1000 (from	LOW
								15.2%		99 fewer to 447 more)	
con	tinuation for an	y reason (es	citalopram) (follow	v-up mean 12 we	eks; assessed w	ith: Number of par	rticipants	discontii	nuing for any re	eason including adverse	events)
	randomised	serious ¹	no serious	no serious	very serious ⁵	reporting bias ³	3/19	0/17	RR 6.3 (0.35	-	⊕OOO
	trials		inconsistency	indirectness			(15.8%)	(0%)	to 113.81)		VERY LOW
								0%	1	-	LOW
scon	tinuation for an	y reason (pa	roxetine) (follow-u	ıp mean 12 week	s; assessed with	: Number of partic	cipants dis	continu	ing for any reas	son including adverse ev	ents)
	randomised	serious ¹	no serious	no serious	very serious ⁵	none	3/21	4/19	RR 0.68 (0.17	67 fewer per 1000 (from	⊕000
	trials		inconsistency	indirectness			(14.3%)	(21.1%)	to 2.65)	175 fewer to 347 more)	VERY LOW
								21.1%		68 fewer per 1000 (from	
2001	tinuation due ta	adverse ev	nto (any SSBI) (fa	llow up 9 12 wa	ka: assessed wi	th: Number of par	ticinanto c		uing due to ad	175 fewer to 348 more)	
iscoii	tinuation due to	auverse eve	ints (any SSKI) (it	niow-up 6-12 we	·	tii. Nuilibei oi pai	licipants t	iiscontiii	iullig due to au	verse events)	
	randomised	serious ¹	no serious	no serious	serious ²	reporting bias ³	35/395		,	38 more per 1000 (from 3	⊕000
	trials		inconsistency	indirectness			(8.9%)	(4.6%)	to 3.12)	more to 98 more)	VERY LOW
								1.1%		9 more per 1000 (from 1	2011
		1.				1				more to 23 more)	
scon	tinuation due to	adverse eve	ents (sertraline) (f	ollow-up mean 1	2 weeks; assesse	ed with: Number o	f participa	nts disc	ontinuing due t	to adverse events)	
	randomised	serious ¹	no serious	no serious	serious ⁴	reporting bias ³	29/292			40 more per 1000 (from 3	⊕000
	trials		inconsistency	indirectness			(9.9%)	(5.8%)	to 2.98)	fewer to 115 more)	VERY LOW
								5.7%	1	39 more per 1000 (from 3	LOW
										fewer to 113 more)	
scon	tinuation due to	adverse eve	ents (fluoxetine) (f	follow-up 8-12 we	eks; assessed w	ith: Number of pa	rticipants	disconti	nuing due to a	dverse events)	
	randomised	no serious	no serious	no serious	very serious ⁵	reporting bias ³	5/63	1/62	`	41 more per 1000 (from 6	⊕OOO
	trials	risk of bias	inconsistency	indirectness			(7.9%)	(1.6%)	to 21.04)	fewer to 323 more)	VERY
									1	28 more per 1000 (from 4	LOW
		1	1	1	i	i	1	1.1%	1	fewer to 220 more)	

1	randomised trials			no serious indirectness	very serious ⁵	reporting bias ³	1/19 (5.3%)	0/17 (0%)	RR 2.7 (0.12 to 62.17)	-	⊕OOO VERY LOW	
								0%		-		
Discontin	uation due to	adverse even	its (paroxetine) (fo	llow-up mean 12	weeks; assesse	d with: Number of	participa	ants disc	continuing due	to adverse events)		
1	randomised trials			no serious indirectness	serious ²	none	0/21 (0%)	0/19 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								0%		not pooled		

- ¹ Risk of bias is unclear or high across multiple domains
 ² OIS not met (events<300)
 ³ Funding from pharmaceutical company
 ⁴ 95% CI crosses one clinical decision threshold

- ⁵ 95% CI crosses two clinical decision thresholds
- 6 I2>50%
- ⁷ I2>80%
- 8 OIS not met (N<400)

SSRI versus TCA for chronic depressive symptoms

			Quality as	sessment			No of p	oatients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI	TCA	Relative (95% CI)	Absolute		
Remissio	n (sertraline v	ersus imip	ramine) (follow-up	mean 12 weeks;	assessed with: s	core ≤7 on HAM-D	& much	/very mu	ich improved o	on CGI-I/≤4 on HAM-D)		
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	133/555 (24%)	88/338 (26%) 28.2%	to 1.39)	29 more per 1000 (from 29 fewer to 102 more) 31 more per 1000 (from 31 fewer to 110 more)	⊕OOO VERY LOW	
			amine) (follow-up uch/very much imp		assessed with: ≥	50% improvement	on HAM	-D & HAI	/I-D≤15 & CGI-l	score 1-2 [much/very mu	ch impro	ved] & CGI-
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	, ,		191/338 (56.5%) 57.7%	RR 0.97 (0.86 to 1.1)	17 fewer per 1000 (from 79 fewer to 57 more) 17 fewer per 1000 (from 81 fewer to 58 more)	⊕OOO VERY LOW	

	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	134	136	-	MD 0.3 higher (1.12 lower to 1.72 higher)	⊕000 VERY LOW
scontin ents)	uation for any	reason (s	 ertraline versus i	 mipramine) (folio	w-up mean 12	weeks; assessed with	h: Numbe	r of parti	icipants disco	ntinuing for any reason inc	luding ac
2	randomised trials	serious ¹	serious ⁵	no serious indirectness	serious ⁶	reporting bias ³		95/345 (27.5%)	RR 0.61 (0.39 to 0.95)	107 fewer per 1000 (from 14 fewer to 168 fewer)	⊕OOO VERY LOW
								28.5%		111 fewer per 1000 (from 14 fewer to 174 fewer)	2311
Discontin	uation due to	adverse e	vents (sertraline	versus imipramir	ne) (follow-up n	nean 12 weeks; asses	sed with:	Number	of participant	s discontinuing due to adv	erse evei
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ³		50/345 (14.5%)	RR 0.45 (0.29 to 0.71)	80 fewer per 1000 (from 42 fewer to 103 fewer)	⊕000 VERY LOW
								15.2%		84 fewer per 1000 (from 44 fewer to 108 fewer)	20

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses one clinical decision threshold

SSRI versus antipsychotic for dysthymia or double depression

			Quality as:	sessment			No	of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI	Antipsychotic	Relative (95% CI)	Absolute		
Remission	n (any SSRI v	ersus ami	sulpride) (follow-u	p 8-12 weeks; as	ssessed with: So	core)						
			no serious inconsistency	no serious indirectness	serious ²	none	130/226 (57.5%)		RR 0.89 (0.77 to 1.02)	74 fewer per 1000 (from 154 fewer to 13 more)	⊕OOO VERY LOW	
								59.5%		65 fewer per 1000 (from 137 fewer to 12 more)		

³ Funding from pharmaceutical company ⁴ OIS not met (N<400)

⁵ I2>50%

⁶ OIS not met (events<300)

					. 2		400/450	445/455	DD 0.00	04.5 4000.5	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	102/156 (65.4%)	115/157 (73.2%)	RR 0.89 (0.77 to 1.04)	81 fewer per 1000 (from 168 fewer to 29 more)	⊕000 VERY LOW
								73.3%		81 fewer per 1000 (from 169 fewer to 29 more)	
iss	ion (paroxetine	versus a	misulpride) (follo	w-up mean 8 we	eks; assessed w	ith: Score ≤7 on F	IAMD)				
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	28/70 (40%)	22/48 (45.8%)	RR 0.87 (0.57 to 1.33)	60 fewer per 1000 (from 197 fewer to 151 more)	⊕000 VERY LOW
								45.8%		60 fewer per 1000 (from 197 fewer to 151 more)	
por	nse (any SSRI v	ersus ami	sulpride) (follow-	up 8-26 weeks; a	assessed with: ≥	50% improvement	t on HAMD/	MADRS)			
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	255/391 (65.2%)	277/370 (74.9%)	RR 0.88 (0.77 to 1.01)	90 fewer per 1000 (from 172 fewer to 7 more)	⊕⊕OO LOW
								73.2%		88 fewer per 1000 (from 168 fewer to 7 more)	
por	nse (sertraline v	versus am	sulpride) (follow	-up 12-26 weeks	assessed with:	≥50% improveme	nt on HAMI			. ,	
por	randomised trials	versus am	isulpride) (follow serious ⁴	no serious indirectness	very serious ³	≥50% improveme	129/182 (70.9%)		RR 0.73 (0.42 to 1.28)	168 fewer to 7 more) 222 fewer per 1000	⊕OOO VERY LOW
spor	randomised	very	, ,,	no serious		•	129/182	D)		168 fewer to 7 more) 222 fewer per 1000 (from 477 fewer to 230	VERY
	randomised trials	very serious ¹	serious ⁴	no serious indirectness	very serious ³	•	129/182 (70.9%)	148/180 (82.2%)		222 fewer per 1000 (from 477 fewer to 230 more) 212 fewer per 1000 (from 456 fewer to 220	VERY
	randomised trials	very serious ¹	serious ⁴	no serious indirectness	very serious ³	none	129/182 (70.9%)	148/180 (82.2%)		222 fewer per 1000 (from 477 fewer to 230 more) 212 fewer per 1000 (from 456 fewer to 220 more)	UERY LOW
spor	randomised trials nse (paroxetine randomised trials	very serious¹ versus an very serious¹	nisulpride) (follow no serious inconsistency	no serious indirectness v-up mean 8 wee no serious indirectness	very serious ³ eks; assessed wi very serious ³	none th: ≥50% improve	129/182 (70.9%) ment on HA 39/70 (55.7%)	78.7% AMD) 26/48 (54.2%)	(0.42 to 1.28)	222 fewer per 1000 (from 477 fewer to 230 more) 212 fewer per 1000 (from 456 fewer to 220 more)	VERY LOW
spor	randomised trials nse (paroxetine randomised trials	very serious¹ versus an very serious¹	nisulpride) (follow no serious inconsistency	no serious indirectness v-up mean 8 wee no serious indirectness	very serious ³ eks; assessed wi very serious ³	none hth: ≥50% improve	129/182 (70.9%) ment on HA 39/70 (55.7%)	78.7% AMD) 26/48 (54.2%)	(0.42 to 1.28) RR 1.03	168 fewer to 7 more) 222 fewer per 1000 (from 477 fewer to 230 more) 212 fewer per 1000 (from 456 fewer to 220 more) 16 more per 1000 (from 141 fewer to 238 more) 16 more per 1000 (from 1600)	UERY LOW

			F	1					1		
								72.5%		101 fewer per 1000 (from 196 fewer to 14 more)	⊕OOO VERY LOW
Depressi	on symptoma	tology (an	y SSRI versus am	isulpride) (follov	v-up 8-13 weeks	; measured with:	HAMD/MA	ADRS change	score; Better i	ndicated by lower values	5)
3	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	349	343	-	SMD 0.19 higher (0.04 to 0.34 higher)	⊕⊕OO LOW
Depressi	on symptoma	tology (se	rtraline versus an	nisulpride) (follo	w-up mean 12 w	eeks; measured v	ith: HAM	D change sco	e; Better indi	cated by lower values)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	150	156	-	SMD 0.25 higher (0.02 to 0.47 higher)	⊕OOO VERY LOW
Depressi	on symptoma	tology (pa	roxetine versus a	│ misulpride) (follo	ow-up mean 8 w	eeks; measured w	ith: HAM	D change sco	e; Better indic	cated by lower values)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	70	48	-	SMD 0.12 higher (0.24 lower to 0.49 higher)	⊕OOO VERY LOW
Depressi	on symptoma	tology (flu	oxetine versus ar	nisulpride) (follo	w-up mean 13 w	reeks; measured v	vith: MAD	RS change so	ore; Better in	dicated by lower values)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	reporting bias ⁶	129	139	-	SMD 0.16 higher (0.08 lower to 0.4 higher)	⊕OOO VERY LOW
Discontin	nuation for any	/ reason (any SSRI versus a	amisulpride) (foll	ow-up 8-26 weel	ks; assessed with	: Number	of participant	s discontinuir	g for any reason includi	ng adverse events
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	83/391 (21.2%)	61/370 (16.5%)	RR 1.3 (0.97 to 1.75)	49 more per 1000 (from 5 fewer to 124 more)	⊕⊕OO LOW
								14.9%		45 more per 1000 (from 4 fewer to 112 more)	
Discontir events)	nuation for any	/ reason (sertraline versus	amisulpride) (fol	low-up 12-26 we	eks; assessed wi	th: Numbe	er of participa	nts discontinu	ing for any reason inclu	ding adverse
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	33/182 (18.1%)	21/180 (11.7%)	RR 1.55 (0.93 to 2.57)	64 more per 1000 (from 8 fewer to 183 more)	⊕⊕OO LOW
								12.3%	1	68 more per 1000 (from 9 fewer to 193 more)	

scontii ents)	nuation for any	y reason (paroxetine versus	s amisulpride) (f	ollow-up mean 8	weeks; assessed	l with: Nun	nber of partic	cipants discont	inuing for any reason in	cluding adver
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	10/70 (14.3%)	8/48 (16.7%)	RR 0.86 (0.36 to 2.01)	23 fewer per 1000 (from 107 fewer to 168 more)	⊕OOO VERY LOW
								16.7%		23 fewer per 1000 (from 107 fewer to 169 more)	
iscontii vents)	nuation for any	y reason (fluoxetine versus	amisulpride) (fo	ollow-up mean 13	3 weeks; assessed	d with: Nur	nber of parti	cipants discon	tinuing for any reason in	cluding adver
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁶	40/139 (28.8%)	32/142 (22.5%)	RR 1.28 (0.85 to 1.91)	63 more per 1000 (from 34 fewer to 205 more)	⊕OOO VERY LOW
								22.5%		63 more per 1000 (from 34 fewer to 205 more)	
Disconti	nuation due to	adverse	events (any SSRI	versus amisulpr	ride) (follow-up 8	-26 weeks; asses	sed with: N	lumber of pa	articipants disc	ontinuing due to advers	e events)
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	32/391 (8.2%)	28/370 (7.6%)	RR 1.05 (0.64 to 1.73)	4 more per 1000 (from 27 fewer to 55 more)	⊕OOO VERY LOW
								7.4%		4 more per 1000 (from 27 fewer to 54 more)	
iscontii	nuation due to	adverse	events (sertraline	versus amisulp	ride) (follow-up 1	12-26 weeks; asse	ssed with:	Number of p	participants dis	continuing due to adver	se events)
	randomised	serious1	no serious	no serious	very serious ³	none	16/182	11/180	RR 1.38	23 more per 1000 (from	⊕000
	trials		inconsistency	indirectness			(8.8%)	(6.1%)	(0.65 to 2.95)		VERY LOW
								5.4%		21 more per 1000 (from 19 fewer to 105 more)	
iscontii	nuation due to	adverse	events (paroxetin	e versus amisul	pride) (follow-up	mean 8 weeks; as	ssessed wi	ith: Number	of participants	discontinuing due to ad	verse events)
	randomised	serious1	no serious	no serious	very serious ³	none	6/70	4/48	RR 1.03	2 more per 1000 (from	⊕000
	trials		inconsistency	indirectness			(8.6%)	(8.3%)	(0.31 to 3.45)		VERY LOW
								8.3%		2 more per 1000 (from 57 fewer to 203 more)	
Disconti	nuation due to	adverse	events (fluoxetine	versus amisulp	oride) (follow-up	mean 13 weeks; a	ssessed w	ith: Number	of participants	discontinuing due to ac	verse events)
I	randomised trials	serious ¹	no serious inconsistency	no serious	very serious ³	reporting bias ⁶	10/139 (7.2%)	13/142 (9.2%)	RR 0.79 (0.36 to 1.73)	19 fewer per 1000 (from 59 fewer to 67 more)	
	uiais		inconsistency	ii iuli ecti iess			(1.2/0)	(3.270)	(0.30 to 1.73)	33 lewel to 07 mole)	

								9.2%		19 fewer per 1000 (from 59 fewer to 67 more)	⊕000 VERY LOW	
--	--	--	--	--	--	--	--	------	--	---	---------------------	--

