Appendix 16c: Clinical evidence profiles for pharmacological and physical interventions

This appendix contains evidence profiles for reviews substantially updated or added to the guideline update (summary evidence profiles are included in the evidence chapters). The use of evidence profiles was introduced since the previous guideline was published.

Evidence profile tables summarise both the quality of the evidence and the results of the evidence synthesis. Each table includes details about the quality assessment of each outcome: quality of the included studies, number of studies and participants, limitations, information about the consistency of the evidence (based on heterogeneity – see Chapter 3), directness of the evidence (that is, how closely the outcome measures, interventions and participants match those of interest) and any other considerations (for example, effect sizes with wide confidence intervals [CIs] would be described as imprecise data). Each evidence profile also includes a summary of the findings: number of patients included in each group, an estimate of the magnitude of effect, quality of the evidence, and the importance of the evidence (where appropriate). The quality of the evidence was based on the quality assessment components (study design, limitations to study quality, consistency, directness and any other considerations) and graded using the following definitions:

High = further research is very unlikely to change our confidence in the estimate of the effects

Moderate = further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate

Low = further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate

Very low = any estimate of effect is very uncertain.

For further information about the process and the rationale of producing an evidence profile table see GRADE (2004) Grading quality of evidence and strength of recommendations. *British Medical Journal*, 328, 1490-1497.

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Tricyclic antidepressants (TCAs)

Are TCAs effective in depression? (TCAs versus placebo - efficacy data)

			Quality asse	cement				Sum	mary of fir	ndings		
			Quanty asse	Silient			No. of	patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Placebo	Relative (95% CI)	Absolute	Quality	
Mean e	ndpoint dep	ression score	es (Better indic	ated by lowe	r values)			<u> </u>				
	randomised trials	no serious limitations			no serious imprecision	none	1225	1220	-	SMD 0.48 lower (0.59 to 0.37 lower)	⊕⊕⊕O MODERATE	
Mean e	ndpoint dep	ression score	es - Amitriptyli	ne (Better ind	licated by lov	wer values)						
	randomised trials			no serious indirectness	no serious imprecision	none	176	172	-	SMD 0.61 lower (0.83 to 0.4 lower)	⊕⊕⊕⊕ HIGH	
Mean e	ndpoint dep	ression score	es - Dosulepin (Better indica	ted by lower	values)		'				
	randomised trials	no serious limitations			no serious imprecision	none	194	192	-	SMD 0.49 lower (0.7 to 0.29 lower)	⊕⊕⊕O MODERATE	

1ean (endpoint dep	ression scor	es - Imipramin	e (Better indic	cated by low	er values)			
13	randomised trials	limitations	serious ¹	indirectness	·	none	803	800	SMD 0.41 lower (0.54 to 0.27 MODERATE lower)
viean	епаротт аер	ression scor	es - Nortriptyii	ne (Better ind	ilcated by lov	ver values)			
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	52	56	SMD 0.8 lower (1.37 ++++++++++++++++++++++++++++++++++++
Mean	depression ch	ange scores	(Better indica	ted by lower v	values)				
3	randomised trials	no serious limitations	serious ³	no serious indirectness	no serious imprecision	none	676	643	SMD 0.47 lower (0.74 to 0.21 MODERATE lower)
Mean	depression ch	lange scores	- Amitriptyline	(Better indic	ated by lowe	er values)			
1	randomised trials	no serious limitations	serious ³	no serious indirectness	no serious imprecision	none	387	404	SMD 0.69 lower (1.07
Mean	depression ch	ange scores	- Imipramine (Better indica	ted by lower	values)			
4	randomised	no serious	no serious	no serious	no serious	none	289	239	- SMD 0.21 lower (0.41 ⊕⊕⊕⊕

	trials	limitations	inconsistency	indirectness	imprecision					to 0.01 lower)	HIGH	
Sensitiv	vity analysis:	Mean depre	ssion change s	cores (Better	indicated by	lower values)					,	
7	randomised trials	no serious limitations		no serious indirectness	no serious imprecision	none	604	569	-	SMD 0.35 lower (0.53 to 0.18 lower)	⊕⊕⊕O MODERATE	
Sensitiv	vity analysis:	Mean depre	ession change s	cores - Amitri	iptyline (Bett	er indicated by I	lower value	s)				
3	randomised trials		no serious inconsistency		no serious imprecision	none	315	330	-	SMD 0.5 lower (0.67 to 0.34 lower)	⊕⊕⊕⊕ HIGH	
Sensiti	vity analysis:	Mean depre	ession change s	cores - Imipra	amine (Bette	r indicated by lo	wer values)					
4	randomised trials		no serious inconsistency		no serious imprecision	none	289	239	-	SMD 0.21 lower (0.41 to 0.01 lower)	⊕⊕⊕⊕ HIGH	
Numbe	er not achievi	ng remissior	1									
9	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	301/478 (63%)	393/476 (82.6%)	RR 0.74 (0.65 to 0.84)	215 fewer per 1000 (from 132 fewer to 289 fewer)	⊕⊕⊕O MODERATE	
								79%		205 fewer per 1000		

	1			T	1	1	T	I		(6 106	
										(from 126	
										fewer to	
										277 fewer)	
Numbe	r not achievi		n - Amitriptylin	e							
3	randomised	no serious	serious ³	no serious	no serious	none				283 fewer	
	trials	limitations		indirectness	imprecision			FO /74		per 1000	
								59/71		(from 465	
								(83.1%)	RR 0.66	fewer to 0	
							42/81			more)	⊕⊕⊕О
							(51.9%)		(0.44 to	illore)	MODERATE
							` ′		1)	261 fewer	
										per 1000	
								76.7%		(from 430	
								70.770		fewer to 0	
										more)	
Numbe	r not achievi	ng remissior	n - Clomipramir	ne			<u> </u>				
					T	ı	1	T			
1	randomised	no serious	serious ²	no serious	no serious	none				327 fewer	
	trials	limitations		indirectness	imprecision			14/18		per 1000	
										(from 513	
								(77.8%)	RR 0.58	fewer to 0	
							9/20 (45%)		(0.34 to	more)	⊕⊕⊕O
							3,20 (43/0)		1)	,	MODERATE
									1)	327 fewer	
										per 1000	
								77.8%		(from 513	
										fewer to 0	
										more)	
Numbe	r not achievi	ng remissior	n - Dosulepin								
1	randomised	no serious	no serious	no serious	serious ⁴	none			RR 1.18	18 more	
			inconsistency				2/17	2/20 (10%)		per 1000	⊕⊕⊕О
							(11.8%)	2,20 (10/0)	-	(from 82	MODERATE
									7.48)	,	
										fewer to	

Numbe	r not achievir	ng remission	- Imipramine					10%		18 more per 1000 (from 82 fewer to 648 more)		
	randomised trials			no serious indirectness	serious ⁵	none	207/294 (70.4%)	258/302 (85.4%)	RR 0.83 (0.75 to 0.91)	145 fewer per 1000 (from 77 fewer to 214 fewer)	⊕⊕⊕O MODERATE	
umber	r not achievir	ng remission	- Nortriptyline	3				83.1%	0.91)	141 fewer per 1000 (from 75 fewer to 208 fewer)		
	randomised trials	no serious limitations			no serious imprecision	none	41/66 (62.1%)	60/65 (92.3%)	RR 0.68 (0.52 to 0.88)	295 fewer per 1000 (from 111 fewer to 443 fewer)	⊕⊕⊕O MODERATE	
								92.4%	0.30)	296 fewer per 1000 (from 111 fewer to 444 fewer)		

	_	1	,	1		_						
	randomised trials		no serious inconsistency		no serious imprecision	none	1041/2444 (42.6%)	1529/2419 (63.2%)	RR 0.69 (0.64 to 0.74)	196 fewer per 1000 (from 164 fewer to 228 fewer)	⊕⊕⊕⊕ HIGH	
ımba	or not achievi	ng rosponso	(50% reduction	a in donrossia	on scores). A	mitrintulino		65.9%	0.747	204 fewer per 1000 (from 171 fewer to 237 fewer)		
IIIDE	ei iiot aciiievii	iig response	(50% reduction	ii iii uepi essic	ni scores) - A	initriptyinie						
	randomised trials	no serious limitations	serious ³		no serious imprecision	none	485/1144 (42.4%)	718/1147 (62.6%)	RR 0.69 (0.61 to 0.78)	194 fewer per 1000 (from 138 fewer to 244 fewer)	⊕⊕⊕O MODERATE	
								67.3%		per 1000 (from 148 fewer to 262 fewer)		
mbe	er not achievii	ng response	(50% reduction	n in depressio	on scores) - D	osulepin					•	
	randomised trials		no serious inconsistency		no serious imprecision	none	94/194 (48.5%)	126/192 (65.6%)	RR 0.74 (0.62 to 0.88)	171 fewer per 1000 (from 79 fewer to 249 fewer)	⊕⊕⊕⊕ HIGH	
										,		

										per 1000 (from 79 fewer to		
Numbe	r not achievii	ng response	(50% reduction	n in depressio	n scores) - In	 nipramine				249 fewer)		
20	randomised trials	no serious limitations			no serious imprecision	none	462/1106 (41.8%)	685/1080 (63.4%)	RR 0.69 (0.62 to 0.76)	197 fewer per 1000 (from 152 fewer to 241 fewer)	⊕⊕⊕O MODERATE	
				, trace				65.2%	0.70)	202 fewer per 1000 (from 156 fewer to 248 fewer)		
Sensitiv	rity analysis:	Number not	acnieving resp	onse (50% re	duction in de	epression scores	5)					
34	randomised trials		no serious inconsistency		no serious imprecision	none	1022/2372 (43.1%)	1471/2345 (62.7%)	RR 0.7 (0.66 to 0.75)	188 fewer per 1000 (from 157 fewer to 213 fewer)	⊕⊕⊕⊕ HIGH	
								65.8%	0.73)	197 fewer per 1000 (from 165 fewer to 224 fewer)		
Sensitiv	vity analysis:	Number not	achieving resp	onse (50% re	duction in de	epression scores) - Amitript	yline				
13	randomised trials				no serious imprecision	none	466/1072 (43.5%)	660/1073 (61.5%)	RR 0.71 (0.65 to	178 fewer per 1000 (from 135	⊕⊕⊕⊕ HIGH	