¹ Risk of bias is unclear or high across multiple domains

7

Sertraline + IPT versus UPT-only for dysthymia

			offiny for dystr	.,								
			Quality as	sessment			No of par	ients		Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline + IPT	IPT- only	Relative (95% CI)	Absolute		
Remission score>70)	•	nean 16 we	eeks; assessed wi	th: Number of pe	ople scoring <7	on Hamilton Ratin	g Scale for D	epressio	on (HAM-D) AN	ID >50% improvement o	n HAMD /	AND GAF
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	11/21 (52.4%)	5/23 (21.7%)	RR 2.41 (1 to 5.79)	307 more per 1000 (from 0 more to 1000 more)	⊕OOO VERY LOW	
								21.7%		306 more per 1000 (from 0 more to 1000 more)		
•	•		s; assessed with: I ssion (HAM-D))	Number of people	e showing ≥40%	improvement on I	Montgomery	Asberg [Depression Ra	ting Scale (MADRS)/≥50	% improv	ement on
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	134/233 (57.5%)	91/201 (45.3%)	RR 1.26 (1.05 to 1.52)	118 more per 1000 (from 23 more to 235 more)	⊕OOO VERY LOW	
								40.7%		106 more per 1000 (from 20 more to 212 more)		
•	• •	•••	low-up 16-26 week ndicated by lower	•	h: Hamilton Ratii	ng Scale for Depre	ession (HAM-	D; chang	ge score)/Mont	gomery Asberg Depress	ion Ratir	ng Scale
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	233	201	-	SMD 0.5 lower (0.7 to 0.31 lower)	⊕OOO VERY LOW	

² OIS not met (events<300) ³ 95% CI crosses two clinical decision thresholds

⁴ I2>50%

⁵ 95% CI crosses one clinical decision threshold

⁶ Data is not reported or cannot be extracted for all outcomes

⁷ OIS not met (N<400)

TCAs ver	rsus placeb	o for dy	sthymia or dou	ıble depressic	n							
			Quality as	sessment			No of p	oatients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Placebo	Relative (95% CI)	Absolute		
	i (imipramine) /<8 on MADR		o 6-26 weeks; asse	ssed with: score	≤4/<7 on HAM-D	/≤6 on HAM-D & ≥1	0-point i	mprovem	nent on GAS &	no longer meet DSM-III o	riteria for	-
_	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	118/346 (34.1%)	84/350 (24%)	RR 1.46 (1.08 to 1.98)	110 more per 1000 (from 19 more to 235 more)	⊕OOO VERY LOW	
								21.9%		101 more per 1000 (from 18 more to 215 more)		
			26 weeks; assesse amilton Rating Sca			s much or very mu	ch impro	oved on C	Clinical Global	mpressions scale (CGI-I)/Number	of people
	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³		152/421 (36.1%)	RR 1.85 (1.51 to 2.26)	307 more per 1000 (from 184 more to 455 more)	⊕OOO VERY LOW	
								33.3%		283 more per 1000 (from 170 more to 420 more)		
			6-26 weeks; asses nt on Hamilton Rat				nuch im	proved o	n Clinical Glob	al Impressions scale (CC	SI-I)/Numb	per of
	randomised trials	very serious¹	serious ⁴	no serious indirectness	no serious imprecision	reporting bias ³		125/337 (37.1%)		319 more per 1000 (from 159 more to 519 more)		

¹ Risk of bias is unclear or high across multiple domains

² OIS not met (events<300)

³ Study partially funded by pharmaceutical company

^{4 95%} CI crosses two clinical decision thresholds

								33.8%		291 more per 1000 (from 145 more to 473 more)	⊕OOO VERY LOW
espons	e (amineptine)	(follow-up	mean 13 weeks;	assessed with: I	Number of peopl	e rated as much or	very much	improve	ed on Clinical (Global Impressions scale	(CGI-I))
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	55/89 (61.8%)	27/84 (32.1%)		296 more per 1000 (from 113 more to 556 more)	⊕OOO VERY LOW
								32.1%		295 more per 1000 (from 112 more to 555 more)	
epressi	on symptomat	ology (any	/ TCA) (follow-up	8-16 weeks; mea	sured with: HAM	ID/MADRS change	score; Bet	ter indica	ated by lower v	alues)	
	randomised trials	very serious ¹	serious ⁴	no serious indirectness	no serious imprecision	none	357	357	-	SMD 0.51 lower (0.85 to 0.17 lower)	⊕OOO VERY LOW
epressi	on symptomat	ology (imi	pramine) (follow-	up 8-16 weeks; m	neasured with: H	AMD change score	; Better in	dicated b	y lower values)	1
	randomised trials	very serious ¹	very serious ⁵	no serious indirectness	serious ⁶	none	250	252	-	SMD 0.44 lower (0.97 lower to 0.08 higher)	⊕OOO VERY LOW
-		ology (am	ineptine) (follow-u	ıp mean 13 week	s; measured wit	h: Montgomery Ask	perg Depre	ession Ra	l ating Scale (M <i>A</i>	DRS; change score); Be	tter indicated by
epressio ower val		very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	h: Montgomery Asi	Derg Depre	ession Ra	ating Scale (MA	SMD 0.61 lower (0.88 to 0.33 lower)	⊕OOO VERY LOW
wer val	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	107	105	-	SMD 0.61 lower (0.88 to	⊕OOO VERY
ower val	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	107	105 nuing for	-	SMD 0.61 lower (0.88 to 0.33 lower)	⊕OOO VERY LOW
wer val	randomised trials	very serious ¹	no serious inconsistency ny TCA) (follow-uno serious	no serious indirectness p 6-26 weeks; as	serious ⁷	none mber of participant	107 Is disconti	105 nuing for	r any reason in	SMD 0.61 lower (0.88 to 0.33 lower) cluding adverse events) 22 more per 1000 (from	⊕000 VERY LOW
wer values	randomised trials nuation for any randomised trials	very serious ¹ v reason (a	no serious inconsistency ny TCA) (follow-uno serious inconsistency	no serious indirectness p 6-26 weeks; as no serious indirectness	serious ⁷ ssessed with: Nu	none mber of participant reporting bias ³	107 as disconti 153/488 (31.4%)	105 nuing for 135/482 (28%) 24.3%	r any reason in RR 1.08 (0.83 to 1.4)	SMD 0.61 lower (0.88 to 0.33 lower) cluding adverse events) 22 more per 1000 (from 48 fewer to 112 more) 19 more per 1000 (from	⊕OOO VERY LOW ⊕OOO VERY LOW
wer val	randomised trials nuation for any randomised trials	very serious ¹ v reason (a	no serious inconsistency ny TCA) (follow-uno serious inconsistency	no serious indirectness p 6-26 weeks; as no serious indirectness	serious ⁷ ssessed with: Nu	none mber of participant reporting bias ³	107 as disconti 153/488 (31.4%)	105 nuing for 135/482 (28%) 24.3% ntinuing	r any reason in RR 1.08 (0.83 to 1.4)	SMD 0.61 lower (0.88 to 0.33 lower) cluding adverse events) 22 more per 1000 (from 48 fewer to 112 more) 19 more per 1000 (from 41 fewer to 97 more)	⊕OOO VERY LOW ⊕OOO VERY LOW

	randomised	serious1	no serious	no serious	very serious8	none	40/111	42/108	RR 0.93 (0.66	27 fewer per 1000 (from	⊕000
	trials	3011003	inconsistency	indirectness	very serious	Horic	(36%)	(38.9%)		132 fewer to 121 more)	VERY
							(00,0)	(00.070)	10,	102 101101 10 121 111010)	LOW
								38.9%		27 fewer per 1000 (from	
								30.9%		132 fewer to 121 more)	
iscon	tinuation due to	adverse e	vents (any TCA) (follow-up 6-26 w	eeks; assessed w	vith: Number of pa	rticipants o	discontin	uing due to ad	verse events)	
	randomised	serious ¹	no serious	no serious	serious ²	reporting bias ³	63/468	10/467	RR 5.77 (3.09	102 more per 1000 (from	⊕OOO
	trials		inconsistency	indirectness			(13.5%)	(2.1%)	to 10.79)	45 more to 210 more)	VERY
											LOW
										67 more per 1000 (from	
								1 4%		. ,	
								1.4%		29 more to 137 more)	
iscon	tinuation due to	adverse e	vents (imipramine	e) (follow-up 6-26	6 weeks; assessed	d with: Number of	participant		tinuing due to	29 more to 137 more)	
Discon	tinuation due to	adverse e	vents (imipramine	no serious	S weeks; assessed	d with: Number of reporting bias ³	58/357	s discon	RR 5.87 (3.05	29 more to 137 more) adverse events) 122 more per 1000 (from	⊕OOO
iscon			<u> </u>		·		•	s discon		29 more to 137 more) adverse events)	VERY
)iscon	randomised		no serious	no serious	·		58/357	s discon	RR 5.87 (3.05	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more)	
iscon	randomised		no serious	no serious	·		58/357	9/359 (2.5%)	RR 5.87 (3.05	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more) 93 more per 1000 (from	VERY
Discon	randomised		no serious	no serious	·		58/357	s discon	RR 5.87 (3.05	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more)	VERY
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	58/357 (16.2%)	9/359 (2.5%)	RR 5.87 (3.05 to 11.29)	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more) 93 more per 1000 (from	VERY
;	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	58/357 (16.2%)	9/359 (2.5%)	RR 5.87 (3.05 to 11.29)	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more) 93 more per 1000 (from 39 more to 196 more)	VERY
	randomised trials	serious ¹ adverse e	no serious inconsistency vents (amineptine	no serious indirectness	serious ²	reporting bias ³	58/357 (16.2%)	9/359 (2.5%) 1.9% pants dis	RR 5.87 (3.05 to 11.29)	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more) 93 more per 1000 (from 39 more to 196 more) e to adverse events)	VERY LOW
5	randomised trials tinuation due to	serious ¹ adverse e	no serious inconsistency vents (amineptine	no serious indirectness e) (follow-up meaning in serious)	serious ²	reporting bias ³	58/357 (16.2%) er of partici	9/359 (2.5%) 1.9% pants dis	RR 5.87 (3.05 to 11.29) scontinuing du	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more) 93 more per 1000 (from 39 more to 196 more) e to adverse events) 36 more per 1000 (from 4	VERY LOW
5	randomised trials tinuation due to	serious ¹ adverse e	no serious inconsistency vents (amineptine	no serious indirectness e) (follow-up meaning in serious)	serious ²	reporting bias ³	58/357 (16.2%) er of partici	9/359 (2.5%) 1.9% pants dis	RR 5.87 (3.05 to 11.29) scontinuing du RR 4.86 (0.58 to 40.96)	29 more to 137 more) adverse events) 122 more per 1000 (from 51 more to 258 more) 93 more per 1000 (from 39 more to 196 more) e to adverse events) 36 more per 1000 (from 4	UERY LOW

¹ Risk of bias is unclear or high across multiple domains ² OIS not met (events<300)

TCA versus antipsychotic for dysthymia or double depression

Quality assessment	No of patients	Effect	Quality	Importance

³ Funding from pharmaceutical company and/or data not reported/cannot be extracted for all outcomes

⁴ I2>50%

⁵ I2>80%

⁶ 95% CI crosses one clinical decision threshold

⁷ OIS not met (N<400)

⁸ 95% CI crosses two clinical decision thresholds

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCA	Antipsychotic	Relative (95% CI)	Absolute		
Remission	n (imipramine	versus ar	misulpride) (follow	v-up mean 26 we	eks; assessed w	vith: Number of pe	ople sco	ring <8 on Moi	ntgomery Asb	erg Depression Rating S	Scale (MA	DRS))
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	24/73 (32.9%)	26/73 (35.6%)	RR 0.92 (0.59 to 1.45)	28 fewer per 1000 (from 146 fewer to 160 more)	⊕000 VERY LOW	
								35.6%		28 fewer per 1000 (from 146 fewer to 160 more)		
Response	(any TCA ver	rsus amis	ulpride) (follow-up	13-26 weeks; as	ssessed with: M	ADRS ≥50% impro	vement/	CGI-I score 1-2	! [much/very m	nuch improved])		
-		- ,	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	140/249 (56.2%)		RR 0.93 (0.81 to 1.08)	39 fewer per 1000 (from 107 fewer to 45 more)	⊕OOO VERY LOW	
								64.4%		45 fewer per 1000 (from 122 fewer to 52 more)		
(CGI-I))					·					roved on Clinical Globa	·	ions scale
		very serious¹	no serious inconsistency	no serious indirectness	serious ⁴	none	55/89 (61.8%)	54/77 (70.1%)	RR 0.88 (0.71 to 1.1)	84 fewer per 1000 (from 203 fewer to 70 more)	⊕OOO VERY LOW	
								70.1%		84 fewer per 1000 (from 203 fewer to 70 more)		
Response (CGI-I))	(imipramine	versus an	nisulpride) (follow	up mean 26 wee	ks; assessed w	ith: Number of peo	ple rate	d as much or v	ery much imp	roved on Clinical Globa	l Impress	ions scale
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	46/73 (63%)	47/73 (64.4%)	RR 0.98 (0.77 to 1.25)	13 fewer per 1000 (from 148 fewer to 161 more)	⊕000 VERY LOW	
								64.4%		13 fewer per 1000 (from 148 fewer to 161 more)		
Response	(amitriptyline	versus a	misulpride) (follo	w-up mean 26 we	eeks; assessed v	with: MADRS ≥50%	improv	ement)				
			no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	39/87 (44.8%)	77/166 (46.4%)	RR 0.97 (0.73 to 1.28)	14 fewer per 1000 (from 125 fewer to 130 more)	⊕OOO VERY LOW	
								46.4%		14 fewer per 1000 (from 125 fewer to 130 more)		
Depressio	n symptomat	ology (an	y TCA versus ami	sulpride) (follow-	-up 13-26 weeks	; measured with: I	MADRS o	change score;	Better indicate	ed by lower values)		

2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	192	266	-	SMD 0.03 lower (0.22 lower to 0.16 higher)	⊕OOO VERY LOW	
	ion symptoma dicated by low			amisulpride) (fo	llow-up mean 13	weeks; measured	with: Mon	tgomery Ask	perg Depression	n Rating Scale (MADRS	change sco	ore);
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	107	101	-	SMD 0.06 higher (0.21 lower to 0.33 higher)	⊕OOO VERY LOW	
Depressi	ion symptomat	tology (an	nitriptyline versu	s amisulpride) (f	ollow-up mean 2	6 weeks; measure	ed with: MA	DRS change	e score; Better i	ndicated by lower value	es)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	85	165	-	SMD 0.12 lower (0.38 lower to 0.14 higher)	⊕OOO VERY LOW	
Disconti	nuation for any	/ reason (any TCA versus	amisulpride) (fol	low-up 13-26 we	eks; assessed wit	h: Number	of participar	nts discontinuin	ng for any reason includ	ing adverse	event
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	116/271 (42.8%)	140/343 (40.8%)	RR 1.08 (0.89 to 1.3)	33 more per 1000 (from 45 fewer to 122 more)	⊕OOO VERY LOW	
								41.1%		33 more per 1000 (from 45 fewer to 123 more)		
Discontii events)	nuation for any	/ reason (amineptine versu	ıs amisulpride) (follow-up mean	13 weeks; assesse	ed with: Nu	mber of part	icipants discon	tinuing for any reason i	ncluding ad	lverse
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	40/111 (36%)	37/104 (35.6%)	RR 1.01 (0.71 to 1.45)	4 more per 1000 (from 103 fewer to 160 more)	⊕OOO VERY LOW	
								35.6%		4 more per 1000 (from 103 fewer to 160 more)		
Discontii events)	nuation for any	/ reason (imipramine versı	us amisulpride) (follow-up mean	26 weeks; assesse	ed with: Nu	mber of part	ticipants discon	ntinuing for any reason	including ad	lverse
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	35/73 (47.9%)	30/73 (41.1%)	to 1.68)	70 more per 1000 (from 78 fewer to 279 more)	⊕OOO VERY LOW	
		1	1					41.1%		70 more per 1000 (from		