Sensitiv	rity analysis:	Number not	achieving resp	onse (50% re	duction in de	epression scores) - Dosulepi	67.3% n	0.78)	fewer to 215 fewer) 195 fewer per 1000 (from 148 fewer to 236 fewer)		
1	randomised trials				no serious imprecision	none	94/194 (48.5%)	126/192 (65.6%)	RR 0.74 (0.62 to 0.88)	171 fewer per 1000 (from 79 fewer to 249 fewer)	⊕⊕⊕ HIGH	
Consitiu	ity analysis	Numbernet	achioving room	onso (50% ro	duction in de	epression scores) Iminyami	65.6%		171 fewer per 1000 (from 79 fewer to 249 fewer)		
	randomised		serious ¹		no serious	none	462/1106 (41.8%)	685/1080 (63.4%)	RR 0.69 (0.62 to 0.76)	197 fewer per 1000 (from 152 fewer to 241 fewer)	⊕⊕⊕O MODERATE	
								65.2%	<i>3</i> 5,	202 fewer per 1000 (from 156 fewer to 248 fewer)		

Moderate heterogeneity

Single study

Are TCAs effective in depression? (TCAs versus placebo - acceptability/tolerability data)

			Quality asses	ssment				Sumn	nary of fir	ndings		
			Quality associ	, o			No. of p	patients	Ef	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Placebo	Relative (95% CI)	Absolute	Quality	
Numbe	r leaving trea	tment early	for any reason									
85	randomised trials			no serious indirectness	serious ¹	none	1864/5039 (37%)	1830/4862 (37.6%) 39%	RR 0.99 (0.92 to 1.06)	4 fewer per 1000 (from	⊕⊕⊕O MODERATE	
Numbe	r leaving trea	atment early	for any reasor	ı - Amitriptyli	ne					31 fewer to 23 more)		
23	randomised trials	no serious limitations		no serious indirectness	no serious imprecision	none	464/1424 (32.6%)	474/1381 (34.3%)	RR 0.93 (0.79 to 1.1)	24 fewer per 1000 (from 72 fewer to 34 more)	⊕⊕⊕O MODERATE	
								35.7%		25 fewer per 1000		

³ Large heterogeneity ⁴ Inconclusive effect size

⁵ Uncertain clinical importance

	Т		ī	Т	T	1	T	1		<u> </u>	T	
										(from 75		
										fewer to 36		
										more)		
Numbe	r leaving trea	itment early	for any reasor	n - Clomipram								
2	randomised	no serious	no serious	no serious	serious ¹	none				45 fewer		
	trials	limitations	inconsistency	indirectness						per 1000		
								7/28 (25%)		(from 175		
									RR 0.82	fewer to		
							C /20 /200/\		(0.3 to	298 more)	$\oplus \oplus \oplus O$	
							6/30 (20%)		2.19)		MODERATE	
									2.19)	43 fewer		
										per 1000		
								23.9%		(from 167		
										fewer to		
										284 more)		
Numbe	r leaving trea	itment early	for any reasor									
3	randomised	no serious	no serious	no serious	serious ¹	none				35 more		
	trials	limitations	inconsistency	indirectness				94/239		per 1000		
								-		(from 83		
								(39.3%)	RR 1.09	fewer to		
							96/236		(0.79 to	197 more)	$\oplus \oplus \oplus O$	
							(40.7%)		1.5)		MODERATE	
									1.5)	30 more		
										per 1000		
								33.3%		(from 70		
										fewer to		
										167 more)		
Numbe	r leaving trea	itment early	for any reasor	n - Imipramin	е							
54	randomised	no serious	no serious	no serious	serious ¹	none	1253/3222	1198/3090	RR 1.01	4 more per	⊕⊕⊕О	
	trials	limitations	inconsistency	indirectness			(38.9%)	(38.8%)	(0.93 to	1000 (from	MODERATE	
							, ,	, ,	(0.93 (0	27 fewer to		
	I		L	I	l	I	i	i		l .		

r	1		1	1	1			•	1	,		
									1.09)	35 more)		
								41%		4 more per 1000 (from 29 fewer to 37 more)		
Numbe	r leaving trea	tment early	for any reason	n - Nortriptyli	ne							
3	randomised trials	no serious limitations	serious ²	no serious indirectness	serious ¹	none	45/127 (35.4%)	57/124 (46%)	RR 0.73 (0.27 to 2.03)	124 fewer per 1000 (from 336 fewer to 473 more)	⊕⊕OO LOW	
Numbe	r leaving trea	itment early	due to side ef	fects				42.9%	2.03)	116 fewer per 1000 (from 313 fewer to 442 more)		
65	randomised trials		no serious inconsistency		no serious imprecision	none	777/4151 (18.7%)	184/4022 (4.6%)	RR 4.02 (3.46 to 4.67)	138 more per 1000 (from 113 more to 168 more)	⊕⊕⊕⊕ HIGH	
								4.6%	4.07)	139 more per 1000 (from 113 more to 169 more)		
Numbe	r leaving trea	itment early	due to side ef	fects - Amitri	otyline							
16	randomised	no serious	no serious	no serious	no serious	none	199/1193	40/1157	RR 4.66	127 more	$\oplus \oplus \oplus \oplus$	

			1						Ι.	ı		
	trials	limitations	inconsistency	indirectness	imprecision		(16.7%)	(3.5%)	(3.38 to	per 1000	HIGH	
									6.44)	(from 82		
										more to		
										188 more)		
										'		
										117 more		
										per 1000		
								3.2%		(from 76		
										more to		
							<u> </u>			174 more)		
Numbe	r leaving trea	tment early	due to side ef	ects - Clomip	ramine							
	_											
1	randomised	no serious	serious ⁴	no serious	serious ¹	none				11 fewer		
	trials	limitations		indirectness				- /		per 1000		
								2/18		(from 96		
								(11.1%)	DD 0 0	fewer to		
									RR 0.9	527 more)	$\oplus \oplus OO$	
							2/20 (10%)		(0.14 to	327 more)	LOW	
									5.74)	11 fewer		
										per 1000		
								11.1%		(from 95		
										fewer to		
										526 more)		
Numbe	r leaving trea	tment early	due to side ef	fects - Dosule	pin					, ,		
				200010								
2	randomised	no serious	no serious	no serious	no serious	none				95 more		
			inconsistency		imprecision					per 1000		
								10/202		(from 23		
								(5%)	RR 2.92	more to		
							30/207		(1.47 to		$\oplus \oplus \oplus \oplus$	
							(14.5%)		5.8)	238 more)	HIGH	
									3.0)	140 more		
										per 1000		
								7.3%		(from 34		
										more to		
										וווטוב נט		

										350 more)	
Numbe	r leaving trea	tment early	due to side ef	fects - Iminra	mine					330 1110107	
44	randomised trials		no serious inconsistency		no serious imprecision	none	534/2665 (20%)	131/2580 (5.1%)	RR 3.91 (3.27 to	148 more per 1000 (from 115 more to 186 more)	⊕⊕⊕⊕ HIGH
								4.7%	4.67)	137 more per 1000 (from 107 more to 172 more)	
Numbe	r leaving trea	tment early	due to side ef	fects - Nortri	otyline						
2	randomised trials		no serious inconsistency		no serious imprecision	none	12/66 (18.2%)	1/65 (1.5%)	RR 7.98 (1.51 to 42.09)	107 more per 1000 (from 8 more to 632 more)	⊕⊕⊕ HIGH
								1.4%	42.09)	98 more per 1000 (from 7 more to 575 more)	
Numbe	r reporting si										
31	randomised trials	no serious limitations	serious ²	no serious indirectness	no serious imprecision	none	1756/2343 (74.9%)	1248/2204 (56.6%)	RR 1.4 (1.25 to 1.56)	226 more per 1000 (from 142 more to	⊕⊕⊕O MODERATE

										317 more)		
								60%		240 more per 1000 (from 150 more to 336 more)		
Number	reporting si	de effects -	Amitriptyline									
	randomised trials	no serious limitations	serious ²	no serious indirectness	no serious imprecision	none	367/485 (75.7%)	228/447 (51%)	RR 1.44 (1.15 to 1.79)	224 more per 1000 (from 77 more to 403 more)	⊕⊕⊕O MODERATE	
								48.4%	1.79)	213 more per 1000 (from 73 more to 382 more)		
vumber	r reporting si		Clomipramine									
	randomised trials	no serious limitations	serious ⁴	no serious indirectness	serious ¹	none	8/10 (80%)	5/10 (50%)	RR 1.6 (0.8 to 3.2)	300 more per 1000 (from 100 fewer to 1100 more)	⊕⊕OO LOW	
								50%	3.2)	300 more per 1000 (from 100 fewer to 1100 more)		
lumber	r reporting si	de effects -	l Dosulepin							[±100 more)		

	randomised trials	no serious limitations		no serious imprecision	none	14/25 (56%)	5/27 (18.5%)	RR 3.02 (1.27 to	374 more per 1000 (from 50 more to 1144 more)	⊕⊕⊕O MODERATE	
Numbra		de effecte	Iminomico				18.5%	7.18)	374 more per 1000 (from 50 more to 1143 more)		
Numbe	r reporting si	ае епестѕ -	imipramine								
	randomised trials	no serious limitations	serious ²	no serious imprecision	none	1304/1757 (74.2%)	959/1657 (57.9%)	RR 1.39 (1.21 to 1.59)		⊕⊕⊕O MODERATE	
							63.3%	2.00,	247 more per 1000 (from 133 more to 373 more)		
Numbe	r reporting si	de effects -	Nortriptyline								
	randomised trials		no serious inconsistency	no serious imprecision	none	63/66 (95.5%)	51/63 (81%)	RR 1.18 (1.03 to 1.34)	146 more per 1000 (from 24 more to 275 more)	⊕⊕⊕ HIGH	
							80.7%		145 more per 1000 (from 24		

					more to	
					274 more)	

¹ Inconclusive effect size

Large heterogeneity
 Moderate heterogeneity
 Single study

Escitalopram

Should escitalopram be used in depression? (Escitalopram versus placebo)

			Quality asse	ssmant				Summ	nary of fin	ndings		
			Quality asse.	331110110			No. of pa	tients	Ef	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Placebo	Relative (95% CI)	Absolute	Quality	
Non-res	ponse - orde	ered by base	line severity						ļ.			
	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	936/1881 (49.8%)	971/1614 (60.2%) 58.5%	RR 0.81 (0.75 to - 0.88)	114 fewer per 1000 (from 72 fewer to 150 fewer) 111 fewer per 1000 (from 70 fewer to 146 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-res	ponse - Esci	talopram 10	mg									
	randomised trials	no serious limitations	serious ²	no serious indirectness	no serious imprecision	none	407/758 (53.7%)	388/628 (61.8%)	RR 0.84 (0.72 to 0.98)	173 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								63.4%		101 fewer per 1000		

	1	ı	T	1	T	1		1	1	ı	1 1	
										(from 13		
										fewer to		
										178 fewer)		
Non-res	sponse - Escit											
	randomised trials	no serious limitations	serious ³		no serious imprecision	none		89/122 (73%)	RR 0.68	233 fewer per 1000 (from 117 fewer to		
							62/125 (49.6%)		(0.55 to 0.84)	328 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								73%	0.64)	234 fewer per 1000 (from 117 fewer to 329 fewer)		
Non-rei	mission - vs P	Placebo										
9	randomised	no serious	serious ¹	no serious	no serious	none				82 fewer		
		limitations			imprecision		921/1508 (61.1%)	935/1363 (68.6%)	RR 0.88 (0.82 to	per 1000 (from 41 fewer to 123 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								71.1%	0.94)	85 fewer per 1000 (from 43 fewer to 128 fewer)		
Non-rei	mission - Esci	italopram 10	mg vs Placebo									
	randomised trials	no serious limitations	serious ²		no serious imprecision	none	397/639 (62.1%)	331/506 (65.4%)	RR 0.92 (0.81 to	52 fewer per 1000 (from 124	⊕⊕⊕O MODERATE	CRITICAL

								66.1%	1.06)	fewer to 39 more) 53 fewer per 1000 (from 126 fewer to		
Mean	endpoint dep	ression scor	es (clinician-ra	ted) - vs Place	bo (better in	dicated by lowe	er scores) (Bet	ter indicat	ed by low	40 more)		
6	randomised trials	no serious limitations	serious ¹		no serious imprecision	none	903	918	-	SMD 0.24 lower (0.35 to 0.13 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean	endpoint dep	ression scor	es (clinician-ra	ted) - Escitalo	pram 10mg v	s Placebo (Bett	er indicated b	y lower va	lues)	L		
3	randomised trials	no serious limitations	serious ²	no serious indirectness		strong association⁴	476	488	-	SMD 0.23 lower (0.46 to 0.01 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean	endpoint dep	ression score	es (clinician-ra	ted) - Escitalo	pram 20mg v	 /s Placebo (Bett	er indicated b	y lower va	lues)			
Mean 1	randomised		es (clinician-ra		no serious	vs Placebo (Bett	er indicated b	y lower va	lues) -	SMD 0.46 lower (0.71 to 0.2 lower)	⊕⊕⊕O MODERATE	CRITICAL
1	randomised trials	no serious limitations	serious ³	no serious indirectness	no serious imprecision	1	123		lues)	lower (0.71 to 0.2		CRITICAL

										lower)		
Mean c	hange depre	ssion scores	(clinician-rate	d) - Escitalopr	am 10mg vs	Placebo (Better	indicated by	lower valu	es)			
		limitations	,	indirectness	serious ⁵	none Placebo (Better	580	445 lower valu	- es)	SMD 0.28 lower (0.41 to 0.15 lower)		CRITICAL
							-	T	, 		T	
	randomised trials	no serious limitations	serious ³		no serious imprecision	none	123	119	-	SMD 0.48 lower (0.74 to 0.22 lower)	⊕⊕⊕O MODERATE	CRITICAL
Leaving	treatment e	arly for any	reason - vs Pla	cebo								
	randomised trials		no serious inconsistency		no serious imprecision	none	413/1881 (22%)	309/1614 (19.1%)	RR 1.11 (0.95 to	21 more per 1000 (from 10 fewer to 56 more)	⊕⊕⊕⊕ HIGH	CRITICAL
							,	19.3%	1.29)	21 more per 1000 (from 10 fewer to 56 more)		
Leaving	treatment e	arly for any	reason - Escita	lopram 10mg	vs Placebo							
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ⁶	none	151/758 (19.9%)	119/628 (18.9%)	RR 0.99 (0.75 to	2 fewer per 1000 (from 47	⊕⊕OO LOW	CRITICAL

Leaving	treatment e	arly for any	reason - Escita	lopram 20mg	vs Placeho			20%	1.3)	fewer to 57 more) 2 fewer per 1000 (from 50 fewer to 60 more)		
1	randomised				serious ⁶	none	36/125 (28.8%)	30/122 (24.6%)	RR 1.17 (0.77 to	42 more per 1000 (from 57 fewer to 189 more)	⊕⊕OO LOW	CRITICAL
								24.6%	1.77)	42 more per 1000 (from 57 fewer to 189 more)		
Leaving	treatment e	arly due to	side effects - vs	Placebo								
11	randomised trials	no serious limitations		no serious indirectness		none	117/1855 (6.3%)	51/1601 (3.2%)	(1.18 to	25 more per 1000 (from 6 more to 55 more)	⊕⊕⊕O MODERATE	CRITICAL
								3%	2.73)	24 more per 1000 (from 5 more to 52 more)		

Leaving	treatment e	early due to	side effects - Es	scitalopram 1	Omg vs Place	bo						
4	randomised trials	no serious limitations	serious ²	no serious indirectness	serious ⁶	none	45/758 (5.9%)	18/628 (2.9%)	RR 2.02 (0.9 to	29 more per 1000 (from 3 fewer to 101 more)	⊕⊕OO LOW	CRITICAL
								2.6%	4.54)	27 more per 1000 (from 3 fewer to 92 more)		
Leaving	treatment e	arly due to	side effects - Es	scitalopram 2	Omg vs Place	bo						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁷	none	13/125 (10.4%)	3/122 (2.5%)	RR 4.23 (1.24 to 14.47)	79 more per 1000 (from 6 more to 331 more) 81 more per 1000 (from 6	⊕⊕⊕O MODERATE	CRITICAL
								2.570		more to 337 more)		
Patient	s reporting si	ide effects -	vs Placebo									
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	932/1299 (71.7%)	771/1191 (64.7%)	RR 1.09 (1.04 to 1.15)	58 more per 1000 (from 26 more to 97 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								66.5%		60 more		

Patients	reporting si	de effects -	Escitalopram 1	Omg vs Place	bo					per 1000 (from 27 more to 100 more)		
	randomised trials		no serious inconsistency		no serious imprecision	none	295/483 (61.1%)	288/491 (58.7%)	RR 1.04 (0.94 to 1.15)	23 more per 1000 (from 35 fewer to 88 more)	⊕⊕⊕ HIGH	CRITICAL
Patients	roporting	da offects	Escitalopram 2	Omg vs Place	ha		· ·	56.1%	1.15)	22 more per 1000 (from 34 fewer to 84 more)		
1	randomised		1 2	no serious	T	none	107/125 (85.6%)	86/122 (70.5%)	RR 1.21 (1.06 to 1.39)		⊕⊕⊕O MODERATE	CRITICAL
								70.5%	2.337	148 more per 1000 (from 42 more to 275 more)		

¹ Moderate heterogeneity

² Large heterogeneity

³ Single study

⁴ Large studies

⁵ Unclear clinical importance

Is escitalopram more effective than other antidepressants in depression?

			Quality asse	ssment				Summa	ary of find	dings		
							No. of p	atients	Ef	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	All other ADs	Relative (95% CI)	Absolute	Quality	
Non-res	sponse - vs o	ther AD										
20	randomised trials		no serious inconsistency		no serious imprecision	none	1131/3090 (36.6%)	1199/2961 (40.5%)	RR 0.89 (0.84 to 0.95)	45 fewer per 1000 (from 20 fewer to 65 fewer)	⊕⊕⊕ HIGH	CRITICAL
								40.2%		44 fewer per 1000 (from 20 fewer to 64 fewer)		
Non-res	sponse - vs o	ther AD (ser	sitivity analys	is)								
19	randomised trials		no serious inconsistency		no serious imprecision	none	1125/2981 (37.7%)	1179/2851 (41.4%)	RR 0.9 (0.85 to 0.96)	41 fewer per 1000 (from 17 fewer to 62 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								41.3%	•	41 fewer		

⁶ Inconclusive effect size ⁷ Large confidence interval

Non-re	mission - vs c									per 1000 (from 17 fewer to 62 fewer)		
18	randomised trials	no serious limitations		no serious indirectness	no serious imprecision	none	1220/2717 (44.9%)	1346/2708 (49.7%)	RR 0.9 (0.85 to 0.95)	50 fewer per 1000 (from 25 fewer to 75 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Non-re	mission - vs c	other AD (se	nsitivity analys	is)				52.5%	0.93)	53 fewer per 1000 (from 26 fewer to 79 fewer)		
17	randomised trials		no serious inconsistency		no serious imprecision	none	1208/2608 (46.3%)	1291/2598 (49.7%) 55.1%	RR 0.93 (0.88 to 0.98)	35 fewer per 1000 (from 10 fewer to 60 fewer) 39 fewer per 1000 (from 11	⊕⊕⊕⊕ HIGH	CRITICAL
Mean e	randomised	no serious		no serious	no serious	indicated by low	ver values) 1506	1503	-	fewer to 66 fewer) SMD 0.1 lower (0.17 to	⊕⊕⊕⊕ HIGH	CRITICAL

										0.02		
										lower)		
Mean	change depre	ssion scores	(clinician-rate	d) - vs other <i>i</i>	AD (Better in	dicated by lowe	r values)					
19	randomised trials		no serious inconsistency		no serious imprecision	none	2586	2572	-	SMD 0.07 lower (0.12 to 0.02 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Leaving	treatment e	arly for any	reason - vs oth	ner AD								
21	randomised trials	no serious limitations		no serious indirectness	no serious imprecision	none	587/3106 (18.9%)	667/3086 (21.6%)	RR 0.85 (0.74 to 0.98)	32 fewer per 1000 (from 4 fewer to 56 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								23.2%	0.36)	35 fewer per 1000 (from 5 fewer to 60 fewer)		
Leavin	g treatment e	early due to	side effects - v	s other AD								
20	randomised trials		no serious inconsistency		no serious imprecision	none	167/2968 (5.6%)	245/2839 (8.6%)	RR 0.64 (0.53 to 0.78)	31 fewer per 1000 (from 19 fewer to 41 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								7.7%		28 fewer per 1000		

Numbe	r reporting s	ide effects -	vs other AD						(from 17 fewer to 36 fewer)		
17	randomised trials		no serious inconsistency	no serious imprecision	none	1550/2425 (63.9%)	1555/2414 (64.4%)	RR 0.94 (0.91 to	39 fewer per 1000 (from 13 fewer to 58 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
							71.4%	0.98)	43 fewer per 1000 (from 14 fewer to 64 fewer)		

Is escitalopram more effective than SSRIs in depression?