¹ Risk of bias is unclear or high across multiple domains

² 95% CI crosses two clinical decision thresholds

³ Data is not reported or cannot be extracted for all outcomes

^{4 95%} CI crosses one clinical decision threshold

⁵ OIS not met (N<400)

1 Maintenance imipramine versus placebo for elapse prevention in chronic depressive symptoms

	Quality assessment							nts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance imipramine	Placebo	Relative (95% CI)	Absolute		
Relapse (1	follow-up mea	n 26 weel	s; assessed with:	Score ≥3 on CG	I-I on 2 cons	ecutive weeks)						
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	9/17 (52.9%)	8/15 (53.3%)	RR 0.99 (0.52 to 1.91)	5 fewer per 1000 (from 256 fewer to 485 more)	⊕OOO VERY LOW	
								53.3%		5 fewer per 1000 (from 256 fewer to 485 more)		
Discontin	uation for any	reason (f	ollow-up mean 26	weeks; assesse	d with: Numl	ber of participants	discontinuing for	r any rea	son including	adverse events)		
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	2/17 (11.8%)	1/15 (6.7%)	RR 1.76 (0.18 to 17.56)	51 more per 1000 (from 55 fewer to 1000 more)	⊕OOO VERY LOW	
								6.7%		51 more per 1000 (from 55 fewer to 1000 more)		

¹ Risk of bias is unclear or high across multiple domains

5

Duloxetine versus placebo for non-major chronic depressive symptoms

	Quality assessment No of Design Risk of Inconsistency Indirectness Imprecision Other									Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo	Relative (95% CI)	Absolute		
Remissior score=0)	(follow-up m	ean 10 we	eks; assessed with	n: Number of peo	ple scoring ≤	4 on Hamilton Rat	ing Scale fo	or Depres	ssion (HAM-D) <i>i</i>	AND HAMD item # 1 (depre	essed mo	od)
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	16/29 (55.2%)	4/28 (14.3%)	RR 3.86 (1.47 to 10.13)	409 more per 1000 (from 67 more to 1000 more)	⊕000 VERY LOW	
								14.3%		409 more per 1000 (from 67 more to 1000 more)		

² 95% CI crosses two clinical decision thresholds

³ Data is not reported or cannot be extracted for all outcomes

•	(follow-up mo		eks; assessed with	: Number of peo	ple showing	≥50% improvemen	t on Hamilto	on Ratino	Scale for Dep	ression (HAM-D) AND muc	h/very mu	ıch
1	randomised	very	no serious	no serious	serious ²	reporting bias ³	19/29	7/28	RR 2.62 (1.31	405 more per 1000 (from	\oplus OOO	
	trials	serious ¹	inconsistency	indirectness			(65.5%)	(25%)	to 5.24)	77 more to 1000 more)	VERY	
											LOW	
								25%		405 more per 1000 (from		
										77 more to 1000 more)		
Depression	on symptomat	ology (foll	ow-up mean 10 we	eks; measured w	rith: Hamiltor	n Rating Scale for D	Depression	(HAM-D;	change score)	; Better indicated by lower	values)	
1	randomised	very	no serious	no serious	serious4	reporting bias ³	29	28	-	SMD 1.31 lower (1.89 to	\oplus OOO	
	trials	serious1	inconsistency	indirectness						0.74 lower)	VERY	
											LOW	

¹ Risk of bias is unclear or high across multiple domains ² OIS not met (events<300)

Phenelzine versus placebo for chronic depressive symptoms

	Quality assessment No of Design Risk of Inconsistency Indirectness Imprecision Consideration									Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Placebo	Relative (95% CI)	Absolute		
Response	(follow-up me	ean 6 week	s; assessed with:	Number of people	e rated as mi	uch or very much i	improved or	Clinical	Global Impres	sions scale (CGI-I))		
1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	7/12 (58.3%)	9/27 (33.3%)	RR 1.75 (0.85 to 3.58)	250 more per 1000 (from 50 fewer to 860 more)	⊕OOO VERY LOW	
								33.3%		250 more per 1000 (from 50 fewer to 859 more)		

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses one clinical decision threshold

8 9

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³ Funding from pharmaceutical company and data is not reported/cannot be extracted for all outcomes

⁴ OIS not met (N<400)

³ Data is not reported or cannot be extracted for all outcomes

Phenelzine versus imipramine for chronic depressive symptoms

THEHEL	THE VEI3U3	iiiipiaii	ille for Ciliotii	c depressive s	symptoms							
			Quality asse	essment			No of p	oatients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Imipramine	Relative (95% CI)	Absolute		
Response	(follow-up m	ean 6 wee	ks; assessed with	: Number of peop	ple rated as n	nuch or very much	improved	on Clinical G	Blobal Impress	sions scale (CGI-I))		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	reporting bias ³	7/12 (58.3%)	14/18 (77.8%)	RR 0.75 (0.44 to 1.28)	194 fewer per 1000 (from 436 fewer to 218 more)	⊕OOO VERY LOW	
								77.8%		195 fewer per 1000 (from 436 fewer to 218 more)		
Depression	n symptomat	ology (foll	low-up mean 6 we	eks; measured w	ith: Hamilton	Rating Scale for	Depression	(HAM-D at e	ndpoint); Bett	er indicated by lower valu	res)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	16	16	-	SMD 0.73 lower (1.45 to 0.01 lower)	⊕000 VERY LOW	
Discontin	uation for any	reason (f	ollow-up mean 6 v	veeks; assessed	with: Numbe	r of participants d	iscontinuin	g for any rea	son including	adverse events)		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	3/19 (15.8%)	4/20 (20%)	RR 0.79 (0.2 to 3.07)	42 fewer per 1000 (from 160 fewer to 414 more)	⊕OOO VERY LOW	
								20%		42 fewer per 1000 (from 160 fewer to 414 more)		
Discontin	uation due to	adverse e	vents (follow-up n	nean 6 weeks; as	sessed with:	Number of partici	pants disco	ntinuing due	e to adverse e	vents)		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	3/19 (15.8%)	4/20 (20%)	RR 0.79 (0.2 to 3.07)	42 fewer per 1000 (from 160 fewer to 414 more)	⊕000 VERY LOW	
								20%		42 fewer per 1000 (from 160 fewer to 414 more)		

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses two clinical decision thresholds

 $^{^{\}rm 3}$ Data is not reported or cannot be extracted for all outcomes $^{\rm 4}$ OIS not met (N<400)

Maintenance phenelzine versus placebo for relapse prevention in chronic depressive symptoms

							, ,					
	Quality assessment Other							nts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance phenelzine	Placebo	Relative (95% CI)	Absolute		
Relapse (f	follow-up mea	an 26 weel	ks; assessed with:	≥3 on CGI-I on 2	consecutive	e weeks)		'				
	randomised trials	· ,	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	3/13 (23.1%)	13/15 (86.7%)	RR 0.27 (0.1 to 0.73)	633 fewer per 1000 (from 234 fewer to 780 fewer)	⊕000 VERY LOW	
								86.7%		633 fewer per 1000 (from 234 fewer to 780 fewer)		
Discontin	uation for any	/ reason (f	follow-up mean 26	weeks; assesse	d with: Numl	ber of participants	discontinuing fo	r any rea	son including	adverse events)		
1	randomised trials	· ,	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	0/13 (0%)	0/15 (0%)	not pooled	not pooled	⊕OOO VERY LOW	
								0%		not pooled		

¹ Risk of bias is unclear or high across multiple domains

Moclobemide versus placebo for dysthymia or chronic depressive symptoms

			Quality asse	essment			No of pati	ients		Effect	Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Placebo	Relative (95% CI)	Absolute		
Remission	n (follow-up n	nean 8 wee	ks; assessed with	: Number of peo	ole scoring ≤	4 on Hamilton Rat	ing Scale for D	Depression	on (HAM-D))			
	randomised trials	- J		no serious indirectness	serious ²	none	33/104 (31.7%)	16/97 (16.5%)	RR 1.92 (1.13 to 3.27)	152 more per 1000 (from 21 more to 374 more)	⊕000 VERY LOW	
								16.5%		152 more per 1000 (from 21 more to 375 more)		

² OIS not met (events<300)
³ Data is not reported or cannot be extracted for all outcomes

	randomised trials n symptomat	very serious ¹ ology (foll	no serious inconsistency ow-up mean 8 wee	no serious indirectness eks; measured wi	serious ² th: Hamilton	none Rating Scale for D	74/104 (71.2%)	29/97 (29.9%) 29.9% AM-D; ch	to 3.31)	413 more per 1000 (from 212 more to 691 more) 413 more per 1000 (from 212 more to 691 more) etter indicated by lower v	#OOO VERY LOW	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	104	97	-	SMD 1.03 lower (1.33 to 0.74 lower)	⊕OOO VERY LOW	
Discontinu	uation for any	reason (f	ollow-up mean 8 w	eeks; assessed v	with: Numbe	r of participants di	scontinuing fo	or any rea	ason including	adverse events)		
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	13/108 (12%)	15/104 (14.4%)	`	25 fewer per 1000 (from 84 fewer to 97 more)	⊕OOO VERY LOW	
								14.4%		24 fewer per 1000 (from 84 fewer to 96 more)		
Discontinu	uation due to	adverse e	vents (follow-up m	ean 8 weeks; ass	sessed with:	Number of particip	ants disconti	nuing du	e to adverse ev	vents)		
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	7/108 (6.5%)	2/104 (1.9%)	RR 3.37 (0.72 to 15.85)	46 more per 1000 (from 5 fewer to 286 more)	⊕OOO VERY LOW	
								1.9%		45 more per 1000 (from 5 fewer to 282 more)		

¹ Risk of bias is unclear or high across multiple domains ² OIS not met (events<300) ³ OIS not met (N<400)

Moclobemide versus imipramine for chronic depressive symptoms

			Quality asse	ssment			No of pa	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Imipramine	Relative (95% CI)	Absolute		
Remission	ı (follow-up m	ean 8 wee	ks; assessed with	: Number of peo	ple scoring	4 on Hamilton Ra	ting Scale for	Depression	(HAM-D))			

⁴ 95% CI crosses two clinical decision thresholds

1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	33/104 (31.7%)	19/94 (20.2%)	RR 1.57 (0.96 to 2.56)	115 more per 1000 (from 8 fewer to 315 more)	⊕OOO VERY LOW	
								20.2%		115 more per 1000 (from 8 fewer to 315 more)		
Response	(follow-up m	ean 8 wee	ks; assessed wit	h: Number of peo	ple showing	≥50% improveme	ent on Hamilton	Rating Sca	le for Depress	ion (HAM-D))		
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	74/104 (71.2%)	65/94 (69.1%)	RR 1.03 (0.86 to 1.23)	21 more per 1000 (from 97 fewer to 159 more)	⊕OOO VERY LOW	
								69.2%		21 more per 1000 (from 97 fewer to 159 more)		
Depression	on symptomat	ology (fol	low-up mean 8 w	eeks; measured v	vith: Hamilto	n Rating Scale fo	r Depression (H	IAM-D; chai	nge score); Be	tter indicated by lower v	ralues)	
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	104	94	-	SMD 0.16 lower (0.44 lower to 0.12 higher)	⊕000 VERY LOW	
Discontin	uation for any	reason (1	follow-up mean 8	weeks; assessed	with: Numb	er of participants	discontinuing f	or any reas	on including a	dverse events)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	none	13/108 (12%)	15/103 (14.6%)	to 1.65)	25 fewer per 1000 (from 86 fewer to 95 more) 25 fewer per 1000 (from	⊕OOO VERY LOW	
			12.11		<u> </u>			14.6%		86 fewer to 95 more)		
Discontin	uation due to	adverse e	vents (follow-up	mean 8 weeks; as	ssessed with	n: Number of parti	cipants discont	inuing due	to adverse eve	ents)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	none	7/108 (6.5%)	11/103 (10.7%)	to 1.51)	42 fewer per 1000 (from 81 fewer to 54 more)	⊕OOO VERY LOW	
								10.7%		42 fewer per 1000 (from 81 fewer to 55 more)		

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses one clinical decision threshold ³ OIS not met (events<300)

⁴ OIS not met (N<400)

⁵ 95% CI crosses two clinical decision thresholds

Moclobemide versus fluoxetine four double depression

			Quality asse	essment			No of par	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Fluoxetine	Relative (95% CI)	Absolute		
Response	(follow-up m	ean 6 wee	ks; assessed with	: ≥50% improven	nent on HAMI	D)					ļ	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	15/21 (71.4%)	8/21 (38.1%)	RR 1.88 (1.02 to 3.45)	335 more per 1000 (from 8 more to 933 more)	⊕000 VERY LOW	
								38.1%		335 more per 1000 (from 8 more to 933 more)		
Discontin	uation for any	reason (f	ollow-up mean 6 v	veeks; assessed	with: Numbe	r of participants d	iscontinuing fo	or any reas	on including a	dverse events)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	0/21 (0%)	0/21 (0%)	not pooled	not pooled	⊕000 VERY LOW	
								0%		not pooled		
Discontin	uation due to	adverse e	vents (follow-up m	nean 6 weeks; as	sessed with:	Number of partici	pants disconti	nuing due	to adverse eve	ents)		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	0/21 (0%)	0/21 (0%)	not pooled	not pooled	#000 VERY LOW	
Ĺ			as multiple demains					0%		not pooled		

¹ Risk of bias is unclear or high across multiple domains

Amisulpride versus placebo for dysthymia or double depression

			Quality asse	ssment			No of pat	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amisulpride	Placebo	Relative (95% CI)	Absolute		

² OIS not met (events<300)
³ One of the authors is employed by pharmaceutical company and data is not reported/cannot be extracted for all outcomes

	randomised	serious1	no serious	no serious	serious ²	reporting bias3	26/73	16/73	RR 1.62 (0.95	136 more per 1000 (from	⊕OOO
	trials		inconsistency	indirectness			(35.6%)	(21.9%)	to 2.77)	11 fewer to 388 more)	VERY LOW
								21.9%		136 more per 1000 (from 11 fewer to 388 more)	
espor	se (follow-up 13	3-26 weeks	s; assessed with:	Number of peop	le rated as m	uch or very much i	mproved on C	Clinical G	lobal Impression	ons scale (CGI-I))	
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	101/150 (67.3%)	52/157 (33.1%)	RR 2.03 (1.59 to 2.61)	341 more per 1000 (from 195 more to 533 more)	⊕OOO VERY LOW
								33.2%		342 more per 1000 (from 196 more to 535 more)	
epres	sion symptomat	tology (fol	low-up mean 13 v	veeks; measured	with: Montgo	omery Asberg Depi	ression Rating	g Scale (N	//ADRS; chang	e score); Better indicated	by lower value
					_				_		_
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	101	105	-	SMD 0.68 lower (0.97 to 0.4 lower)	⊕OOO VERY LOW
Discon	trials	serious¹	inconsistency	indirectness		none of participants dis			- son including a	0.4 lower)	VERY
Discon	trials	serious¹	inconsistency	indirectness				r any reas	RR 0.87 (0.68	0.4 lower)	VERY
Discon	trials tinuation for any	serious ¹ / reason (f	inconsistency ollow-up 13-26 w	indirectness eeks; assessed v	vith: Number	of participants dis	continuing for	78/181	RR 0.87 (0.68	0.4 lower) adverse events) 56 fewer per 1000 (from	VERY LOW
	trials tinuation for any randomised trials	serious ¹ / reason (f	ollow-up 13-26 w no serious inconsistency	eeks; assessed v	vith: Number	of participants dis	67/177 (37.9%)	78/181 (43.1%) 44.1%	RR 0.87 (0.68 to 1.12)	0.4 lower) adverse events) 56 fewer per 1000 (from 138 fewer to 52 more) 57 fewer per 1000 (from 141 fewer to 53 more)	VERY LOW
!	trials tinuation for any randomised trials	serious ¹ / reason (f	ollow-up 13-26 w no serious inconsistency	eeks; assessed v	vith: Number	of participants dis	67/177 (37.9%)	78/181 (43.1%) 44.1%	RR 0.87 (0.68 to 1.12)	0.4 lower) adverse events) 56 fewer per 1000 (from 138 fewer to 52 more) 57 fewer per 1000 (from 141 fewer to 53 more)	VERY LOW