			Quality asses	ssment				Summ	ary of find	dings		
							No. of pa	atients	Ef	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	SSRIs	Relative (95% CI)	Absolute	Quality	
Non-res	ponse (vs SS	SRIs) - SSRI C	italopram						•			

¹ Large heterogeneity
² Moderate heterogeneity

6	randomised trials	no serious limitations		no serious imprecision	none	346/955 (36.2%)	361/858 (42.1%)		76 fewer per 1000 (from 34 fewer to 114 fewer)	⊕⊕⊕O MODERATE	CRITICAL
							46.9%	0.92)	84 fewer per 1000 (from 38 fewer to 127 fewer)		
Non-re	sponse (vs SS	SRIs) - SSRI F	luoxetine								
3	randomised trials		no serious inconsistency	serious ²	none	159/399 (39.8%)	166/384 (43.2%)	RR 0.92 (0.78 to 1.08)	35 fewer per 1000 (from 95 fewer to 35 more)	⊕⊕⊕O MODERATE	CRITICAL
							35.9%	1.08)	29 fewer per 1000 (from 79 fewer to 29 more)		
Non-re	sponse (vs SS	RIs) - SSRI S	ertraline								
2	randomised trials		no serious inconsistency	serious ²	none	87/243 (35.8%)	87/246 (35.4%)	RR 1.01 (0.8 to 1.28)	4 more per 1000 (from 71 fewer to 99 more)	⊕⊕⊕O MODERATE	CRITICAL
							34.8%		3 more per 1000 (from 70		

										fewer to		
										97 more)		
Non-re	sponse (vs SS	SRIs) - SSRI P	aroxetine									
2	randomised trials		no serious inconsistency		serious ²	none	99/398 (24.9%)	104/386 (26.9%)	RR 0.92 (0.73 to 1.17)	22 fewer per 1000 (from 73 fewer to 46 more)	⊕⊕⊕O MODERATE	CRITICAL
								27.4%	,	22 fewer per 1000 (from 74 fewer to 47 more)		
Non-re	sponse (sens	itivity analys	sis)									
12	randomised trials		no serious inconsistency		no serious imprecision	none	685/1886 (36.3%)	698/1764 (39.6%)	RR 0.89 (0.82 to	44 fewer per 1000 (from 12 fewer to 71 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								37.5%	0.97)	41 fewer per 1000 (from 11 fewer to 68 fewer)		
Non-re	sponse (sens	itivity analys	sis) - SSRI Cital	opram								
5	randomised trials	no serious limitations	serious ¹	no serious indirectness		strong association ³	340/846 (40.2%)	341/748 (45.6%)	RR 0.85 (0.76 to 0.95)	68 fewer per 1000 (from 23	⊕⊕⊕⊕ HIGH	CRITICAL

										109 fewer)		
								50.9%		76 fewer per 1000 (from 25 fewer to 122 fewer)		
Non-res	sponse (sens	itivity analys	sis) - SSRI Fluo	xetine								
3	randomised trials		no serious inconsistency			none	159/399 (39.8%)	166/384 (43.2%)	RR 0.92 (0.78 to	35 fewer per 1000 (from 95 fewer to 35 more)	⊕⊕⊕ HIGH	CRITICAL
Non roo	mana (sans	itivitu analy	sis) - SSRI Sertr	aliaa				35.9%	1.08)	29 fewer per 1000 (from 79 fewer to 29 more)		
NOII-163	sponse (sens	itivity allaly:	515 <i>)</i> - 33Ki 3ei ti	aiiie								
2	randomised trials		no serious inconsistency		no serious imprecision	none	87/243 (35.8%)	87/246 (35.4%)	RR 1.01 (0.8 to	4 more per 1000 (from 71 fewer to 99 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								34.8%	1.28)	3 more per 1000 (from 70 fewer to 97 more)		
Non-res	sponse (sens	itivity analys	sis) - SSRI Paro	xetine								

2	randomised trials	no serious limitations		no serious indirectness	serious ²	none	99/398 (24.9%)	104/386 (26.9%)	RR 0.92 (0.73 to	22 fewer per 1000 (from 73 fewer to 46 more)	⊕⊕OO LOW	CRITICAL
								27.4%	1.17)	22 fewer per 1000 (from 74 fewer to 47 more)		
Numbe	r not achievi	ng remissior	n at endpoint (vs SSRIs)								
11	randomised trials	no serious limitations		no serious indirectness		none	642/1622 (39.6%)	753/1621 (46.5%)	RR 0.85 (0.79 to 0.92)	70 fewer per 1000 (from 37 fewer to 98 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								42.6%	0.92)	64 fewer per 1000 (from 34 fewer to 89 fewer)		
Numbe	r not achievi	ng remissior	n at endpoint (vs SSRIs) - SSI	RI Citalopran	า						
4	randomised trials	no serious limitations			no serious imprecision	none	206/582 (35.4%)	303/605 (50.1%)	RR 0.71 (0.62 to 0.81)	145 fewer per 1000 (from 95 fewer to 190 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								54.9%		159 fewer per 1000 (from 104		

										fewer to 209 fewer)		
Numbe	r not achievi	ng remissio	n at endpoint (vs SSRIs) - SS	RI Sertraline							
	randomised trials		no serious inconsistency		serious ²	none	123/243 (50.6%)	122/246 (49.6%)	RR 1.02 (0.86 to 1.22)	109 more)	⊕⊕⊕O MODERATE	CRITICAL
								48.8%	,	10 more per 1000 (from 68 fewer to 107 more)		
Numbe	r not achievi	ng remissioi	n at endpoint (
3	randomised trials		no serious inconsistency		serious ²	none	179/399 (44.9%)	187/384 (48.7%)	RR 0.92 (0.8 to	29 more)	⊕⊕⊕O MODERATE	CRITICAL
								40.8%	1.00)	33 fewer per 1000 (from 82 fewer to 24 more)		
Numbe	r not achievi	ng remissio	n at endpoint (vs SSRIs) - SS	RI Paroxetine	2						
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	134/398 (33.7%)	141/386 (36.5%)	RR 0.92 (0.76 to 1.11)		⊕⊕OO LOW	CRITICAL

										40 more)		
			n at endpoint (vs SSRIs) (sen	sitivity analy	rsis)		37%		30 fewer per 1000 (from 89 fewer to 41 more)		
	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	630/1513 (41.6%)	698/1511 (46.2%)	RR 0.9 (0.83 to 0.98)	46 fewer per 1000 (from 9 fewer to 79 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Numbe	r not achievi	ng remission	n at endpoint (vs SSRIs) (sen	sitivity analy	rsis) - SSRI Citalo	ppram	41.7%	0.98)	42 fewer per 1000 (from 8 fewer to 71 fewer)		
		T			_	T	, prum		I	00.5		
	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	194/473 (41%)	248/495 (50.1%)	RR 0.82 (0.72 to 0.94)	90 fewer per 1000 (from 30 fewer to 140 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								59.9%	ŕ	108 fewer per 1000 (from 36 fewer to 168 fewer)		
Numbe	r not achievi	ng remission	at endpoint (vs SSRIs) (sen	sitivity analy	rsis) - SSRI Sertra	aline			168 fewer)		

2	randomised trials		no serious inconsistency			none	123/243 (50.6%)	122/246 (49.6%)	(0.00 to	10 more per 1000 (from 69 fewer to 109 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								48.8%	1.22)	10 more per 1000 (from 68 fewer to 107 more)		
Numbe	r not achievi	ng remissior	n at endpoint (vs SSRIs) (sen	sitivity analy	sis) - SSRI Fluox	etine					
3	randomised trials		no serious inconsistency		no serious imprecision	none	179/399 (44.9%)	187/384 (48.7%)	RR 0.92 (0.8 to 1.06)	39 fewer per 1000 (from 97 fewer to 29 more) 33 fewer per 1000	⊕⊕⊕ HIGH	CRITICAL
								40.8%		(from 82 fewer to 24 more)		
Numbe	r not achievi	ng remissior	n at endpoint (vs SSRIs) (sen	sitivity analy	rsis) - SSRI Parox	etine					
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	134/398 (33.7%)	141/386 (36.5%)	RR 0.92 (0.76 to 1.11)	29 fewer per 1000 (from 88 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
								37%		30 fewer per 1000 (from 89		

										fewer to		
										41 more)		
N/10010 (.a. (alipiaiam	motod) (va CCD	ls) (Botton inc	licated by lay					41 111010)		
iviean e	enapoint sco	res (ciinician	rated) (vs SSR	is) (Better inc	ilcated by lov	wer values)						
9	randomised trials		no serious inconsistency			none	1219	1215	-	SMD 0.11 lower (0.19 to	⊕⊕⊕⊕ HIGH	CRITICAL
										0.03 lower)		
Mean e	endpoint sco	res (clinician	rated) (vs SSR	ls) - SSRI Cita	lopram (Bett	er indicated by	lower values)					
4	randomised trials		no serious inconsistency			none	566	577	-	SMD 0.12 lower (0.24 lower to 0 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean e	endpoint sco	res (clinician	rated) (vs SSR	ls) - SSRI Fluo	xetine (Bette	er indicated by I	ower values)					
3	randomised trials		no serious inconsistency		no serious imprecision	none	384	375	-	SMD 0.2 lower (0.34 to 0.06 lower)	⊕⊕⊕ HIGH	CRITICAL
Mean e	endpoint sco	res (clinician	rated) (vs SSR	ls) - SSRI Sert	raline (Bette	r indicated by lo	ower values)					
1	randomised trials		no serious inconsistency		serious ²	none	104	107	-	SMD 0.02 lower (0.29 lower to	⊕⊕⊕O MODERATE	CRITICAL

										higher)		
Mean e	ndpoint scor	es (clinician	rated) (vs SSR	ls) - SSRI Parc	exetine (Bett	er indicated by I	ower values)					
1	randomised trials		no serious inconsistency		serious ²	none	165	156	-	SMD 0.11 higher (0.11 lower to 0.33 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean c	hange (clinic	ian rated) (v	s SSRIs) (Bette	r indicated by	y lower value	es)				•		
13	randomised trials		no serious inconsistency			none	1667	1670	-	SMD 0.1 lower (0.18 to 0.02 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean c	hange (clinic	ian rated) (v	rs SSRIs) - SSRI	Citalopram (E	Better indica	ted by lower val	ues)					
6	randomised trials		no serious inconsistency			none	812	827	-	SMD 0.17 lower (0.28 to 0.05 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean c	hange (clinic	ian rated) (v	s SSRIs) - SSRI	Fluoxetine (B	etter indicat	ed by lower val	ues)					
3	randomised trials		no serious inconsistency			none	227	222	-	SMD 0.06 lower (0.24 lower to 0.13	⊕⊕⊕ HIGH	CRITICAL

										higher)		
Mean c	change (clinic	ian rated) (\	rs SSRIs) - SSRI	Sertraline (Be	etter indicate	ed by lower valu	es)					
2	randomised trials		no serious inconsistency	no serious indirectness		none	235	242	-	SMD 0.01 higher (0.17 lower to 0.19 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean c	change (clinic	ian rated) (v	/s SSRIs) - SSRI	Paroxetine (E	Better indicat	ted by lower val	ues)					
2	randomised trials	no serious limitations	· ·	no serious indirectness	serious ²	none	393	379	-	SMD 0.06 lower (0.38 lower to 0.27 higher)	⊕OOO VERY LOW	CRITICAL
Leaving	the study ea	arly for any	reason (vs SSR	s)								
14	randomised trials		no serious inconsistency		serious ²	none	338/2011 (16.8%)	372/1999 (18.6%)	RR 0.86 (0.71 to 1.03)	26 fewer per 1000 (from 54 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
								17.3%	1.03)	24 fewer per 1000 (from 50 fewer to 5 more)		

Leaving	the study ea	arly for any	reason (vs SSRI	s) - SSRI Cital	opram							
6	randomised trials	no serious limitations		no serious indirectness	serious ²	none	145/955 (15.2%)	149/969 (15.4%)	RR 0.82 (0.6 to	28 fewer per 1000 (from 62 fewer to 17 more)	⊕⊕OO LOW	CRITICAL
								19.6%	1.11)	35 fewer per 1000 (from 78 fewer to 22 more)		
Leaving	the study ea	arly for any	reason (vs SSR	s) - SSRI Fluo	xetine							
4	randomised trials	no serious limitations		no serious indirectness	serious ²	none	82/415 (19.8%)	87/398 (21.9%)	RR 0.91 (0.58 to	20 fewer per 1000 (from 92 fewer to 92 more)	⊕⊕OO LOW	CRITICAL
								19.9%	,	18 fewer per 1000 (from 84 fewer to 84 more)		
Leaving	the study ea	arly for any	reason (vs SSR	s) - SSRI Serti	raline							
2	randomised trials		no serious inconsistency		very serious ²	none	47/243 (19.3%)	40/246 (16.3%)	RR 1.19 (0.81 to 1.74)	31 more per 1000 (from 31 fewer to 120 more)	⊕⊕OO LOW	CRITICAL
								16%		30 more		

Leaving	the study ea	arly for any r	reason (vs SSRI	s) - SSRI Paro	xetine					per 1000 (from 30 fewer to 118 more)		
2	randomised trials		no serious inconsistency		no serious imprecision	none	64/398 (16.1%)	96/386 (24.9%)	RR 0.65 (0.49 to 0.85)	87 fewer per 1000 (from 37 fewer to 127 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Leaving	the study each	arly due to s	ide effects (vs	SSRIs)				23.2%	·	81 fewer per 1000 (from 35 fewer to 118 fewer)		
	-	-										1
13	randomised trials		no serious inconsistency		no serious imprecision	none	109/1883 (5.8%)	133/1756 (7.6%)	RR 0.75 (0.58 to	19 fewer per 1000 (from 3 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								6.3%	0.96)	16 fewer per 1000 (from 3 fewer to 26 fewer)		
Leaving	the study ea	arly due to s	ide effects (vs	SSRIs) - SSRI (Citalopram							
5	randomised trials		no serious inconsistency		no serious imprecision	none	47/837 (5.6%)	49/732 (6.7%)	RR 0.8 (0.49 to	13 fewer per 1000 (from 34	⊕⊕⊕⊕ HIGH	CRITICAL

Leaving	the study ea	arly due to s	ide effects (vs	SSRIs) - SSRI I	-luoxetine			6.3%	1.29)	fewer to 19 more) 13 fewer per 1000 (from 32 fewer to 18 more)		
	randomised trials		no serious inconsistency			none	27/411 (6.6%)	34/394 (8.6%)	RR 0.77 (0.47 to 1.26)	20 fewer per 1000 (from 46 fewer to 22 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Leaving	the study ea	arly due to s	ide effects (vs	SSRIs) - SSRI S	Sertraline			7.6%	,	17 fewer per 1000 (from 40 fewer to 20 more)		
				T	T							
2	randomised trials		no serious inconsistency			none	10/238 (4.2%)	9/245 (3.7%)	RR 1.11 (0.38 to 3.22)	4 more per 1000 (from 23 fewer to 82 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								3.7%	3.22)	4 more per 1000 (from 23 fewer to 82 more)		

Leaving	the study ea	arly due to s	ide effects (vs	SSRIs) - SSRI I	Paroxetine							
2	randomised trials	no serious limitations		no serious indirectness	serious ²	none	25/397 (6.3%)	41/385 (10.6%)	RR 0.65 (0.31 to 1.36)	37 fewer per 1000 (from 73 fewer to 38 more)	⊕⊕OO LOW	CRITICAL
			rious no serious no serious no no serious no no serious no no serious no serious no serious no no serious no no serious no serious no no serious no seriou		9.6%	1.50)	34 fewer per 1000 (from 66 fewer to 35 more)					
Patient	s reporting s	ide effects (vs SSRIs)									
14	randomised trials		no serious inconsistency		no serious imprecision	none	1229/1994 (61.6%)	1230/1980 (62.1%)	RR 0.94 (0.91 to 0.98)	37 fewer per 1000 (from 12 fewer to 56 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								71.4%	0.36)	43 fewer per 1000 (from 14 fewer to 64 fewer)		
Patient	s reporting s	ide effects (vs SSRIs) - SSRI	Citalopram			•					•
6	randomised trials	no serious limitations		no serious indirectness	serious ²	none	551/949 (58.1%)	511/956 (53.5%)	RR 0.95 (0.86 to 1.04)	27 fewer per 1000 (from 75 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
								70.9%		35 fewer		

Patient	s reporting si	ide effects (\	vs SSRIs) - SSRI	Fluoxetine						per 1000 (from 99 fewer to 28 more)		
4	randomised trials		no serious inconsistency		serious ²	none	231/410 (56.3%)	243/394 (61.7%)	RR 0.92 (0.83 to 1.01)	49 fewer per 1000 (from 105 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Patient	s renorting s	ide effects (v	vs SSRIs) - SSRI	Sertraline				64.1%	1.01)	51 fewer per 1000 (from 109 fewer to 6 more)		
- delette												
2	randomised trials		no serious inconsistency		serious ²	none	198/238 (83.2%)	218/245 (89%)	RR 0.94 (0.86 to	53 fewer per 1000 (from 125 fewer to 18 more)	⊕⊕⊕O MODERATE	CRITICAL
								88.8%	1.02)	53 fewer per 1000 (from 124 fewer to 18 more)		
Patient	s reporting si	ide effects (v	rs SSRIs) - SSRI	Paroxetine								
2	randomised trials		no serious inconsistency		serious ²	none	249/397 (62.7%)	258/385 (67%)	RR 0.93 (0.84 to	47 fewer per 1000 (from 107	⊕⊕⊕O MODERATE	CRITICAL

Patient	s reporting s	ide effects (v	vs SSRIs) (sensi	tivity analysis	s)			66.1%	1.04)	fewer to 27 more) 46 fewer per 1000 (from 106 fewer to 26 more)		
13	randomised trials		no serious inconsistency			none	1222/1886 (64.8%)	1195/1766 (67.7%)	RR 0.94 (0.9 to 0.98)	41 fewer per 1000 (from 14 fewer to 68 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Dationt		do official (rs CCDIe) /somei	Aireita e con le coi	- CCDI Cital			71.4%	0.00,	43 fewer per 1000 (from 14 fewer to 71 fewer)		
Patient	s reporting s	ide effects (v	vs SSRIs) (sensi	LIVILY analysis	s) - 33Ki Citai	opram						
5	randomised trials		no serious inconsistency		no serious imprecision	none	544/841 (64.7%)	476/742 (64.2%)	RR 0.95 (0.89 to	32 fewer per 1000 (from 71 fewer to 13 more)	⊕⊕⊕ HIGH	CRITICAL
								73.1%	1.02)	37 fewer per 1000 (from 80 fewer to 15 more)		

Patient	s reporting s	ide effects (vs SSRIs) (sensi	tivity analysis	s) - SSRI Fluo	xetine						
4	randomised trials		no serious inconsistency		no serious imprecision	none	231/410 (56.3%)	243/394 (61.7%)	RR 0.92 (0.82 to	49 fewer per 1000 (from 111 fewer to 19 more)	⊕⊕⊕ HIGH	CRITICAL
								64.1%	1.03)	51 fewer per 1000 (from 115 fewer to 19 more)		
Patient	s reporting s	ide effects (vs SSRIs) (sensi	tivity analysi	s) - SSRI Sert	raline						
2	randomised trials		no serious inconsistency		no serious imprecision	none	198/238 (83.2%)	218/245 (89%)	RR 0.93 (0.87 to 1)	62 fewer per 1000 (from 116 fewer to 0 more)	⊕⊕⊕ HIGH	CRITICAL
								88.8%	1)	62 fewer per 1000 (from 115 fewer to 0 more)		
Patient	s reporting s	ide effects (vs SSRIs) (sensi	tivity analysi	s) - SSRI Parc	exetine						·
2	randomised trials		no serious inconsistency			none	249/397 (62.7%)	258/385 (67%)	RR 0.94 (0.85 to 1.04)	40 fewer per 1000 (from 101 fewer to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								66.1%		40 fewer		

					per 1000	
					(from 99	
					fewer to	
					26 more)	

¹ Large heterogeneity
² Inconclusive effect size
³ Small confidence interval
⁴ Moderate heterogeneity

Is escitalopram more effective than non-SSRI antidepressants in depression?