¹ Risk of bias is unclear or high across multiple domains ² 95% CI crosses one clinical decision threshold

³ Data is not reported or cannot be extracted for all outcomes

⁴ OIS not met (events<300) ⁵ OIS not met (N<400)

Complex depression (chapter 10)

CBT/behavioural therapies versus psychodynamic therapies

			Quality ass	essment			No of p	atients		Effect		_
											Quality	Importan
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT/behavioural therapies	Psychodynamic therapies	Relative (95% CI)	Absolute		
epressi	on symptom	atology a	t endpoint (meas	ured with: BDI;	Better indic	ated by lower valu	ues)					
	randomised	very	no serious	no serious	serious ²	none	26	25	-	MD 6.35 lower	⊕000	CRITICA
	trials	serious1	inconsistency	indirectness						(13.18 lower to	VERY	
										0.47 higher)	LOW	
epressi	on symptom	atology (1	ollow-up 12 wee	ks; measured w	 vith: BDI; Bet	ter indicated by lo	ower values)					
										1	1	
		very	no serious		serious ²	none	26	25	-	MD 0.3 lower (0.86		CRITICA
	trials	serious ¹	inconsistency	indirectness						lower to 0.25	VERY	
										higher)	LOW	
	on symptom	atology (f	ollow-up 24 wee	ks: measured w	rith: BDI; Bet	ter indicated by lo	ower values)				l	
epressi	o o jp.co	uco.og, (.										
						_	·			I		l
	randomised	very	no serious	no serious	serious ³	none	12	12	-	MD 9.00 lower	⊕000	CRITICA
						_	·	12	-	(16.09 to 1.91	VERY	CRITICA
	randomised	very	no serious	no serious		_	·	12	-			CRITICAI
	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	_	12	12	-	(16.09 to 1.91	VERY	CRITICA
epressi	randomised trials on symptom	very serious ¹ atology (1	no serious inconsistency follow-up 36 week	no serious indirectness ks; measured w	serious ³	none ter indicated by lo	12 Dwer values)		-	(16.09 to 1.91 lower)	VERY LOW	
epressi	randomised trials on symptom randomised	very serious ¹ atology (t	no serious inconsistency follow-up 36 week	no serious indirectness ks; measured w	serious ³ vith: BDI; Bet	none	12	12	-	(16.09 to 1.91 lower)	VERY LOW	
epressi	randomised trials on symptom	very serious ¹ atology (1	no serious inconsistency follow-up 36 week	no serious indirectness ks; measured w	serious ³	none ter indicated by lo	12 Dwer values)		-	(16.09 to 1.91 lower)	VERY LOW	CRITICAL
epressi	randomised trials on symptom randomised trials	very serious ¹ atology (for very serious ¹	no serious inconsistency ollow-up 36 week no serious inconsistency	no serious indirectness ks; measured w no serious indirectness	serious ³ vith: BDI; Bet very serious ⁴	none ter indicated by lo	12 ower values) 12		-	(16.09 to 1.91 lower) MD 3.00 lower (11.84 lower to	VERY LOW ⊕OOO VERY	
epressi	randomised trials on symptom randomised trials on symptom	very serious ¹ atology (for very serious ¹	no serious inconsistency ollow-up 36 week no serious inconsistency	no serious indirectness ks; measured w no serious indirectness	serious ³ vith: BDI; Bet very serious ⁴	none ter indicated by lo	12 ower values) 12 ver values)	12	-	(16.09 to 1.91 lower) MD 3.00 lower (11.84 lower to 5.84 higher)	VERY LOW ⊕OOO VERY	CRITICA
epressi	randomised trials on symptom randomised trials on symptom	very serious ¹ very serious ¹ very serious ¹	no serious inconsistency ollow-up 36 week no serious inconsistency	no serious indirectness ks; measured w no serious indirectness ; measured with	serious ³ vith: BDI; Bet very serious ⁴ h: BDI; Bette very	none ter indicated by lo	12 ower values) 12		-	(16.09 to 1.91 lower) MD 3.00 lower (11.84 lower to 5.84 higher) MD 0.25 higher	VERY LOW ⊕OOO VERY	
epressi	randomised trials on symptom randomised trials on symptom	very serious ¹ atology (t very serious ¹	no serious inconsistency ollow-up 36 weel no serious inconsistency ollow-up 1 years	no serious indirectness ks; measured w no serious indirectness ; measured with	serious ³ vith: BDI; Bet very serious ⁴ h: BDI; Bette	none ter indicated by lo	12 ower values) 12 ver values)	12	-	(16.09 to 1.91 lower) MD 3.00 lower (11.84 lower to 5.84 higher)	UERY LOW ⊕OOO VERY LOW	CRITICA
epressi	randomised trials on symptom randomised trials on symptom randomised	very serious ¹ very serious ¹ very serious ¹	no serious inconsistency follow-up 36 weel no serious inconsistency follow-up 1 years no serious	no serious indirectness ks; measured w no serious indirectness ; measured with	serious ³ vith: BDI; Bet very serious ⁴ h: BDI; Bette very	none ter indicated by lo	12 ower values) 12 ver values)	12	-	(16.09 to 1.91 lower) MD 3.00 lower (11.84 lower to 5.84 higher) MD 0.25 higher	⊕OOO VERY LOW	CRITICA

6

Pharmacotherapy versus combination therapy (pharmacotherapy + SPSP)

Quality assessment	No of patients	Effect	Quality	Importance

¹ High or unclear ROB across multiple domains

² I2 >80%

³ 95% CI crosses two clinical decision thresholds

⁴ High risk of bias for selective outcome reporting and allocation concealment unlikely to affect results, however unclear effect of bias from missing outcome data

⁵ Confidence intervals cross 1 minimally important difference. Sample size less than optimal information size (<400 for continuous outcomes or <300 events for dichotomous outcomes).

- ⁶ High ROB across multiple domains ⁷ OIS not met (<400 participants)
- 3
- Psychotic depression (chapter 10)
- Antidepressants versus other pharmacological interventions
- Antidepressants versus placebo

		<u>'</u>										
			Quality asse	essment			No of patie	ents		Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant	Placebo	Relative (95% CI)	Absolute		
Depressiv	ve symptoms	at endpoi	nt (HAMD 17) - TCA	versus placebo	(Better indic	ated by lower valu	ies)			L		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	69	67	-	MD 3 lower (4.71 to 1.29 lower)	⊕⊕OO LOW	CRITICAL
Remission	n - TCA versu	s placebo										
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	very serious ⁴	none	4/10 (40%)	0/10 (0%)	RR 9 (0.55 to 147.95)	-	⊕000 VERY LOW	CRITICAL
Response	e - TCA versus	placebo						0 70		-		
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	53/69 (76.8%)	15/67 (22.4%) 22.4%	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
Discontin	uation - TCA	versus pla	cebo	<u> </u>	'	<u>'</u>			 	-		
2	randomised trials	serious ³	no serious inconsistency	no serious indirectness	very serious ⁴	none	7/86 (8.1%)	3/87 (3.4%)	RR 1.88 (0.4 to 8.82)	30 more per 1000 (from 21 fewer to 270 more) 101 more per 1000 (from	⊕OOO VERY LOW	CRITICAL
								11.5%		69 fewer to 899 more)		

- Unclear ROB across multiple domians
 OIS not met (<400 participants)
 High ROB in one domain and unclear in several others
 95% CI crosses two clinical decision thresholds

 - ⁵ OIS not met (<300 events)

Antidepressants versus antidepressants 6

			Quality asse	ssment			No of p	oatients		Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant	Antidepressant	Relative (95% CI)	Absolute		
Depressi	ve symptoms	s at endpoir	nt - TCA versus S	NRI (Better indi	icated by low	ver values)						
1			no serious inconsistency	no serious indirectness	very serious ¹	none	17	12	-	MD 1.1 higher (1.47 lower to 3.67 higher)	⊕⊕OO LOW	CRITICAL
Depressi	ve symmptoi	ms at endpo	oint - TCA (clomi	oramine) versus	TCA (imipra	amine) (Better ind	licated by lower	values)				
1			no serious inconsistency	no serious indirectness	very serious ¹	none	12	10	-	MD 0.3 higher (8.72 lower to 9.32 higher)	⊕⊕OO LOW	CRITICAL
Remission	on - SSRI vers	sus SNRI				<u> </u>						<u> </u>
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	9/11 (81.8%)	6/11 (54.5%)	RR 1.5 (0.82 to 2.75)	273 more per 1000 (from 98 fewer to 955 more)	⊕⊕OO LOW	CRITICAL
								54.6%		273 more per 1000 (from 98 fewer to 956 more)		
Remission	on - SSRI (ser	rtraline) ver	sus SSRI (paroxe	tine)								
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	13/18 (72.2%)	3/14 (21.4%)	RR 3.37 (1.19 to 9.57)	508 more per 1000 (from 41 more to 1000 more)	⊕⊕OO LOW	CRITICAL

								1			
									507 more per 1000		
							21.4%		(from 41 more to		
									1000 more)		
mission - TCA	versus SNRI										
random	ised no serio	no serious	no serious	serious ³	none	15/20	11/12	RR 0.82	165 fewer per 1000	⊕⊕⊕О	CRITIC
trials	risk of bi		indirectness			(75%)	(91.7%)			MODERATE	
						,	,	,	101 more)		
								-	165 fewer per 1000		
							91.7%		(from 367 fewer to		
									101 more)		
sponse - TCA	versus atypic	al ADM	<u>'</u>					<u>'</u>			
random	ised serious ⁴	no serious	no serious	very	none	9/15	7/15	RR 1.29	135 more per 1000	⊕OOO	CRITIC
trials		inconsistency	indirectness	serious1		(60%)	(46.7%)	(0.65 to	(from 163 fewer to	VERY LOW	
						(1111)	(2.54)	719 more)	72.11.2011	
									135 more per 1000		
							46.7%		(from 163 fewer to		
									719 more)		
sponse - TCA	versus SNRI		_	'							
random	ised no serio	s no serious	no serious	serious ³	none	16/20	12/13	RR 0.87	120 fewer per 1000	⊕⊕⊕О	CRITIC
trials	risk of bi		indirectness	Scrious	none	(80%)	(92.3%)	(0.66 to	(from 314 fewer to		Ortifi
uidio	Hok or bi	as inconsistency	indirectricos			(0070)	(02.070)	1.13)	120 more)	MODEIVATE	
									120 fewer per 1000		
							92.3%		(from 314 fewer to		
							92.570		120 more)		
sponse - TCA	versus SSRI										
random	ised serious ⁴	no serious	no serious	serious ³	none	16/25	7/25	RR 2.29	361 more per 1000	⊕⊕OO	CRITIC
trials		inconsistency	indirectness			(64%)	(28%)	(1.14 to	(from 39 more to	LOW	
								4.58)	1000 more)		
									361 more per 1000		
							28%		(from 39 more to		
									1000 more)		
continuation	- TCA versus	atypical antidepre	ssant								

1 r	randomised	serious4	no serious	no serious	very	none	4/15	8/15	RR 0.5	267 fewer per 1000	⊕OOO	CRITICAL
	trials	0011000	inconsistency	indirectness	serious ¹		(26.7%)	(53.3%)	(0.19 to	(from 432 fewer to	VERY LOW	011110712
							(======================================	(0010)0)	1.31)	165 more)	VEIXI EOII	
									,,,	,		
										266 fewer per 1000		
								53.3%		(from 432 fewer to		
										165 more)		
Discontin	uation - TCA	versus SS	RI	•								
 	randomised	serious4	no serious	no serious	very	none	4/25	2/25	RR 2 (0.4 to	80 more per 1000	⊕000	CRITICAL
	trials	Serious	inconsistency	indirectness	serious ¹	TIONE	(16%)	(8%)	9.95)	(from 48 fewer to	VERY LOW	CRITICAL
	iiiais		inconsistency	indirectiness	SCHOUS		(1070)	(070)	3.33)	716 more)	VLKI LOW	
										7 To more)		
									1	80 more per 1000		
								8%		(from 48 fewer to		
										` 716 more)		
Discontin	uation - TCA	versus SN	RI	-			-	-				
						1	1 202			I		
		no serious	no serious	no serious	very	none	3/20	1/13	RR 1.95	73 more per 1000	⊕⊕⊙⊙	CRITICAL
t	trials	risk of bias	inconsistency	indirectness	serious ⁵		(15%)	(7.7%)	(0.23 to	(from 59 fewer to	LOW	
									16.79)	1000 more)		
									4	72 mars par 1000		
								7.7%		73 more per 1000 (from 59 fewer to		
								1.170		1000 more)		
Discontin	uation - TCA	(clominrar	nine) versus TC	A (iminramine)						1000 111010)		
) i scontini	uation - 102	(Cloninpiai	illie, versus ro	- (minpramme)								
l r	randomised	serious ²	no serious	no serious	very	none	0/12	2/12	RR 0.2	133 fewer per 1000	⊕000	CRITICAL
t	trials		inconsistency	indirectness	serious1		(0%)	(16.7%)	(0.01 to	(from 165 fewer to	VERY LOW	
									3.77)	462 more)		
										134 fewer per 1000		
								16.7%		(from 165 fewer to		
										463 more)		
Discontin	uation - SSF	RI (sertraline	e) versus SSRI (p	paroxetine)								
1 r	randomised	serious ²	no serious	no serious	serious ³	none	0/18	5/14	RR 0.07 (0	332 fewer per 1000	⊕⊕00	CRITICAL
	trials		inconsistency	indirectness			(0%)	(35.7%)	to 1.2)	(from 357 fewer to	LOW	
			,				(2.2.7)	(,	,	71 more)	2011	
										,		
									7	332 fewer per 1000		
								35.7%		(from 357 fewer to		
										71 more)		

scontin	nuation - SSF	RI versus SI	IRI									
	randomised	serious ²	no serious	no serious	very	none	0/11	2/11	RR 0.2	145 fewer per 1000		CRITICA
	trials		inconsistency	indirectness	serious ¹		(0%)	(18.2%)	(0.01 to 3.74)	(from 180 fewer to 498 more)	VERY LOW	
										146 fewer per 1000		
								18.2%		(from 180 fewer to 499 more)		
scontir	nuation due t	to side effec	ts - TCA (clomip	ramine) versus	TCA (imipra	mine)						
	1					1						
	randomised	serious ²	no serious	no serious	very	none	0/12	2/12	RR 0.2	133 fewer per 1000	⊕000	CRITIC
	randomised trials	serious ²		no serious indirectness	very serious ¹	none	0/12 (0%)	2/12 (16.7%)	RR 0.2 (0.01 to	133 fewer per 1000 (from 165 fewer to		CRITIC
		serious ²				none						CRITIC
		serious ²				none			(0.01 to	(from 165 fewer to 462 more)	VERY LOW	CRITIC
		serious ²				none			(0.01 to	(from 165 fewer to	VERY LOW	CRITIO

¹ 95% CI crosses two clinical decision thresholds

Antidepressants versus antipsychotics

			Quality assessr		No of p	atients	Eff	ect	Quality	Importance		
No of studies	Design	Risk of bias	Other considerations	Antidepressant	Antipsychotic	Relative (95% CI)	Absolute	_	•			
Remission	nission - TCA versus antipsychotic										l.	
				no serious indirectness	very serious ¹	none	7/19 (36.8%)	3/17 (17.6%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
								17.7%		not pooled		

² Unclear ROB across multiple domains

³ 95% CI crosses one clinical decision threshold

⁴ High ROB in at least one domain and unclear in several others

⁵ No explanation was provided

Discontinu	iscontinuation - TCA versus antipsychotic												
								=					
1	randomised	no serious risk	no serious	no serious	very	none	2/19	1/17	not	not	$\oplus \oplus OO$	CRITICAL	
	trials	of bias	inconsistency	indirectness	serious ¹		(10.5%)	(5.9%)	pooled	pooled	LOW		
										not			
								5.9%		pooled			
1 / /			1							pooled			