			Quality asses	ssment				Sumn	nary of fi	ndings		
							No. of pa	tients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Other ADs (non SSRIs)	Relative (95% CI)	Absolute	Quality	
Non-res	ponse - SNR	I Duloxetine										
	randomised trials	no serious limitations		no serious indirectness	serious ²	none	242/558 (43.4%)	274/562 (48.8%)	RR 0.81 (0.57 to 1.15)	93 fewer per 1000 (from 210 fewer to 73 more)	⊕⊕OO LOW	CRITICAL
								54.4%	·	103 fewer per 1000 (from 234 fewer to 82 more)		
Non-res	ponse - SNR	l Venlafaxine	9									
	randomised trials		no serious inconsistency		serious ²	none	79/246 (32.1%)	90/245 (36.7%)	RR 0.86 (0.68 to 1.09)	51 fewer per 1000 (from 118 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
								39.3%		55 fewer per 1000 (from 126		

										fewer to 35		
										more)		
Non-re	sponse - Bup	ropion XL										
2	randomised trials	no serious limitations	no serious inconsistency		serious ²	none	119/291 (40.9%)	117/280 (41.8%)	RR 0.98 (0.78 to 1.22)		⊕⊕⊕O MODERATE	CRITICAL
								41.8%		8 fewer per 1000 (from 92 fewer to 92 more)		
Numbe	r not achievi	ng remission	at endpoint -	SNRI Duloxet	ine							
3	randomised trials		no serious inconsistency		serious ²	none	310/558 (55.6%)	315/562 (56%)	(0.83 to	17 fewer per 1000 (from 95 fewer to 73 more)	⊕⊕⊕O MODERATE	CRITICAL
								64.5%	1.13)	19 fewer per 1000 (from 110 fewer to 84 more)		
Numbe	r not achievi	ng remission	at endpoint -	SNRI Venlafa	kine							
2	randomised trials		no serious inconsistency		no serious imprecision	none	98/246 (39.8%)	111/245 (45.3%)	RR 0.88 (0.72 to 1.07)	54 fewer per 1000 (from 127 fewer to 32 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Numbe	r not achievi	ng remission	at endpoint -	Bupropion xl				47.4%		57 fewer per 1000 (from 133 fewer to 33 more)		
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	170/291 (58.4%)	167/280 (59.6%)	RR 0.98 (0.79 to 1.21)	12 fewer per 1000 (from 125 fewer to 125 more)	⊕⊕OO LOW	CRITICAL
Mean	ndpoint scor	as (clinician	rated) - SNRI F	ulovatina (Re	atter indicate	ed by lower value	ac)	59.6%	1.21)	12 fewer per 1000 (from 125 fewer to 125 more)		
ivicali c	naponit scoi	es (cilifician	raceuj - Sivili E	dioxetine (be	stter maicate	ou by lower value	-31					
1	randomised trials		no serious inconsistency		serious ²	none	141	146	-	SMD 0.19 lower (0.42 lower to 0.04 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean e	ndpoint scor	es (clinician	rated) - SNRI V	'enlafaxine (B	etter indicat	ed by lower valu	ies)	·		'		
1	randomised trials		no serious inconsistency		serious ²	none	146	142	-	SMD 0.08 higher (0.15 lower to 0.32 higher)	⊕⊕⊕O MODERATE	CRITICAL

Mean c	hange (clinic	ian rated) - S	SNRI Duloxetin	e (Better indi	cated by low	er values)						
	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	410	399	-	SMD 0.03 higher (0.11 lower to 0.17 higher)	⊕⊕⊕ HIGH	CRITICAL
Mean c	hange (clinic	ian rated) - S	SNRI Venlafaxir	ne (Better ind	icated by lov	ver values)						
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	243	240	-	SMD 0.04 lower (0.37 lower to 0.29 higher)	⊕⊕OO LOW	CRITICAL
Mean c	hange (clinic	ian rated) - I	Bupropion XL (I	Better indicat	ed by lower	values)						
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	266	263	-	SMD 0.05 lower (0.22 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Leaving	the study ea	l orly for any r	eason - SNRI D	uloxetine								
	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	119/558 (21.3%)	168/562 (29.9%)	RR 0.7 (0.49 to 1)	90 fewer per 1000 (from 152 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
								31.1%		93 fewer per 1000		

Leaving	the study ea	urly for any r	eason - SNRI V	enlafavine						(from 159 fewer to 0 more)		
2	randomised trials	no serious	no serious		serious ²	none	49/246 (19.9%)	55/245 (22.4%)	RR 0.88 (0.63 to 1.23)	27 fewer per 1000 (from 83 fewer to 52 more)	⊕⊕⊕O MODERATE	CRITICAL
								24.2%	·	29 fewer per 1000 (from 90 fewer to 56 more)		
Leaving	the study ea	irly for any r	eason - Buprop	oion XL								
2	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	81/291 (27.8%)	72/280 (25.7%)	RR 1.08 (0.82 to	21 more per 1000 (from 46 fewer to 105 more)	⊕⊕⊕O MODERATE	CRITICAL
								25.8%	1.41)	21 more per 1000 (from 46 fewer to 106 more)		
Leaving	the study ea	ırly due to si	de effects - SN	RI Duloxetine								
3	randomised trials	no serious limitations	serious ¹	no serious indirectness		none	30/558 (5.4%)	63/562 (11.2%)	RR 0.47 (0.25 to	59 fewer per 1000 (from 12	⊕⊕⊕O MODERATE	CRITICAL

Leaving	the study ea	arly due to si	de effects - SN	RI Venlafaxin	e			12.3%		fewer to 84 fewer) 65 fewer per 1000 (from 14 fewer to 92 fewer)		
	randomised trials	no serious limitations		no serious indirectness	serious ²	none	16/246 (6.5%)	32/245 (13.1%)	RR 0.47 (0.17 to 1.31)	69 fewer per 1000 (from 108 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
Leaving	the study ea	arly due to si	de effects - Bu	propion XL				13.5%		72 fewer per 1000 (from 112 fewer to 42 more)		
2	randomised		very serious ¹		serious ²	none	12/281 (4.3%)	17/276 (6.2%)	RR 0.78 (0.16 to	14 fewer per 1000 (from 52 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL
							(4.3%)	6.2%	3.7)	14 fewer per 1000 (from 52 fewer to 167 more)		

Patien	ts reporting si	ide effects -	SNRI Duloxetin	ie							
2	randomised trials	no serious limitations	no serious inconsistency		none	223/283 (78.8%)	223/289 (77.2%)	RR 1.02 (0.94 to 1.11)	15 more per 1000 (from 46 fewer to 85 more)	⊕⊕⊕⊕ HIGH	CRITICAL
							77.3%	1.11)	15 more per 1000 (from 46 fewer to 85 more)		
Patien	ts reporting si	ide effects -	SNRI Venlafaxi	ne							
1	randomised trials		no serious inconsistency		none	98/148 (66.2%)	102/145 (70.3%)	RR 0.94 (0.81 to 1.1)	42 fewer per 1000 (from 134 fewer to 70 more)	⊕⊕⊕⊕ HIGH	CRITICAL
							70.3%	1.1)	42 fewer per 1000 (from 134 fewer to 70 more)		

¹ Large heterogeneity ² Inconclusive effect size

Is escitalopram more effective than other antidepressants in depression? (Sub-analysis highlighting citalopram)

			Quality asses	sment				Summa	ry of find	ings		
			Quality asses	Silicit			No. of p	atients	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	All other ADs (citalopram separated)	Relative (95% CI)	Absolute	Quality	Importance
Non-res	sponse											
_	randomised trials		no serious inconsistency			none	635/1713 (37.1%)	730/1724 (42.3%)	RR 0.87 (0.81 to	55 fewer per 1000 (from 25 fewer to 80 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								42.8%	·	56 fewer per 1000 (from 26 fewer to 81 fewer)		
Non-res	sponse - Escit	alopram 10n	ng vs Other an	tidepressant								
	randomised trials		no serious inconsistency		serious ¹	none	315/678 (46.5%)	322/662 (48.6%)	RR 0.96 (0.86 to 1.06)	19 fewer per 1000 (from 68 fewer to 29 more)	⊕⊕⊕O MODERATE	CRITICAL
								44.6%		18 fewer per 1000 (from 62		

										fewer to				
										27 more)				
Non-re	sponse - Escita	alopram 10n	ng vs Citalopra	m										
			no serious inconsistency		serious ¹	none	108/294 (36.7%)	127/307 (41.4%)	RR 0.89 (0.73 to 1.08)	46 fewer per 1000 (from 112 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL		
								43.4%	1.00)	48 fewer per 1000 (from 117 fewer to 35 more)				
Non-re	Ion-response - Escitalopram 20mg vs Other antidepressant													
_			no serious inconsistency		no serious imprecision	none	113/474 (23.8%)	148/478 (31%)	RR 0.77 (0.63 to 0.95)	71 fewer per 1000 (from 15 fewer to 115 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL		
								25.8%		59 fewer per 1000 (from 13 fewer to 95 fewer)				
Non-re	sponse - Escita	alopram 20n	ng vs Citalopra	m										
	randomised trials	no serious limitations		no serious indirectness	no serious imprecision	none	99/267 (37.1%)	133/277 (48%)	RR 0.77 (0.63 to	110 fewer per 1000 (from 34	⊕⊕⊕O MODERATE	CRITICAL		

								48.6%	0.93)	fewer to 178 fewer) 112 fewer per 1000 (from 34 fewer to 180		
										fewer)		
Non-re	mission											
	randomised trials		no serious inconsistency		no serious imprecision	none	639/1469 (43.5%)	703/1474 (47.7%)	RR 0.91 (0.82 to 1)	43 fewer per 1000 (from 86 fewer to 0 more)	⊕⊕⊕ HIGH	CRITICAL
								42.6%	1)	38 fewer per 1000 (from 77 fewer to 0 more)		
Non-re	mission - Escit	alopram 10	mg vs Other ar	ntidepressant	i							
			no serious inconsistency		serious ¹	none	372/678 (54.9%)	367/662 (55.4%)	RR 0.98 (0.88 to 1.11)		⊕⊕⊕O MODERATE	CRITICAL
								53.5%		11 fewer per 1000 (from 64 fewer to		

										59 more)		
Non-re	mission - Escit	alopram 10	ng vs Citalopra	am					•			
	l	T										
1	randomised trials		no serious inconsistency		serious ¹	none	49/175 (28%)	59/182 (32.4%)	RR 0.86 (0.63 to 1.19)	45 fewer per 1000 (from 120 fewer to 62 more)	⊕⊕⊕O MODERATE	
								32.4%		45 fewer per 1000 (from 120 fewer to 62 more)		
Non-re	mission - Escit	alopram 20	ng vs Other ar	tidepressant	;							
3	randomised trials		no serious inconsistency			none	151/474 (31.9%)	186/478 (38.9%)	RR 0.82 (0.7 to	70 fewer per 1000 (from 12 fewer to 117 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								34.4%	. 0.97)	62 fewer per 1000 (from 10 fewer to 103 fewer)		
Non-re	mission - Escit	alopram 20	ng vs Citalopra	am								
1	randomised trials		no serious inconsistency			none	67/142 (47.2%)	91/152 (59.9%)	RR 0.79 (0.63 to	126 fewer per 1000 (from 12	⊕⊕⊕⊕ HIGH	CRITICAL