¹ 95% CI crosses two clinical decision thresholds

1

2

Antidepressants versus combined antipsychotic and antidepressants

Antiuck	nessants v	versus co	ппыпеч апцр	sychotic and	и апписрі	Coodiito						
			Quality asse	ssment			No of patients			Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant versus antipsychotic + antidepressant	Control	Relative (95% CI)	Absolute		
Depressi	on symptom	atology at	endpoint (HAMD-	17) - SNRI vers	us antipsych	otic + SNRI (Bette	er indicated by lower valu	es)				
4					1	I	40	0.4		NAD 0.01 (0.44		ODITION
	randomised trials	no serious		no serious	,	none	12	24	-	MD 0.3 lower (2.44		CRITICAL
	แลเร	IISK OI DIAS	inconsistency	indirectness	serious ¹					lower to 1.84 higher)	LOW	
Depressi	on symptom	atology at	endpoint (HAMD-	17) - Tetracycli	c versus anti	psychotic +TCA (Better indicated by lower	values)				
	randomised	very	no serious	no serious	,	none	17	18	-	MD 0.9 higher (5	\oplus OOO	CRITICAL
	trials	serious ²	inconsistency	indirectness	serious ¹					lower to 6.8 higher)	VERY LOW	
Depressi	on symptom	atology at	endpoint (HAMD-	17) - TCA versu	s antipsycho	otic + SNRI (Bette	r indicated by lower value	es)				
1	randomised	no serious	no serious	no serious	very	none	17	24	_	MD 1.4 lower (4.12	⊕⊕ОО	CRITICAL
	trials			indirectness	serious ¹					lower to 1.32	LOW	0
										higher)		
Remission	on - TCA vers	sus TCA + a	ntipsychotic									
1	randomised	no serious	no serious	no serious	serious ³	none	7/17	14/18	RR 0.53	366 fewer per	⊕⊕⊕О	CRITICAL
	trials	risk of bias	inconsistency	indirectness			(41.2%)	(77.8%)	(0.28 to	1000 (from 16	MODERATE	
									0.98)	fewer to 560 fewer)		
		I .	1	1		ı		1		1		

		1	1		1							1
								77.8%		366 fewer per 1000 (from 16		
								11.0%		fewer to 560 fewer)		
	n CNDI vor	oue entines	chatia I CNDI							iewei to 300 iewei)		
mission	n - SNKI vers	sus antipsy	rchotic + SNRI									
		no serious		no serious	serious ³	none	11/12	20/24	RR 1.1	83 more per 1000	$\oplus \oplus \oplus O$	CRITI
tr	trials	risk of bias	inconsistency	indirectness			(91.7%)	(83.3%)	(0.86 to	(from 117 fewer to	MODERATE	
									1.41)	342 more)		
										83 more per 1000		
								83.3%		(from 117 fewer to		
										342 more)		
nissior	n - TCA vers	us antipsy	chotic + SNRI	<u> </u>			•	•				
lr	randomised	no serious	no serious	no serious	serious ³	none	15/17	20/24	RR 1.06	50 more per 1000	⊕⊕⊕О	CRIT
			inconsistency	indirectness	0011000	nono	(88.2%)	(83.3%)	(0.83 to	(from 142 fewer to		
							(551275)	(001070)	1.36)	300 more)	MODEROTIE	
										50 more per 1000		
								83.3%		(from 142 fewer to		
								03.370		300 more)		
sponse	e - SNRI vers	sus antipsy	chotic + SNRI							,		
l _a	randomised	no serious	lno corious	no serious	serious ⁴	none	12/12	23/24	RR 1.02	19 more per 1000	0000	CRIT
			inconsistency	indirectness	serious	none	(100%)	(95.8%)	(0.88 to	(from 115 fewer to	⊕⊕⊕O	_
u	uiais	lisk oi bias	inconsistency	indirectriess			(100%)	(93.6%)	1.18)	172 more)	MODERATE	
									1.10)	172 more)		
										19 more per 1000		
								95.8%		(from 115 fewer to		
										172 more)		
ponse	e - Tetracycli	ic versus a	ntipsychotic + T	CA								
r		very	no serious	no serious	serious ³	none	12/17	17/18	RR 0.75	236 fewer per	⊕OOO	CRIT
t	trials	serious ²	inconsistency	indirectness			(70.6%)	(94.4%)	(0.54 to	1000 (from 434	VERY LOW	
									1.04)	fewer to 38 more)		
		1								236 fewer per		
								94.4%		1000 (from 434		

	randomised	no serious	no serious	no serious	serious4	none	16/17	23/24	RR 0.98	19 fewer per 1000	⊕⊕⊕О	CRITICAL
			inconsistency	indirectness	SCHOUS	Horic	(94.1%)	(95.8%)		(from 144 fewer to		ONTHOAL
	indio.	non or blac	inconcionation	in an ooth ood			(01.170)	(00.070)	1.14)	134 more)	MODEIVATE	
									,			
										19 fewer per 1000		
								95.8%		(from 144 fewer to		
										134 more)		
Discontir	nuation - SNF	RI versus ar	ntipsychotic + SN	IRI								
	randomised	no serious	no serious	no serious	very	none	1/13	2/26	RR 1 (0.1 to	0 fewer per 1000	⊕⊕OO	CRITICAL
			inconsistency	indirectness	serious ¹		(7.7%)	(7.7%)	10.04)	(from 69 fewer to	LOW	
			Ţ				,		,	695 more)		
										0 fewer per 1000		
								7.7%		(from 69 fewer to		
										696 more)		
Discontir	nuation - Tetr	acyclic ver	sus antipsychoti	c + TCA								
	randomised	very	no serious	no serious	very	none	9/21	7/25	RR 1.53	148 more per 1000	⊕OOO	CRITICAL
			inconsistency	indirectness	serious ¹	none	(42.9%)	_	(0.69 to 3.4)		VERY LOW	CRITICAL
	liidis	Serious	inconsistency	indirectiless	Serious		(42.9%)	(20%)	(0.09 (0.3.4)	672 more)	VERT LOW	
										072 111016)		
										148 more per 1000		
								28%		(from 87 fewer to		
								2070		672 more)		
Discontin	uation - TC/	Voreue an	tipsychotic + SN	ļ Di						0.2		
) SCOTTE	iuation - Top	A versus ari	iipsycholic + 3N	M								
	randomised	no serious	no serious	no serious	very	none	3/20	2/26	RR 1.95	73 more per 1000	⊕⊕OO	CRITICAL
	trials	risk of bias	inconsistency	indirectness	serious1		(15%)	(7.7%)	(0.36 to	(from 49 fewer to	LOW	
									10.58)	737 more)		
										73 more per 1000		
								7.7%		(from 49 fewer to		
										738 more)		
Discontin	nuation - TCA	A versus an	tipsychotic + TC	A								
	randomised	serious ⁵	no serious	no serious	very	none	16/68	17/67	RR 0.92	20 fewer per 1000	⊕OOO	CRITICAL
	trials		inconsistency	indirectness	serious ¹		(23.5%)	(25.4%)		(from 124 fewer to		
			,				,	,	1.66)	` 167 more)		
									,	,		
									1	19 fewer per 1000		
		1						23.5%		(from 115 fewer to		
								20.070		(IIOIII I IO ICWCI TO		

7

8

Disconti	Discontinuation due to side effects - TCA versus antipsychotic + TCA													
2	randomised	serious ⁵	no serious	no serious	very	none	5/68	10/67	RR 0.52	72 fewer per 1000	\oplus OOO	CRITICAL		
	trials		inconsistency	indirectness	serious ¹		(7.4%)	(14.9%)	(0.19 to	(from 121 fewer to	VERY LOW			
									1.39)	58 more)				
										64 fewer per 1000				
								13.4%		(from 109 fewer to				
										52 more)				

¹ 95% CI crosses two clinical decision thresholds

Combined antidepressants and antipsychotics versus other pharmacological interventions

Antidepressants plus antipsychotics versus antidepressants plus placebo

			Quality ass	essment			No of patient	s		Effect	Quality	I mportance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant + antipsychotic	Antidepressant + placebo	Relative (95% CI)	Absolute		
Depress	ion sympton	natology	at endpoint (HAI	MD-17) - TCA +	antipsychot	ic versus TCA +	placebo (Better indicated b	y lower values)				
1	randomised trials			no serious indirectness	very serious ²	none	14	16	-	MD 1 higher (4.24 lower to 6.24 higher)	⊕OOO VERY LOW	CRITICAL
Remissi	on - TCA + a	ntipsych	otic versus TCA	+ placebo								
1	randomised trials			no serious indirectness	very serious ²	none	7/14 (50%)	7/16 (43.8%)	RR 1.14 (0.53 to 2.45)	61 more per 1000 (from 206 fewer to 634 more)	⊕OOO VERY LOW	CRITICAL
								43.8%		61 more per 1000 (from 206 fewer to 635 more)		

² High or unclear ROB in most domains

³ 95% CI crosses one clinical decision threshold

⁴ OIS not met (<300 participants)

⁵ Unclear ROB across multiple domains

3

Antidepressants plus antipsychotics versus antipsychotics plus placebo

			Quality asse	ssment			No of patients			Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant + antipsychotic versus antipsychotic + placebo	Control	Relative (95% CI)	Absolute		
Remissio	n - SSRI + aı	ntipsychoti	c versus antipsy	chotic + placel	00			-				
		no serious risk of bias		no serious indirectness	serious ¹	none	54/81 (66.7%)	31/61 (50.8%)		158 more per 1000 (from 10 fewer to 381 more)	⊕⊕⊕O MODERATE	CRITICAL
								50.8%		157 more per 1000 (from 10 fewer to 381 more)		
Treatmen	it discontinu	ation - SSR	RI + antipsychotic	c versus antips	ychotic + pla	icebo						
	randomised trials	no serious risk of bias		no serious indirectness	serious ¹	none	48/129 (37.2%)	69/130 (53.1%)		159 fewer per 1000 (from 42 fewer to 249 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								53.1%		159 fewer per 1000 (from 42 fewer to 250 fewer)		
¹ 95% CI o	crosses one c	linical decis	ion threshold									

¹ High ROB in one domain, unclear ROB in several others

² 95% CI crosses two clinical decision thresholds

2

7

8

3 Antipsychotics versus other pharmacological interventions

4 Antipsychotics versus placebo

			Quality asse	essment			No of pati	ents		Effect		
			Quality 1000				no or pau	<u>.</u>		2001	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic	Placebo	Relative (95% CI)	Absolute		
Response	ponse - Olanzapine versus placebo											
	randomised trials	serious ¹		no serious indirectness	very serious²	none	32/63 (50.8%)	(52.8%)	RR 0.94 (0.67 to 1.31)	32 fewer per 1000 (from 174 fewer to 164 more) 33 fewer per 1000 (from	⊕000 VERY LOW	CRITICAL
Treatment discontinuation - Olanzapine versus placebo												
	randomised trials	serious ¹		no serious indirectness	serious ³	none	38/101 (37.6%)	47/100 (47%)	RR 0.8 (0.58 to 1.09)	94 fewer per 1000 (from 197 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
			high DOD in one					47.2%		94 fewer per 1000 (from 198 fewer to 42 more)		

¹ Unclear ROB in most domains and high ROB in one

² 95% CI crosses two clinical decision thresholds

³ 95% CI crosses one clinical decision threshold

Antipsychotics versus antipsychotics plus antidepressants

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic	Antipsychotic + antidepressant	Relative (95% CI)	Absolute			
Response	Response - antipsychotic versus SSRI + antipsychotic												
1	randomised trials	serious ¹		no serious indirectness	serious ²	none	15/35 (42.9%)	14/14 (100%) 100%	RR 0.45 (0.3 to 0.66)	550 fewer per 1000 (from 340 fewer to 700 fewer) 550 fewer per 1000 (from 340 fewer to 700 fewer)	⊕⊕OO LOW	CRITICAL	
Treatmen	t discontinua	ition - ant	ipsychotic versus	antipsychotic	+SSRI					roo lewely			
1	randomised trials	serious ¹		no serious indirectness	serious ³	none	13/48 (27.1%)	11/25 (44%)	RR 0.62 (0.32 to 1.17)	167 fewer per 1000 (from 299 fewer to 75 more)	⊕⊕OO LOW	CRITICAL	
								44%		167 fewer per 1000 (from 299 fewer to 75 more)			

¹ Unclear ROB in most domains, and high ROB in one

3

4

Benzodiazepines versus other pharmacological interventions 5

Benzodiazepines versus placebo

			Quality asse	essment			No of patier	nts		Effect	Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines	Placebo	Relative (95% CI)	Absolute			
Depression	Depression symptomatology at endpoint (HAMD-17) - Lorazepam versus placebo (Better indicated by lower values)												
1	randomised trials			no serious indirectness	serious ²	none	59	67	-	MD 3.7 lower (5.6 to 1.8 lower)	⊕⊕OO LOW	CRITICAL	

² OIS not met (<300 participants) ³ 95% CI crosses one clinical decision threshold

oonse r	randomised trials - Lorazepam randomised trials	serious ¹ versus p serious ¹	no serious inconsistency lacebo	no serious indirectness	serious ²	none	62	67		MD 3.2 lower (5.03 to	⊕⊕OO LOW	CRITIC
r	randomised		lacebo							1.37 lower)	LOVV	4
		serious ¹										
		Serious	no serious	no serious	serious ³	none	40/59	15/67	RR 3.03 (1.88	454 more per 1000	⊕⊕OO	CRITI
·	lilais		inconsistency	indirectness	Serious	none	(67.8%)	(22.4%)	to 4.89)	(from 197 more to 871	LOW	CKIII
			inconsistency	illuli ectiless			(07.076)	(22.470)	10 4.09)	more)	LOVV	
										455 more per 1000		
								22.4%		(from 197 more to 871		
								22.170		more)		
onse	- Alprazolan	n versus p	olacebo									
r	randomised	serious ¹	no serious	no serious	serious ³	none	41/62	15/67	RR 2.95 (1.83	437 more per 1000	⊕⊕00	CRIT
t	trials		inconsistency	indirectness			(66.1%)	(22.4%)	to 4.77)	(from 186 more to 844	LOW	
			·						·	more)		
										437 more per 1000		
								22.4%		(from 186 more to 844		
										more)		
tment	discontinua	tion - Lor	azepam versus p	lacebo								
r	randomised	serious ¹	no serious	no serious	very	none	7/66	7/74	RR 1.12 (0.42	11 more per 1000 (from		CRIT
t	trials		inconsistency	indirectness	serious ⁴		(10.6%)	(9.5%)	to 3.03)	55 fewer to 192 more)	VERY	
								0.50/		11 more per 1000 (from	LOW	1
								9.5%		55 fewer to 193 more)		
ment	discontinua	tion - Alp	razolam versus p	lacebo								
r	randomised	serious ¹	no serious	no serious	very	none	8/70		RR 1.21 (0.46	20 more per 1000 (from	⊕000	CRIT
t	trials		inconsistency	indirectness	serious ⁴		(11.4%)	(9.5%)	to 3.16)	51 fewer to 204 more)	VERY	
										20 more per 1000 (from	LOW	4
								9.5%		51 fewer to 205 more)		
ontinu	ation due to	side effe	cts - Lorazepam	versus placebo								
r	randomised	serious ¹	no serious	no serious	very	none	1/66	0/74	RR 3.36 (0.14	-	⊕000	CRIT
t	trials		inconsistency	indirectness	serious4		(1.5%)	(0%)	to 81.05)		VERY	

Discon	discontinuation due to side effects - Alprazolam versus placebo														
					,		1								
1	randomised	serious ¹	no serious	no serious	very	none	3/70	0/74	RR 7.39 (0.39	-	\oplus OOO	CRITICAL			
	trials		inconsistency	indirectness	serious4		(4.3%)	(0%)	to 140.62)		VERY				
											LOW				
								0%		-					

- ¹ Unclear ROB in most domains

- OIS not met (<400 participants)
 OIS not met (<300 events)
 95% CI crosses two clinical decision thresholds