								59.9%	0.98)	fewer to 222 fewer) 126 fewer per 1000 (from 12 fewer to 222		
Mean e	ndpoint depr	ession score	s (clinician-rat	ed) (Better in	dicated by l	ower values)				fewer)		
6	randomised trials		no serious inconsistency			none	938	954	-	SMD 0.19 lower (0.28 to 0.1 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean e	ndpoint depr	ession score	s (clinician-rat	ed) - Escitalo	pram 10mg v	s Other antide	oressant (Bett	er indicated	by lowe	r values)		
3	randomised trials		no serious inconsistency			none	392	384	-	SMD 0.19 lower (0.33 to 0.05 lower)	⊕⊕⊕ HIGH	CRITICAL
Mean e	endpoint depr	ession score	s (clinician-rat	ed) - Escitalo	pram 10mg v	vs Citalopram (E	etter indicate	ed by lower v	alues)			
2	randomised trials		no serious inconsistency			none	282	299	-	SMD 0.17 lower (0.33 to 0.01	⊕⊕⊕⊕ HIGH	CRITICAL

										lower)		
Mean e	ndpoint depr	ession score	s (clinician-rat	ed) - Escitalo	pram 20mg v	vs Other antide	pressant (Bett	er indicated	by lowe	r values)		
	randomised trials		no serious inconsistency		serious ¹	none	141	146	-	SMD 0.19 lower (0.42 lower to 0.04 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean e	ndpoint depr	ession score	s (clinician-rat	ed) - Escitalo	pram 20mg v	vs Citalopram (E	Better indicate	ed by lower v	alues)	•		
	randomised trials		no serious inconsistency		serious ¹	none	123	125	-	SMD 0.22 lower (0.47 lower to 0.03 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean c	hange scores	(clinician-ra	ted) (Better in	dicated by lo	wer values)					ı		
	randomised trials		no serious inconsistency		no serious imprecision	none	1408	1434	-	SMD 0.13 lower (0.2 to 0.05 lower)		CRITICAL
Mean c	hange scores	(clinician-ra	ted) - Escitalor	oram 10mg vs	Other antid	lepressant (Bett	er indicated k	y lower valu	es)			
	randomised trials		no serious inconsistency		serious ¹	none	496	493	-	SMD 0 higher (0.13 lower to 0.12	⊕⊕⊕O MODERATE	CRITICAL

										higher)		
Mean c	hange scores	clinician-ra	 ted) - Escitalop	ram 10mg vs	Citalopram	(Better indicate	d by lower va	ilues)				
		T	<u> </u>	T		ı ı			ı	Т	Π	
		no serious			no serious	none				SMD 0.17		
	trials	limitations		indirectness	imprecision		390	407		lower (0.31 to	⊕⊕⊕O	CRITICAL
							390	407	_	0.03	MODERATE	CRITICAL
										lower)		
	-		. 1) 5 11 1	20	C'. I	/p						
iviean c	nange scores	(ciinician-ra	tea) - Escitaiop	oram 20mg vs	Citalopram	(Better indicate	a by lower va	ilues)				
2	randomised	no serious	no serious	no serious	no serious	none				SMD 0.22		
	trials	limitations	inconsistency	indirectness	imprecision					lower	$\oplus \oplus \oplus \oplus$	
							261	267	-	(0.39 to	HIGH	CRITICAL
										0.05 lower)		
										lowery		
Mean c	hange scores	(clinician-ra	ted) - Escitalop	oram 20mg vs	Citalopram	(Better indicate	d by lower va	lues)				
	no					none				SMD 0.22		
	methodology									lower		
	chosen						261	267	-	(0.39 to 0.05		
										lower)		
										,		
Leaving	treatment ea	irly for any r	reason									
12					no serious	none				58 fewer		
	trials	limitations	inconsistency	indirectness	imprecision		338/1838	444/1848	RR 0.76	•	$\oplus \oplus \oplus \oplus$	
							(18.4%)	(24%)	(0.68 to 0.87)	(from 31 fewer to	HIGH	CRITICAL
									0.87)	77 fewer to		
										iciici j		

								25.6%		61 fewer per 1000 (from 33 fewer to 82 fewer)		
Leaving	g treatment ea	arly for any i	eason - Escital	opram 10mg	vs Other an	tidepressant						
4	randomised trials		no serious inconsistency		no serious imprecision	none	130/678 (19.2%)	159/662 (24%)	RR 0.8 (0.65 to	48 fewer per 1000 (from 5 fewer to 84 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								20.1%	0.30)	40 fewer per 1000 (from 4 fewer to 70 fewer)		
Leaving	treatment ea	arly for any i	eason - Escital	opram 10mg	vs Citalopra	m						
3	randomised trials		no serious inconsistency		no serious imprecision	none	56/403 (13.9%)	81/417 (19.4%)	RR 0.72 (0.53 to	54 fewer per 1000 (from 4 fewer to 91 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
							(13.3%)	25.6%	0.98)	72 fewer per 1000 (from 5 fewer to 120 fewer)	mon	
Leaving	g treatment ea	arly for any i	eason - Escital	opram 20mg	vs Other an	tidepressant						
4	randomised	no serious	no serious	no serious	no serious	none	106/490	147/492	RR 0.73	81 fewer	$\oplus \oplus \oplus \oplus$	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision		(21.6%)	(29.9%)	(0.58 to 0.9)	per 1000 (from 30 fewer to 125 fewer)	HIGH	
								28.6%		77 fewer per 1000 (from 29 fewer to 120 fewer)		
Leaving	treatment ea	orly for any r	eason - Escital	opram 20mg	vs Citalopra	m						
	randomised trials	no serious limitations		no serious indirectness	serious ¹	none	46/267 (17.2%)	57/277 (20.6%)	RR 0.83 (0.58 to	35 fewer per 1000 (from 86 fewer to 35 more)	⊕⊕OO LOW	CRITICAL
								21%	1.17)	36 fewer per 1000 (from 88 fewer to 36 more)		
Leaving	treatment ea	orly due to si	de effects									
	randomised trials		no serious inconsistency		no serious imprecision	none	107/1722 (6.2%)	176/1728 (10.2%)		`	⊕⊕⊕ HIGH	CRITICAL
								8.8%		34 fewer per 1000		

1	randomised	no serious		no serious	Omg vs Other	r antidepressan none	t			(from 20 fewer to 46 fewer)		
1	randomised	no serious	no serious	no serious		_	t			46 fewer) 17 fewer		
1	randomised	no serious	no serious	no serious		_	i .			17 fewer		
1	randomised	no serious	no serious	no serious		_						
					serious ¹	none						
	trials	limitations	inconsistency	indirectness						4000		
								49/662		per 1000		
								-		(from 36		
								(7.4%)	RR 0.77	fewer to		
							39/675		(0.52 to	12 more)	$\oplus \oplus \oplus O$	CRITICAL
							(5.8%)		1.16)		MODERATE	CRITICAL
									1.16)	13 fewer		
										per 1000		
								5.8%		(from 28		
										fewer to		
										9 more)		
eaving	treatment ea	rly due to si	de effects - Es	citalopram 10	Omg vs Citalo	pram						
2	randomised	no serious	no serious	no serious	no serious	none				43 fewer		
	trials	limitations	inconsistency	indirectness	imprecision			29/307		per 1000		
										(from 1		
								(9.4%)	RR 0.54	fewer to		
							15/294		(0.2+0	66 fewer)	$\oplus \oplus \oplus \oplus$	CRITICAL
							(5.1%)		0.99)		HIGH	CRITICAL
									,	43 fewer		
										per 1000		
								9.4%		(from 1		
										fewer to		
										66 fewer)		
_eaving	treatment ea	irly due to si	de effects - Es	citalopram 20	Omg vs Othei	r antidepressan						
1	randomised	no serious	no serious	no serious	no serious	none	36/490	78/492	RR 0.46	86 fewer	$\oplus \oplus \oplus \oplus$	CDITICAL
	trials	limitations	inconsistency	indirectness	imprecision		(7.3%)	(15.9%)		per 1000	HIGH	CKITICAL
								•	(0.52 (0	(from 51		
1	randomised	no serious	no serious	no serious	no serious		36/490	-	RR 0.46 (0.32 to	per 1000		CRITICAL

								15.7%	0.68)	fewer to 108 fewer) 85 fewer per 1000 (from 50 fewer to 107		
										fewer)		
Leaving	treatment ea	arly due to s	ide effects - Es	citalopram 2	Omg vs Citalo	pram						
	randomised trials		no serious inconsistency		serious ¹	none	17/263 (6.5%)	20/267 (7.5%)	RR 0.86 (0.46 to	10 fewer per 1000 (from 40 fewer to 45 more)	⊕⊕⊕O MODERATE	CRITICAL
								7.6%	1.0)	11 fewer per 1000 (from 41 fewer to 46 more)		
Numbe	r reporting sid	de effects										
	randomised trials		no serious inconsistency			none	839/1352 (62.1%)	901/1365 (66%)	RR 0.94 (0.89 to 0.99)	40 fewer per 1000 (from 7 fewer to 73 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								72.3%		43 fewer per 1000 (from 7 fewer to		

										80 fewer)		
Numbe	r reporting sid	le effects - E	scitalopram 10	Omg vs Other	antidepress	ant			•			
	T		l			T						
3	randomised trials		no serious inconsistency		serious ¹	none	232/400 (58%)	242/389 (62.2%)	RR 0.94 (0.85 to 1.05)	37 fewer per 1000 (from 93 fewer to 31 more)	⊕⊕⊕O MODERATE	CRITICAL
								56.7%	2.00,	34 fewer per 1000 (from 85 fewer to 28 more)		
Numbe	r reporting sid	de effects - E	scitalopram 10	Omg vs Citalo	pram							
2	randomised trials		no serious inconsistency			none	204/294 (69.4%)	241/307 (78.5%)	RR 0.88 (0.8 to	94 fewer per 1000 (from 24 fewer to 157 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								79.7%	. 0.97)	96 fewer per 1000 (from 24 fewer to 159 fewer)		
Numbe	r reporting sid	de effects - E	scitalopram 20	Omg vs Other	antidepress	ant						
3	randomised trials		no serious inconsistency		serious ¹	none	275/391 (70.3%)	285/392 (72.7%)	RR 0.97 (0.89 to	22 fewer per 1000 (from 80	⊕⊕⊕O MODERATE	CRITICAL