Benzodiazepines versus antidepressants

			· ·									
			Quality ass	essment			No of p	atients		Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines	Antidepressants	Relative (95% CI)	Absolute		
Depression	on symptoma	tology at	endpoint (HAMD	-17) - Lorazepar	n versus TC	A (Better indicate	d by lower values)					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	59	69	-	MD 0.7 lower (2.59 lower to 1.19 higher)	⊕000 VERY LOW	CRITICAL
Depression	on symptoma	tology at	endpoint (HAMD	-17) - Alprazola	m versus TC	A (Better indicate	d by lower values					
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	62	69	-	MD 0.2 lower (2.02 lower to 1.62 higher)	⊕000 VERY LOW	CRITICAL
Response	e - Lorazepar	n versus	ГСА									
	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	40/59 (67.8%)	53/69 (76.8%) 76.8%	RR 0.88 (0.71 to 1.1)	92 fewer per 1000 (from 223 fewer to 77 more) 92 fewer per 1000 (from 223 fewer to 77 more)	⊕⊕OO LOW	CRITICAL
Response	e - Alprazolar	n versus	TCA									

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	41/62 (66.1%)	53/69 (76.8%)	RR 0.86 (0.69 to 1.07)	108 fewer per 1000 (from 238 fewer to 54 more) 108 fewer per 1000 (from 238 fewer to	⊕⊕OO LOW	CRITICAL
								7 0.0 / 0		54 more)		
Treatmen	nt discontinua	ation - Lo	razepam versus	TCA	· ·					·		
			·									
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	7/66 (10.6%)	3/72 (4.2%)	RR 2.55 (0.69 to 9.44)	65 more per 1000 (from 13 fewer to 352 more)	⊕000 VERY LOW	CRITICAL
											2011	
								4.2%		65 more per 1000 (from 13 fewer to 354 more)		
Treatmen	nt discontinua	ation - Alp	razolam versus	TCA		<u>, </u>						
1		serious ¹	no serious	no serious	serious ³	none	8/70	3/72	RR 2.74	73 more per 1000	⊕⊕00	CRITICAL
	trials		inconsistency	indirectness			(11.4%)	(4.2%)	(0.76 to	(from 10 fewer to	LOW	
									9.92)	372 more)		
									1	73 more per 1000		
								4.2%		(from 10 fewer to		
										375 more)		
Disconti	nuation due to	o side eff	ects - Lorazepan	n versus TCA		<u>'</u>						
				_								
1		serious ¹	no serious	no serious	very	none	1/66	0/72	RR 3.27	-	⊕OOO	CRITICAL
	trials		inconsistency	indirectness	serious ²		(1.5%)	(0%)	(0.14 to		VERY	
								0%	78.87)		LOW	
Discorti	unation due to	o oido off	 ects - Alprazolar	n vorque TCA		<u> </u>		0%		-		
DISCONTI	iuation due to	o side em	ecis - Aiprazolar	ii versus ICA								
1	randomised	serious ¹	no serious	no serious	very	none	3/70	0/72	RR 7.2 (0.38	-	⊕OOO	CRITICAL
•	trials	3003	inconsistency	indirectness	serious ²		(4.3%)	(0%)	to 136.84)		VERY	2,
			,						,		LOW	
								0%		-		
¹ Unclear	ROB in most of	domains										

¹ Unclear ROB in most domains

² 95% CI crosses two clinical decision thresholds

³ 95% CI crosses one clinical decision threshold

1 Benzodiazepines versus benzodiazepines

Jenzoa	пагеритез	VC13G3 k	penzodiazepin				T		I		1	l
			Quality ass	assmant			No of r	patients		Effect		
			Quality ass	essinent			140 01 1	Jalients		Lilect		
											Quality	Importan
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines	Benzodiazepines	Relative (95% CI)	Absolute		
Depressi	on symptom	atology at	endpoint (HAMD	-17) - Lorazepa	m versus alp	razolam (Better in	ndicated by lower	values)				
	randomised	serious ¹	no serious	no serious	very	none	59	62	-	MD 0.5 lower (2.5	⊕000	CRITICA
	trials	SCHOUS		indirectness	serious ²	Hone	33	02		lower to 1.5 higher)	VERY	ORTHOA
Respons	e - Lorazepaı	m versus	alprazolam									
1	randomised	serious ¹	no serious	no serious	serious ³	none	40/59	41/62	RR 1.03	20 more per 1000	0000	CRITICA
	trials	Serious		indirectness	serious	Hone	(67.8%)	(66.1%)	(0.8 to 1.32)		⊕⊕OO LOW	CRITICAL
								22.40/		20 more per 1000		
								66.1%		(from 132 fewer to 212 more)		
reatmer	nt discontinu	ation - Lo	razepam versus a	lprazolam								
		serious ¹		no serious	,	none	7/66	8/70	RR 0.93	8 fewer per 1000	⊕OOO	CRITICA
	trials		inconsistency	indirectness	serious ²		(10.6%)	(11.4%)	(0.36 to 2.42)	(from 73 fewer to 162 more)	VERY LOW	
										8 fewer per 1000		
								11.4%		(from 73 fewer to 162 more)		
Discontir	nuation due t	o side eff	ects - Lorazepam	versus alprazo	lam							
	randomised trials	serious ¹		no serious indirectness	very serious ²	none	1/66 (1.5%)	3/70 (4.3%)	RR 0.35 (0.04 to 3.31)	28 fewer per 1000 (from 41 fewer to 99 more)	⊕000 VERY LOW	CRITICA
								4.20/	,	28 fewer per 1000		
								4.3%		(from 41 fewer to 99 more)		

- ¹ Unclear ROB across most domains
- ² 95% CI crosses two clinical decision thresholds
- ³ 95% CI crosses one clinical decision threshold

4

Relapse prevention (chapter 11)

5 6

Cognitive or cognitive behavioural therapies vs control

8

			Quality ass	essment			No of patient	s		Effect	Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive or cognitive behavioural therapies	Control	Relative (95% CI)	Absolute	Quality	Importance
Relapse	at endpoint (follow-up 10)-78 months; ass	essed with: LIF	E/SCID (discon	tinuation coded a	s relapse))					
6	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	99/357 (27.7%)	133/330 (40.3%)	RR 0.7 (0.57 to 0.85)	173 fewer)	⊕⊕⊕O MODERATE	
								36.5%		110 fewer per 1000 (from 55 fewer to 157 fewer)		
Relapse	at 1-2 month	follow-up (a	assessed with: LI	FE/SCID (disco	ntinuation code	ed as relapse))						
3	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	70/203 (34.5%)	85/181 (47%)	RR 0.73 (0.57 to 0.93)	127 fewer per 1000 (from 33 fewer to 202 fewer)	⊕⊕⊕O MODERATE	
								44.2%		119 fewer per 1000 (from 31 fewer to 190 fewer)		

Relapse	at 3-month fo	ollow-up (as	sessed with: LIF	E/SCID (discor	tinuation code	ed as relapse))					
2	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	39/138 (28.3%)	57/133 (42.9%)	RR 0.66 (0.45 to 0.95)	146 fewer per 1000 (from 21 fewer to 236 fewer)	⊕⊕⊕O MODERATE
								44.4%		151 fewer per 1000 (from 22 fewer to 244 fewer)	
Relapse	at 5-7 month	follow-up (a	assessed with: L	IFE/SCID (disco	ontinuation co	ded as relapse))					
4	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	124/300 (41.3%)	146/271 (53.9%)	RR 0.76 (0.64 to 0.9)	129 fewer per 1000 (from 54 fewer to 194 fewer)	⊕⊕⊕O MODERATE
								54.6%		131 fewer per 1000 (from 55 fewer to 197 fewer)	
Relapse	at 8-9 month	follow-up (a	assessed with: L	IFE/SCID (disc	ontinuation co	ded as relapse))					
4	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	142/300 (47.3%)	160/271 (59%)	RR 0.8 (0.68 to 0.93)	118 fewer per 1000 (from 41 fewer to 189 fewer)	⊕⊕⊕⊕ HIGH
								57.7%		115 fewer per 1000 (from 40 fewer to 185 fewer)	
Relapse	at 11-12 mon	th follow-up	(assessed with	: CIDI/DSM-IV/D	SM-IV-TR/LIFE	E/SCID (discontinua	ation coded as rela	ipse))			
8	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	262/554 (47.3%)	279/481 (58%)	RR 0.81 (0.72 to 0.91)	110 fewer per 1000 (from 52 fewer to 162 fewer)	⊕⊕⊕O MODERATE
								57.7%		110 fewer per 1000 (from 52 fewer to 162 fewer)	
Relapse	at 15-16 mon	th follow-up	(assessed with	: LIFE/SCID (dis	scontinuation	coded as relapse))					
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	125/224 (55.8%)	130/202 (64.4%)		84 fewer per 1000 (from 167 fewer to 6 more)	⊕⊕⊕O MODERATE

										84 fewer per 1000		
								64.4%		(from 167 fewer to 6 more)		
Relapse a	at 18-month 1	follow-up (a	ssessed with: LI	FE/SCID (discor	ntinuation code	d as relapse))						
	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	110/183 (60.1%)	109/159 (68.6%)	RR 0.88 (0.75 to 1.03)	82 fewer per 1000 (from 171 fewer to 21 more)	⊕⊕⊕O MODERATE	
								69.2%		83 fewer per 1000 (from 173 fewer to 21 more)		
Relapse	at 21-month 1	follow-up (a	ssessed with: LI	FE/SCID (discor	ntinuation code	ed as relapse))					·	
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	127/183 (69.4%)		RR 0.91 (0.8 to 1.04)	68 fewer per 1000 (from 152 fewer to 30 more)	⊕⊕⊕O MODERATE	
								76.2%		69 fewer per 1000 (from 152 fewer to 30 more)		
Relapse a	at 2-year follo	ow-up (asse	essed with: CIDI/I	LIFE/RDC (disco	entinuation cod	ed as relapse))						
4	randomised trials	no serious risk of bias	serious ³	no serious indirectness	serious ¹	reporting bias ²	109/231 (47.2%)	128/213 (60.1%)	RR 0.7 (0.5 to 0.98)	180 fewer per 1000 (from 12 fewer to 300 fewer)	⊕OOO VERY LOW	
								63.4%		190 fewer per 1000 (from 13 fewer to 317 fewer)		
Relapse a	at 6-year follo	ow-up (asse	essed with: RDC	(discontinuatior	n coded as rela	pse))						
	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	11/23 (47.8%)	20/22 (90.9%)	RR 0.53 (0.34 to 0.82)	427 fewer per 1000 (from 164 fewer to 600 fewer)	⊕OOO VERY LOW	
		200						90.9%		427 fewer per 1000 (from 164 fewer to 600 fewer)		

¹ OIS not met (events<300)
² No endpoint data, only follow-up available, for a significant number of studies in this analysis

³ I2>50%

⁴ Risk of bias is high or unclear across multiple domains

1 Cognitive or cognitive behavioural therapies versus active intervention

			Quality ass	essment			No of pati	ients		Effect	Quality	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive or cognitive behavioural therapies	Active intervention	Relative (95% CI)	Absolute	Quality	Importance
Relapse	at endpoint ((follow-up 3	5-78 weeks; ass	essed with: DS	M-IV/LIFE/SCIE	O (discontinuation	coded as relapse)					
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	80/173 (46.2%)	96/176 (54.5%)	RR 0.84 (0.69 to 1.03)	87 fewer per 1000 (from 169 fewer to 16 more)	⊕⊕⊕O MODERATE	
								66.1%		106 fewer per 1000 (from 205 fewer to 20 more)		
Relapse	at 2-month f	ollow-up (a	ssessed with: LII	FE (discontinua	ation coded as	relapse))						
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	35/86 (40.7%)	40/86 (46.5%)	RR 0.88 (0.62 to 1.23)	56 fewer per 1000 (from 177 fewer to 107 more)	⊕⊕OO LOW	
								46.5%		56 fewer per 1000 (from 177 fewer to 107 more)		
Relapse	at 3-4 month	follow-up	assessed with: I	HAMD/MADRS	(discontinuation	on coded as relap	se))					
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	9/39 (23.1%)	19/41 (46.3%)	RR 0.5 (0.26 to 0.97)	232 fewer per 1000 (from 14 fewer to 343 fewer)	⊕⊕OO LOW	
								47.3%		236 fewer per 1000 (from 14 fewer to 350 fewer)		
Relapse	at 5-month f	ollow-up (a	ssessed with: LII	FE (discontinua	ation coded as	relapse))						

1		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	39/86 (45.3%)	48/86 (55.8%)	RR 0.81 (0.6 to 1.1)	106 fewer per 1000 (from 223 fewer to 56 more)	⊕⊕OO LOW	
								55.8%		106 fewer per 1000 (from 223 fewer to 56 more)		
Relapse	at 8-10 mont	h follow-up	(assessed with	HAMD/MADR	S/LIFE (discon	tinuation coded as	s relapse))					
3		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ⁵	61/125 (48.8%)	74/127 (58.3%)	RR 0.82 (0.61 to 1.1)	105 fewer per 1000 (from 227 fewer to 58 more)	⊕⊕OO LOW	
								57%		103 fewer per 1000 (from 222 fewer to 57 more)		
Relapse	at 11-13 mor	nth follow-u	p (assessed with	h: LIFE/SCID (d	liscontinuation	coded as relapse))					
4	randomised trials	serious ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁵	156/273 (57.1%)	162/277 (58.5%)	RR 0.98 (0.85 to 1.13)	12 fewer per 1000 (from 88 fewer to 76 more)	⊕⊕OO LOW	
								60.6%		12 fewer per 1000 (from 91 fewer to 79 more)		
Relapse	at 15-month	follow-up (assessed with: L	IFE (discontin	uation coded a	is relapse))						
1		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	54/86 (62.8%)	53/86 (61.6%)	RR 1.02 (0.81 to 1.29)	12 more per 1000 (from 117 fewer to 179 more)	⊕⊕OO LOW	
								61.6%		12 more per 1000 (from 117 fewer to 179 more)		
Relapse	at 18-month	follow-up (assessed with: L	IFE (discontin	uation coded a	s relapse))						
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	58/86 (67.4%)	56/86 (65.1%)	RR 1.04 (0.84 to 1.28)	26 more per 1000 (from 104 fewer to 182 more)	⊕⊕OO LOW	
								65.1%		26 more per 1000 (from 104 fewer to 182 more)		

Relapse	at 21-22 mon	th follow-u	p (assessed with	n: DSM-IV/LIFE	(discontinuati	on coded as relap	se))					
2		no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁵	176/298 (59.1%)	175/298 (58.7%)	RR 1.01 (0.88 to 1.15)	6 more per 1000 (from 70 fewer to 88 more)	⊕⊕⊕O MODERATE	
								61%		6 more per 1000 (from 73 fewer to 91 more)		
Relapse	at 2-year foll	ow-up (ass	essed with: LIFE	(discontinuati	on coded as re	elapse))						
1		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	61/86 (70.9%)	58/86 (67.4%)	RR 1.05 (0.86 to 1.28)	34 more per 1000 (from 94 fewer to 189 more)	⊕⊕OO LOW	
								67.4%		34 more per 1000 (from 94 fewer to 189 more)		

¹ 95% CI crosses one clinical decision threshold

Self-help with support versus attention-placebo

			Quality asse	essment			No of p	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-help with support	Attention- placebo	Relative (95% CI)	Absolute		
Relapse a	t endpoint (fo	llow-up m	iean 10 weeks; ass	sessed with: MA	DRS (discont	inuation coded as	relapse))					
1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	25/42 (59.5%)	32/42 (76.2%)	RR 0.78 (0.58 to 1.06)	168 fewer per 1000 (from 320 fewer to 46 more)	⊕⊕OO LOW	
								76.2%		168 fewer per 1000 (from 320 fewer to 46 more)		

² Funding from pharmaceutical company
³ OIS not met (events<300)
⁴ No endpoint data, only follow-up available

⁵ No endpoint data (only follow-up available) or funding from pharmaceutical company ⁶ Risk of bias is high or unclear across multiple domains

Relapse	at 6-month fol	low-up (as	ssessed with: MAD	ORS (discontinua	ation coded a	is relapse))						
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	25/42 (59.5%)	33/42 (78.6%)	RR 0.76 (0.56 to 1.02)	189 fewer per 1000 (from 346 fewer to 16 more)	⊕⊕OO LOW	
								78.6%		189 fewer per 1000 (from 346 fewer to 16 more)		

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses one clinical decision threshold

IPT vs control

			Quality assess	sment			No of p	oatients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Control	Relative (95% CI)	Absolute		
Relapse a	t endpoint (fol	low-up mean	156 weeks; assess	ed with: HAMD/R	DC (disconti	nuation coded as I	relapse))				
2	randomised trials			no serious indirectness	serious ¹	none	38/51 (74.5%)	47/52 (90.4%)	RR 0.84 (0.7 to 1)		⊕⊕⊕O MODERATE	
								90.5%		145 fewer per 1000 (from 271 fewer to 0 more)		

¹ OIS not met (events<300)

IPT versus active intervention

			Quality asses	sment			No	of patients		Effect	Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Active intervention	Relative (95% CI)	Absolute			
Relapse a	Relapse at endpoint (follow-up mean 156 weeks; assessed with: HAMD/RDC (discontinuation coded as relapse))												

2	randomised	no serious	no serious	no serious	serious ¹	none	38/51	31/56	RR 1.35	194 more per 1000	⊕⊕⊕О	
	trials	risk of bias	inconsistency	indirectness			(74.5%)	(55.4%)	(1.02 to 1.79)	(from 11 more to 437	MODERATE	
										more)		
										194 more per 1000		
								55.4%		(from 11 more to 438		
										more)		

¹ OIS not met (events<300)

Combined IPT + AD versus pill placebo

			Quality ass	sessment			No of pati	ents		Effect	Quality	Importance
No of studies	Design						Combined IPT + AD	Pill placebo	Relative (95% CI)	Absolute		
Relapse a	t endpoint (fol	low-up 10	4-156 weeks; a	ssessed with: HA	MD/SCID/RD	DC (discontinuation	n coded as rela	pse))				
3	randomised trials	serious ¹		no serious indirectness	serious ³	none	35/78 (44.9%)	60/70 (85.7%)	RR 0.52 (0.3 to 0.9)	411 fewer per 1000 (from 86 fewer to 600 fewer)	⊕000 VERY LOW	
								89.7%		431 fewer per 1000 (from 90 fewer to 628 fewer)		

¹ Risk of bias is high or unclear across multiple domains

4 5

6 Combined IPT + AD versus AD

			Quality asses	ssment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined IPT + AD	AD	Relative (95% CI)	Absolute		
Relapse a	t endpoint (fo	ollow-up 16-1	56 weeks; assess	ed with: HAMD/S	CID/RDC (di	iscontinuation cod	led as relapse))				
4				no serious indirectness	serious ¹	none	64/138 (46.4%)	89/155 (57.4%)	RR 0.83 (0.64 to 1.06)	98 fewer per 1000 (from 207 fewer to 34 more)	⊕⊕⊕O MODERATE	

² I2>50%

³ OIS not met (events<300)

				55.7%	95 fewer per 1000 (from 201 fewer to 33	
					more)	

¹ 95% CI crosses one clinical decision threshold

SSRIs versus control

			Quality asse	essment			No of p	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Control	Relative (95% CI)	Absolute		
Relapse a	nt endpoint (fo	ollow-up 24-10)4 weeks; assesse	ed with: CGI-I/DS	M-III-R/DSM-IV/H	IAMD/MADRS/LIFI	E/SCID (di	scontinu	ation coded as	s relapse))		
20	randomised trials	serious ¹	very serious ²	no serious indirectness	no serious imprecision	reporting bias ³		986/1695 (58.2%) 62.3%	to 0.73)	215 fewer per 1000 (from 157 fewer to 262 fewer) 231 fewer per 1000 (from 168 fewer to 280 fewer)	VERY LOW	
Relapse a	t 2-month fol	low-up (asses	sed with: LIFE (di	scontinuation co	oded as relapse))				,		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	40/86 (46.5%)	(55.1%)	RR 0.84 (0.62 to 1.15)	88 fewer per 1000 (from 209 fewer to 83 more) 88 fewer per 1000 (from	⊕⊕OO LOW	
Relapse a	at 5-month fol	low-up (asses	sed with: LIFE (di	scontinuation co	oded as relapse))		55.1%		209 fewer to 83 more)		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	48/86 (55.8%)	40/69 (58%)	RR 0.96 (0.73 to 1.27)	23 fewer per 1000 (from 157 fewer to 157 more)	⊕000 VERY LOW	
								58%		23 fewer per 1000 (from 157 fewer to 157 more)		
Relapse a	t 8-month fol	low-up (asses	sed with: LIFE (di	scontinuation co	oded as relapse))						
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	49/86 (57%)	42/69 (60.9%)	RR 0.94 (0.72 to 1.22)	37 fewer per 1000 (from 170 fewer to 134 more)	⊕⊕OO LOW	
								60.9%		37 fewer per 1000 (from 171 fewer to 134 more)		

Relapse at	t 11-month fo	llow-up (asse	essed with: LIFE (d	discontinuation o	oded as relapse	e))						
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	50/86 (58.1%)	46/69 (66.7%)	RR 0.87 (0.68 to 1.11)	87 fewer per 1000 (from 213 fewer to 73 more)	⊕⊕OO LOW	
								66.7%		87 fewer per 1000 (from 213 fewer to 73 more)		
Relapse at	t 15-month fo	llow-up (asse	essed with: LIFE (d	discontinuation of	oded as relapse	())						
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	53/86 (61.6%)	47/69 (68.1%)	RR 0.9 (0.72 to 1.14)	68 fewer per 1000 (from 191 fewer to 95 more)	⊕⊕OO LOW	
								68.1%		68 fewer per 1000 (from 191 fewer to 95 more)		
Relapse at	t 18-month fo	llow-up (asse	essed with: LIFE (d	discontinuation of	oded as relapse	e))						
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	56/86 (65.1%)		RR 0.88 (0.72 to 1.09)	89 fewer per 1000 (from 207 fewer to 67 more)	⊕⊕OO LOW	
								73.9%		89 fewer per 1000 (from 207 fewer to 67 more)		
Relapse at	t 21-month fo	llow-up (asse	essed with: LIFE (d	discontinuation of	oded as relapse))						
	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	57/86 (66.3%)	53/69 (76.8%)	RR 0.86 (0.71 to 1.05)	108 fewer per 1000 (from 223 fewer to 38 more)	⊕⊕OO LOW	
								76.8%		108 fewer per 1000 (from 223 fewer to 38 more)		
Relapse at	t 2-year follov	v-up (assess	ed with: LIFE (disc	ontinuation code	ed as relapse))							
		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	58/86 (67.4%)	55/69 (79.7%)	RR 0.85 (0.7 to 1.02)	120 fewer per 1000 (from 239 fewer to 16 more)	⊕⊕OO LOW	
								79.7%		120 fewer per 1000 (from 239 fewer to 16 more)		

¹ Risk of bias is high or unclear across multiple domains

4 5

² I2>80%

Funding from pharmaceutical company
 95% CI crosses one clinical decision threshold

⁵ 95% CI crosses two clinical decision thresholds

SSRI maintenance same dose versus SSRI maintenance reduced dose

			Quality asse	essment			No of p	oatients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI maintenance same dose	SSRI maintenance reduced dose	Relative (95% CI)	Absolute		
Relapse	at endpoint (follow-up r	mean 121 weeks;	assessed with	: DSM-IV and	HAMD (disconti	nuation coded as	relapse))				
	trials			no serious indirectness	serious ¹	none	8/34 (23.5%)	18/34 (52.9%)	RR 0.44 (0.22 to 0.88)	296 fewer per 1000 (from 64 fewer to 413 fewer)	⊕⊕⊕O MODERATE	
								52.9%		296 fewer per 1000 (from 63 fewer to 413 fewer)		

¹ OIS not met (events<300)

TCAs versus control

			Quality asse	ssment			No of p	atients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Control	Relative (95% CI)	Absolute		
Relapse at	endpoint (foll	ow-up 16-1	156 weeks; assesse	ed with: CGI/DSM-	IV/HAMD/MA	DRS/RDC (discont	inuation	coded	as relapse))			
-	randomised trials			no serious indirectness	serious ²		104/218 (47.7%)			234 fewer per 1000 (from 139 fewer to 314 fewer)	⊕⊕OO LOW	
								79.4%		254 fewer per 1000 (from 151 fewer to 341 fewer)		

¹ Risk of bias is high or unclear across multiple domains ² OIS not met (events<300)

TCAs versus active intervention

			Quality ass	sessment			No	of patients		Effect	Quality	Importance
No of studies	Design Inconsistency Indirectness Imprecision					Other considerations	TCAs	Active intervention	Relative (95% CI)	Absolute		
Relapse at	t endpoint (fol	low-up 10	4-156 weeks; a	ssessed with: RD	C (discontin	uation coded as re	elapse))					
-	randomised trials	serious ¹		no serious indirectness	serious ³	none	71/117 (60.7%)	88/119 (73.9%)	RR 0.81 (0.61 to 1.07)	141 fewer per 1000 (from 288 fewer to 52 more)	⊕000 VERY LOW	
								73%		139 fewer per 1000 (from 285 fewer to 51 more)		

¹ Risk of bias is high or unclear across multiple domains

SNRIs versus control

			Quality as	sessment		No of p	oatients		Effect	Quality	Importance	
No of studies	tudies Design bias Inconsistency Indirectness Imprecision consideration								Relative (95% CI)	Absolute		
Relapse a	Relapse at endpoint (follow-up 26-52 weeks; assessed with: CGI/DSM-IV/HAMD (discontinuation coded as relapse))											
7	randomised trials	serious ¹	no serious inconsistency		no serious imprecision	reporting bias ²		713/1197 (59.6%)	RR 0.69 (0.64 to 0.74)	185 fewer per 1000 (from 155 fewer to 214 fewer)	⊕⊕OO LOW	
								66.9%		207 fewer per 1000 (from 174 fewer to 241 fewer)		

¹ Risk of bias is high or unclear across multiple domains ² Funding from pharmaceutical company

Mirtazapine versus control

Quality assessment	No of patients	Effect	Quality	Importance

² I2>50%

³ 95% CI crosses one clinical decision threshold

	No of Pick of Other											
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mirtazapine	Control	Relative (95% CI)	Absolute		
Relapse at	elapse at endpoint (follow-up mean 40 weeks; assessed with: HAMD (discontinuation coded as relapse))											
	randomised trials			no serious indirectness	serious ²	reporting bias ³	25/77 (32.5%)	41/84 (48.8%)	RR 0.67 (0.45 to 0.98)	161 fewer per 1000 (from 10 fewer to 268 fewer)	⊕OOO VERY LOW	
								48.8%		161 fewer per 1000 (from 10 fewer to 268 fewer)		

¹ Risk of bias is high or unclear across multiple domains

Any AD versus control

5

	Quality assessment No of Other									Effect	Quality	Importance
No of studies	studies Design Risk of bias Inconsistency Indirectness Imprecision consider						Any AD	Control	Relative (95% CI)	Absolute		
Relapse at	Relapse at endpoint (follow-up 52-78 weeks; assessed with: HAMD/SCID (discontinuation coded as relapse))											
2 randomised no serious no serious no serious serious serious none 39/62 (62.9%) (8									' '	⊕⊕⊕O MODERATE		
							81.4%		179 fewer per 1000 (from 334 fewer to 33 more)			

¹ 95% CI crosses one clinical decision threshold

Combined CT/CBT + AD versus CT/CBT

	Quality assessment							nts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined CT/CBT + AD	СТ/СВТ	Relative (95% CI)	Absolute		

² OIS not met (events<300)
³ Funding from pharmaceutical company

Rela	apse a	t 13-month fo	llow-up (a	ssessed with: SCI	D (discontinuation	on coded as	relapse))					
1			- ,		no serious indirectness	serious ²	reporting bias ³	107/128 (83.6%)	,	142 fewer per 1000 (from 33 fewer to 234 fewer)	⊕000 VERY LOW	
								83.6%		142 fewer per 1000 (from 33 fewer to 234 fewer)		

¹ Risk of bias is high across multiple domains

Lithium versus control

	dies Design bias Inconsistency Indirectness Imprecision consideration							No of patients Effect			Quality	Importance
No of studies	Design Inconsistency Indirectness Imprecision						Lithium	Control	Relative (95% CI)	Absolute		
Relapse at	elapse at endpoint (follow-up mean 104 weeks; assessed with: RDC (discontinuation coded as relapse))											
1	randomised trials			no serious indirectness	serious ²	none	27/37 (73%)	27/34 (79.4%)		64 fewer per 1000 (from 230 fewer to 151 more)	⊕⊕OO LOW	
								79.4%		64 fewer per 1000 (from 230 fewer to 151 more)		

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses one clinical decision threshold

Lithium augmentation versus control

			Quality asse	essment			No of patier	nts		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium augmentation	Control	Relative (95% CI)	Absolute		
Relapse a	lapse at endpoint (follow-up 17-104 weeks; assessed with: HAMD/RDC (discontinuation co						as relapse))					
3	randomised no serious serious¹ no serious very none trials risk of bias indirectness serious²						35/81 (43.2%)	51/83 (61.4%)		203 fewer per 1000 (from 406 fewer to 190 more)		

² OIS not met (events<300)
³ No endpoint data, only follow-up available

		48.7	% 161 fewer per 1000 (from 321 fewer to 151 more)	⊕000 VERY LOW	
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¹ I2>50%

Antipsychotic versus control

			Quality as:	sessment			No of pati	ents		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic	Control	Relative (95% CI)	Absolute		
Relapse at	Relapse at endpoint (follow-up mean 52 weeks; assessed with: CGI or MADRS (discontinuation coded as relapse))											
	randomised trials				no serious imprecision	reporting bias ²	381/391 (97.4%)	380/385 (98.7%)		10 fewer per 1000 (from 30 fewer to 10 more)	⊕⊕OO LOW	
								98.7%		10 fewer per 1000 (from 30 fewer to 10 more)		

¹ Risk of bias is high or unclear across multiple domains ² Funding from pharmaceutical company

Antipsychotic augmentation versus AD monotherapy

			Quality as:	sessment			No of pat	tients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotic augmentation	AD monotherapy	Relative (95% CI)	Absolute		
Relapse a	at endpoint (fo	ollow-up 2	24-27 weeks; as	ssessed with: H	AMD/MADRS	/CGI (discontinua	tion coded as relap	se))				
2	randomised trials	serious ¹		no serious indirectness	serious ³	reporting bias ⁴	162/344 (47.1%)	183/343 (53.4%)	RR 0.9 (0.69 to 1.17)	53 fewer per 1000 (from 165 fewer to 91 more)	⊕OOO VERY LOW	
								55.9%		56 fewer per 1000 (from 173 fewer to 95 more)		

² 95% CI crosses two clinical decision thresholds

- 1 Risk of bias is high or unclear across multiple domains 2 l2>50%
- ³ 95% CI crosses one clinical decision threshold
- ⁴ Funding from pharmaceutical company

ECT versus active intervention

			Quality asse	essment			No	of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECT	Active intervention	Relative (95% CI)	Absolute		
Relapse a	t endpoint (fo	llow-up 26	i-52 weeks; assess	sed with: HAMD/I	MADRS (disc	ontinuation coded	as relap	ose))				
2	randomised trials	- ,	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	74/126 (58.7%)	78/131 (59.5%)	RR 0.98 (0.8 to 1.2)	12 fewer per 1000 (from 119 fewer to 119 more)	⊕OOO VERY LOW	
								62.6%	-	13 fewer per 1000 (from 125 fewer to 125 more)		
Relapse a	t 3-month foll	ow-up (Ma	intenance ECT + p	harmacotherapy	versus phai	rmacotherapy) (as	sessed v	vith: HAMD (dis	scontinuation of	coded as relapse))		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ⁶	15/25 (60%)	10/18 (55.6%)	RR 1.08 (0.64 to 1.82)	44 more per 1000 (from 200 fewer to 456 more)	⊕OOO VERY LOW	
								55.6%		44 more per 1000 (from 200 fewer to 456 more)		
Relapse a	t 3-month foll	ow-up (Ma	intenance ECT + p	harmacotherapy	versus CBT	group + pharmac	otherapy	v) (assessed wi	th: HAMD (disc	continuation coded as re	lapse))	
1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁶	15/25 (60%)	4/17 (23.5%)	RR 2.55 (1.02 to 6.37)	365 more per 1000 (from 5 more to 1000 more)	⊕OOO VERY LOW	
								23.5%		364 more per 1000 (from 5 more to 1000 more)		
Relapse a	t 9-month foll	ow-up (Ma	intenance ECT + p	harmacotherapy	versus phai	macotherapy) (as:	sessed v	vith: HAMD (dis	scontinuation of	coded as relapse))	1	1
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ⁶	18/25 (72%)	12/18 (66.7%)	RR 1.08 (0.72 to 1.62)	53 more per 1000 (from 187 fewer to 413 more)	⊕OOO VERY LOW	
								66.7%		53 more per 1000 (from 187 fewer to 414 more)		

Relap	se at 9-month fo	llow-up (M	aintenance ECT	+ pharmacotherapy	y versus CBT	group + pharmac	otherapy	/) (assessed wi	th: HAMD (dis	continuation coded as rel	apse))	
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁶	18/25 (72%)	6/17 (35.3%)	RR 2.04 (1.02 to 4.06)	367 more per 1000 (from 7 more to 1000 more)	⊕000 VERY LOW	
								35.3%		367 more per 1000 (from 7 more to 1000 more)		

¹ Risk of bias is high across multiple domains

Access to services (chapter 12)

Telephone administered psychological interventions versus usual care

Tele- problem solving therapy versus in-person problem solving therapy

			Quality assess	sment			No of	patients		Effect		
											Overlife	luon autan a a
											Quality	Importance
No of		Risk of				Other	Tele- problem	In-person problem	Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	solving therapy	solving therapy	(95%	Absolute		
Studies		Dias				Considerations	Solving therapy	Solving therapy	CI)			
Scores ob	tained in a tre	eatment ac	cceptance tool (me	asured with:	Treatment E	valuation Inventor	ry (TEI); Better inc	dicated by higher va	lues)			
1	randomised	very	no serious	serious ²	serious ³	none	43	42	-	MD 4.06 higher	\oplus OOO	IMPORTANT
	trials	serious ¹	inconsistency							(0.87 to 7.25 higher)	VERY	
											LOW	

¹ High risk of bias in two domains and unclear in other

15

12 13

7

9 10

² OIS not met (events<300)

³ Potential conflicts of interest

⁴ Risk of bias is high or unclear across multiple domains

⁵ 95% CI crosses two clinical decision thresholds

⁶ No endpoint data, only follow-up available

² US study with potential applicability issues

³ Criterion for optimal information size not met (<400 participants)

1 Clinic based telepsychiatry using a video-webcam versus usual care

	ased telep	Sychiati	y using a vide	o-webcam	versus us	sual care			1		1	1
			Quality asses	ssment			No of patients			Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinic-based telepsychiatry using a video Webcam	TAU	Relative (95% CI)	Absolute	,	
Number o	of subjects w	ho made a	mental health ap	ppointment (fo	ollow-up mea	an 6 months; asse	essed with: Not reported)	-	Į.		<u> </u>	
1	randomised trials		no serious inconsistency	serious ²	serious ³	none	77/80 (96.3%)	29/87 (33.3%)	RR 2.89 (2.14 to 3.9)	630 more per 1000 (from 380 more to 967 more)	⊕000 VERY LOW	
								33.3%		629 more per 1000 (from 380 more to 966		
Number o	of subjects w	ho made a	nrimary care an	nointment (fo	llow-up mea	n 6 months: asses	ssed with: Not reported)	00.070		more)		
1	randomised		no serious	·		none	56/80	76/87	RR 0.8 (0.68	175 fewer per 1000	2000	1
ı	trials	senous	inconsistency	serious-	serious	none	(70%)	(87.4%)		(from 52 fewer to 280 fewer)	⊕000 VERY LOW	
								87.4%		175 fewer per 1000 (from 52 fewer to 280 fewer)		
Number u	used antidepr	ressants (follow-up mean 6	months; asse	essed with: N	Not reported)				lewery		
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	56/80 (70%)	40/87 (46%)	RR 1.52 (1.16 to 1.99)	239 more per 1000 (from 74 more to 455 more)	⊕000 VERY LOW	
								46%		239 more per 1000 (from 74 more to 455 more)		
			•	•	•		ad with Nat reported. Bett	!!!	4			•
Mean nur	nber of comp	leted mer	ntal health appoin	tments (follow	w-up mean 6	months; measure	ea with: Not reported; bett	er indica	ited by lower	values)		

6

7

8

Telephone CBT versus enhanced usual care

			Quality asse	essment			No of	patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telephone CBT	Enhanced usual care	Relative (95% CI)	Absolute		
Number re	porting they	were stais	sfied with the trea	tment provided	•							
	randomised trials				very serious ²	none	24/64 (37.5%)	12/33 (36.4%)		11 more per 1000 (from 149 fewer to 287 more)		CRITICAL

¹ High ROB in one domain and unclear ROB in two others

10 11

¹ Unclear blinding of outcome assessment

² US study with potential applicability issues

³ Events<300

⁴ 95% CI crosses both line of no effect and threshold for clinically significant benefit (SMD 0.5)

⁵ N<400

⁶ Non-blind outcome assessment (self-report)

² 95% CI crosses two clinical decision thresholds

Telephone-administered monitoring interventions versus usual care

Telephone disease management versus usual care

			Quality assess	sment			No of patients			Effect		
No of		Dialent		1		Other	Talambana dia sasa		Deletive		Quality	Importance
No of studies	Design Risk of bias Inconsister			Indirectness	Imprecision	Other considerations	Telephone disease management	TAU	Relative (95% CI)	Absolute		
			mental health/subs			t (follow-up mean	4 months; assessed v					
	randomised trials		no serious inconsistency	serious ²	serious ^{2,3}	none	19/46 (41.3%)	5/51 (9.8%)		315 more per 1000 (from 70 more to 919 more)	⊕OOO VERY	
								9.8%		315 more per 1000 (from 70 more to 918 more)	LOW	

6

Close monitoring versus usual care

	STITEOTHIS V											
			Quality assess	ment			No of patie	ents		Effect		
											Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Close monitoring	TAU	Relative (95% CI)	Absolute		
								<u> </u>				
Number at	tending prima	ry care vis	sits during study po	eriod (follow-	up mean 6 m	onths; assessed w	ith: Case revi	ew)				
1		- ,		serious ²	serious ³	none	92/130	62/93	,	40 more per 1000 (from 73	⊕000	
	trials	serious ¹	inconsistency				(70.8%)	(66.7%)	to 1.27)	fewer to 180 more)	VERY LOW	
								66.7%		40 more per 1000 (from 73 fewer to 180 more)		
Number w	ho had any MI	H care (inc	luding behavioral l	nealth specia	list) during t	he study period (fo	llow-up mean	6 month	s; assessed wi	th: Case review)		'

¹ Non-blind outcome assessment (self-report)
² US study with potential applicability issues and veteran population so may not be applicable to all men

³ Events<300

1 2 3 4 5

Depression in adults: treatment and management Appendix L

1	randomised	very	no serious	serious ²	serious4	none	43/130	6/93	RR 5.13 (2.28	266 more per 1000 (from	⊕ООО	
	trials	serious ¹	inconsistency				(33.1%)	(6.5%)	to 11.54)	83 more to 680 more)	VERY	
									4		LOW	
								6.5%		268 more per 1000 (from		
								2.070		83 more to 685 more)		
Number v	vho started an	antidepres	ssant during the st	udy period (fe	ollow-up me	an 6 months; asses	sed with: Cas	e review	r)			
		•	•	, · · · · ·	•	•			,			
				`		,						
1	randomised	very	no serious	serious ²	serious ³	none	21/130	9/93	RR 1.67 (0.8 to	65 more per 1000 (from 19	⊕000	
1	randomised trials	very serious ¹		`		· 1			RR 1.67 (0.8 to	65 more per 1000 (from 19 fewer to 240 more)	⊕000 VERY	
1		1 .	no serious	`		· 1	21/130	9/93	RR 1.67 (0.8 to			
1		1 .	no serious	`		· 1	21/130	9/93	RR 1.67 (0.8 to 3.48)		VERY	

Outcome assessment was non-blind and there were statistically significant baseline differences between groups (more males, more financial troubles, more subjects with trauma exposure, more with a past history of depression and more with a GAD diagnosis in the intervention group)

6

Simple collaborative care versus usual care

											ı	
			Quality asse	essment			No of patien	its		Effect		
											Quality	Importanc
No of		Risk of				Other	Simple		Relative			
studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	collaborative	TAU	(95% CI)	Absolute		
		3.00					care		(00 /0 01)			
												<u> </u>
Number w	ho attended 2	≥1 appoint	tment with mental	health specialis	t (follow-up n	nean 12 months; a	ssessed with: Dat	abase re	eview)			
		serious ¹	serious ²	serious ³	serious4	none				65 more per 1000 (from	\oplus OOO	
•	trials						(38.7%)	(32.3%)	to 1.86)	74 fewer to 277 more)	VERY	
											LOW	
								32.3%		65 more per 1000 (from		
								02.070		74 fewer to 278 more)		
Number w	ho have had	a depress	ion-related primar	y care visit (follo	w-up mean	12 months; assess	ed with: Database	review)				
1	randomised	serious ¹	no serious	serious ³	serious ⁵	none	141/168	106/186	RR 1.47	268 more per 1000		
	trials		inconsistency				(83.9%)	(57%)	(1.28 to 1.7)	(from 160 more to 399		
										more)		

² US study with potential applicability issues and veteran population so may not be applicable to all men

³ 95% CI crosses both line of no effect and threshold for clinically significant benefit (RR 1.25)

⁴ Events<300

	1	1	1	1	ı	1				I		
										268 more per 1000	⊕000	
								57%		(from 160 more to 399	VERY	
								0.70		more)	LOW	
										,		
ımber	of patients wh	ose unhe	lpful medications	(those potential	ly exacerbati	ng depression) v	were terminated					
	randomised	serious ⁶	no serious	no serious	very	none	23/100	17/75	RR 1.01	2 more per 1000 (from		CRITICA
	trials		inconsistency	indirectness	serious ⁷		(23%)	(22.7%)	(0.58 to 1.76)	95 fewer to 172 more)	VERY	
											LOW	
ceived	l ≥ 90 days of	therapy w	ith a minimally th	erapeutic dosag	e of antidepr	essant (follow-u	p mean 12 months;	assessed	with: Databas	se review)		
	randomised	serious ¹	serious ²	serious ³	serious ⁴	none	224/324	182/301	RR 1.13	79 more per 1000 (fron	1 ⊕000	
	trials						(69.1%)	(60.5%)	(0.95 to 1.35)			
							,	,	,	,	LOW	
								61%		79 more per 1000 (fron	า	
								01%		31 fewer to 214 more)		
	of adults start	serious ⁶	no serious	no serious	serious ⁵	none	26/100	6/75	RR 3.25	180 more per 1000	⊕⊕ОО	CRITICA
	trials		inconsistency	indirectness			(26%)	(8%)	(1.41 to 7.5)	(from 33 more to 520	LOW	
										more)		
umber	of patients for	whom a p	osychiatric consu	Itation was soug	ht							
	randomised	serious ⁶	no serious	no serious	very	none	12/100	11/75	RR 0.82	26 fewer per 1000 (from		CRITICA
	trials		inconsistency	indirectness	serious ⁷		(12%)	(14.7%)	(0.38 to 1.75)	91 fewer to 110 more)		
											LOW	
		group diffe	rences at baseline	in Hedrick 2003 (more subjects	with previous de	pression in intervention	on group)				
	d > 50%											
			ty issues and veter				en					
		ne of no eff	fect and threshold	for clinically signif	icant benefit (RR 1.25)						
Events<												
	ROB in multipl											
15% Cl (crosses two cli	nical decis	ion thresholds									
o-loca	ited versus	geogra	ohically separa	ate services								
			Quality asse	ssment			No of patie	ents		Effect	Quality	Importan
			•									

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-located services	Geographically separate services	Relative (95% CI)	Absolute		
Number o	of patient wh	o engage	d with treatment									
	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	481/640 (75.2%)	338/657 (51.4%)	RR 1.46 (1.34 to 1.59)	237 more per 1000 (from 175 more to 304 more)		CRITICAL
Number o	of treatment	visits (Be	tter indicated by	higher values)								
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	687	703	-	MD 1.28 higher (0.87 to 1.69 higher)	⊕⊕OO LOW	CRITICAL
Proportio	on of people v	who had	at least 1 mental	health visit (Co	py)	-						
	randomised trials		no serious inconsistency	serious ⁴	serious ⁵	none	268/999 (26.8%)	189/1023 (18.5%)	RR 1.45 (1.23 to 1.71)	83 more per 1000 (from 42 more to 131 more)	⊕OOO VERY LOW	CRITICAL

¹ Unclear ROB in multiple domains

6

7

8

Culturally-adapted psychological interventions versus usual care

Culturally adapted motivational therapy versus usual care

		Quality asses	sment			No of patients			Effect		
										Quality	Importance
No of studies	Design Risk bias	Inconsistancy	Indirectness	Imprecision	Other considerations	Culturally adapted motivational therapy	Usual	Relative (95% CI)	Absolute		
Number of peo	ople who attend	ed at least 1 psychol	therapy session	on		,		(3.2.2.)			

² 95% CI crosses one clinical decision threshold

³ High risk of bias in one domain and unclear in other

⁴ US study with potential applicability issues ⁵ 95% CI crosses both line of no effect and threshold for clinically significant benefit (RR 1.25)

	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	17/26 (65.4%)	12/24 (50%)	RR 1.31 (0.8 to 2.13)	155 more per 1000 (from 100 fewer to 565 more)	⊕000 VERY LOW	CRITICAL
[TIME 2] A	Adherence sc	ore (meas	ured with: Medica	tion Event M	onitoring Sys	stem (MEMS); Bett	er indicated by higher	values)		<u> </u>		
	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ⁴	none	26	24	-	MD 30.22 higher (11.3 to 49.14 higher)	⊕OOO VERY LOW	CRITICAL
[TIME 3] A	Adherence sc	ore (meas	ured with: Medica	tion Event M	onitoring Sys	stem (MEMS); Bett	er indicated by lower v	alues)	<u> </u>			
	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ⁴	none	26	24	-	MD 26.24 higher (22.55 to 29.93 higher)	⊕OOO VERY LOW	CRITICAL
Proportion	n of fully atte	nded days	s (measured with:	Composite A	Adherence So	ore (CAS); Better	indicated by higher val	ues)				
	randomised trials	very serious ⁵	no serious inconsistency	serious ²	serious ⁴	none	98	97	-	MD 0.09 higher (0 to 0.18 higher)	⊕OOO VERY LOW	CRITICAL
Patient sa	tisfaction (m	easured w	vith: Client Satisfa	ction Questic	onnaire (CSQ); Better indicated	by lower values)					
	randomised trials	very serious ⁵	no serious inconsistency	serious ²	very serious ⁶	none	98	97	-	MD 0.18 lower (1.13 lower to 0.77 higher)	⊕OOO VERY LOW	CRITICAL

¹ High risk of bias in one domain

4

7

Culturally-adapted CBT versus usual care

Quality assessment	No of patients	Effect	Quality	Importance

US study with potential applicability issues
 95% CI crosses both line of no effect and threshold for clinically significant benefit (RR 1.25)

⁴ Criterion for optimal information size not met (<400 participants)

⁵ High risk of bias in two domains

⁶ 95% CI crosses both lines of no effect for clinically significant differences (SMD -0.5 and 0.5)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Culturally- adapted CBT	TAU	Relative (95% CI)	Absolute		
Number of participants stating that they were 'very satisfied' with treatment												
1		- ,		no serious	serious ²	none	50/69			254 more per 1000 (from		CRITICAL
	trials	serious ¹	inconsistency	indirectness			(72.5%)	(47.1%)	to 2.06)	71 more to 499 more)	VERY LOW	

3

1 2

4

¹ High ROB in multiple domains ² 95% CI crosses one clinical decision threshold