									1.06)	fewer to 44 more)		
								71.4%		21 fewer per 1000 (from 79 fewer to 43 more)		
Numbe	r reporting sid	de effects - E	scitalopram 20	Omg vs Citalo	pram							
			no serious inconsistency			none	128/267 (47.9%)	133/277 (48%)	RR 0.97 (0.86 to 1.1)	14 fewer per 1000 (from 67 fewer to 48 more)	⊕⊕⊕O MODERATE	CRITICAL
								51.4%	1.1,	15 fewer per 1000 (from 72 fewer to 51 more)		

¹ Inconclusive effect size ² Large heterogeneity

Duloxetine

Should duloxetine be used for depression? (Acute phase efficacy data)

			Quality asses	ssment				Sum	mary of fi	ndings		
			Quality asset	, sinem			No. of p	atients	Ef	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo	Relative (95% CI)	Absolute	Quality	
Mean c	hange scores	at endpoint	- data for dose	es above licer	nsed dose (60) mg) - Sensitivit	y analysis: 6	0 mg (mea	sured wit	h: HAMD-17	; range of s	cores: 0-52;
Better i	ndicated by I	ower values)									
4	randomised trials	no serious limitations	no serious inconsistency		no serious imprecision	none	729	511	-	MD 1.85 lower (2.71 to 0.98 lower)	⊕⊕⊕O MODERATE	
Mean c	hange scores	at endpoint	- data for dose	es above licer	nsed dose (60	mg) - 80 mg (B	etter indicat	ed by low	er values)		•	
4	randomised trials	no serious limitations	no serious inconsistency		no serious imprecision	none	353	369	-	MD 1.97 lower (2.83 to 1.11 lower)	⊕⊕⊕O MODERATE	
Mean c	hange scores	at endpoint	- data for dose	es above licer	nsed dose (60) mg) - 120 mg (l	 Better indica	ited by lov	ver values)		
3	randomised trials	no serious limitations	no serious inconsistency		no serious imprecision	none	261	260	-	MD 2.57 lower (3.77 to 1.37 lower)	⊕⊕⊕O MODERATE	

Mean	change scores	at endpoint	t - data for dose	es above lice	nsed dose (60) mg) - 40 mg - 1	.20 mg (Bett	er indicate	d by lowe	er values)		
L	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ²	none	81	72	-	MD 0.9 lower (3.08 lower to 1.28 higher)	VERY LOW	
/lean	change scores	at endpoint	- overall (Bett	er indicated	by lower valu	es)						
LO	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision	none	1229	1020	-	MD 1.9 lower (2.44 to 1.35 lower)	⊕⊕⊕O MODERATE	
lon-r	esponse - data	for doses a	bove licensed d	lose (60 mg)	- 60 mg (HAN	1D < 50% reduct	ion)					
5	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision	none	589/1034 (57%)	565/808 (69.9%)	RR 0.8 (0.73 to 0.88)	14 fewer per 100 (from 8 fewer to 19 fewer)	⊕⊕⊕O MODERATE	
lon-r	esponse - data	for doses a	bove licensed d	ose (60 mg)	- 80 mg (HAN	1D < 50% reduct	ion)					
	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ³	none	235/566 (41.5%)	228/371 (61.5%)	RR 0.74 (0.6 to 0.9)	16 fewer per 100 (from 6 fewer to 25 fewer)	⊕⊕OO LOW	
lon-r	esponse - data	for doses a	bove licensed d	lose (60 mg)	- 120 mg (HA	MD < 50% reduc	ction)	<u> </u>	ı	<u> </u>		
	randomised	no serious	no serious	serious ¹	very	none	38/70	45/70	RR 0.84 (0.64 to	10 fewer per 100	⊕OOO	

Non-res	sponse - data			ose (60 mg) -	T	mg (HAMD < 50	(54.3%) % reduction	(64.3%)	1.11)	(from 23 fewer to 7 more)	VERY LOW	
1	randomised trials	no serious limitations	no serious inconsistency		very serious ²	none	42/82 (51.2%)	54/77 (70.1%)	RR 0.73 (0.57 to 0.94)	19 fewer per 100 (from 4 fewer to 30 fewer)	⊕OOO VERY LOW	
Non-re	sponse - over	all (HAMD <	50% reduction)								
12	randomised trials	no serious limitations	serious		no serious imprecision	none	904/1752 (51.6%)	892/1326 (67.3%)	RR 0.78 (0.74 to 0.83)	15 fewer per 100 (from 11 fewer to 17 fewer)	⊕⊕OO LOW	
Non-re	mission - data	for doses a	bove licensed of	dose (60 mg)	- Sensitivity	analysis: 60 mg						
5	randomised trials	no serious limitations	no serious inconsistency		no serious imprecision	none	583/893 (65.3%)	519/667 (77.8%)	RR 0.83 (0.78 to 0.89)	13 fewer per 100 (from 9 fewer to 17 fewer)	⊕⊕⊕O MODERATE	
Non-re	mission - data	for doses a	bove licensed of	dose (60 mg)	- 80 mg							
4	randomised trials	no serious limitations	no serious inconsistency		no serious imprecision	none	213/363 (58.7%)	266/371 (71.7%)	RR 0.82 (0.74 to 0.91)	13 fewer per 100 (from 6 fewer to 19	⊕⊕⊕O MODERATE	

										fewer)		
Non-re	emission - data	for doses a	bove licensed	dose (60 mg)	- 40 mg - 120) mg						
1	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ²	none	50/82 (61%)	54/77 (70.1%)	RR 0.87 (0.69 to 1.09)	9 fewer per 100 (from 22 fewer to 6 more)	⊕OOO	
Non-re	emission - data	for doses a	bove licensed	dose (60 mg)	- 120 mg							
3	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision	none	149/266 (56%)	183/262 (69.8%)	RR 0.8 (0.7 to 0.92)	14 fewer per 100 (from 6 fewer to 21 fewer)	⊕⊕⊕O MODERATE	
lon-re	emission - ove	rall										
11	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision	none	995/1604 (62%)	891/1185 (75.2%)	RR 0.83 (0.79 to 0.87)	13 fewer per 100 (from 10 fewer to 16 fewer)	⊕⊕⊕O MODERATE	
Depres values	randomised		n 5 average pai	in (measured	no serious	m 5 average pai	n in last 24 h	nrs; range c	of scores:	1-11; Better MD 0.74 lower (1.13	⊕⊕⊕О	lower
	uiais	111111111111111111111111111111111111111	inconsistency		IIIIbi ecisioli					to 0.34	IVIODERATE	

Ī						lower)	

Is duloxetine effective for depression? (Acute phase acceptability and tolerability data)

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo - acceptability and tolerability	Relative (95% CI)	Absolute	Quality	Importance
Leaving treatment early - any reason (data by doses above licensed dose 60mg) - 60 mg												
6	randomised trials		no serious inconsistency		no serious imprecision	none	318/1034 (30.8%)	227/808 (28.1%)	RR 1.13 (0.98 to 1.3)	(from 1	⊕⊕⊕O MODERATE	
Leaving treatment early - any reason (data by doses above licensed dose 60mg) - Sensitivity analysis: 80 mg												
3	randomised trials		no serious inconsistency		very serious ²	none	60/279 (21.5%)	68/281 (24.2%)	RR 0.88 (0.66 to 1.17)	· -	⊕OOO VERY LOW	

¹ Selective outpatients from multiple sites
² Single study; inconclusive effect size
³ Significant heterogeneity (> 50%) random effects model used

3	randomised trials		no serious inconsistency	serious ¹	very serious ²	none	44/266 (16.5%)	55/262 (21%)	RR 0.79 (0.56 to 1.12)	4 fewer per 100 (from 9 fewer to 3 more)	⊕OOO VERY LOW	
eavin	g treatment e	early - any re	eason (data by	doses abov	e licensed dos	se 60mg) - 40 m	g - 120 mg				1	
1	randomised trials		no serious inconsistency	serious ¹	very serious ³	none	25/82 (30.5%)	31/75 (41.3%)	RR 0.74 (0.48 to 1.13)		⊕OOO VERY LOW	
eaving	g treatment e	early - any re	eason (overall)		1						<u> </u>	
11	randomised trials		no serious inconsistency	serious ¹	serious ⁴	none	447/1661 (26.9%)	350/1234 (28.4%)	RR 1.02 (0.91 to 1.15)	'	⊕⊕OO LOW	
Leaving	g treatment e	early - adver	se reactions (d	lata by dose	s above licens	sed dose 60 mg	- 60 mg					
6	randomised trials	no serious limitations	serious ⁵	serious ¹	no serious imprecision	none	110/1034 (10.6%)	38/808 (4.7%)	RR 2.29 (1.31 to 4)	6 more per 100 (from 1 more to 14 more)	⊕⊕OO LOW	

4	randomised	no serious		ata by doses	above licens no serious imprecision	none	35/363	16/371 (4.3%)	RR 2.11 (1.18 to 3.76)	5 more per 100 (from 1 more to 12 more)	⊕⊕⊕O MODERATE	
Leaving	treatment e	arly - adver	se reactions (d	ata by doses	above licens	sed dose 60 mg)	- 120 mg					
3	randomised trials		no serious inconsistency	serious ¹	serious ⁶	none	14/266 (5.3%)	8/262 (3.1%)	-	2 more per 100 (from 1 fewer to 9 more)	⊕⊕OO LOW	
Leaving	treatment e	arly - adver	se reactions (o	verall)								
11	randomised trials		no serious inconsistency	serious ¹	no serious imprecision	none	159/1663 (9.6%)	57/1249 (4.6%)	RR 2.22 (1.66 to 2.95)	6 more per 100 (from 3 more to 9 more)	⊕⊕⊕O MODERATE	
Leaving	treatment e	arly - lack o	f efficacy (data	by doses ab	ove licensed	dose 60 mg) - 6	0 mg (sensi	tivity analysis)				
4	randomised trials		no serious inconsistency	serious ¹	no serious imprecision	none	38/911 (4.2%)	60/686 (8.7%)		6 fewer per 100 (from 4 fewer to 7 fewer)	⊕⊕⊕O MODERATE	

	randomised	no serious	no serious	serious ¹	very	none				3 fewer		
			inconsistency	Serious	serious ²	lione			RR 0.55	per 100		
	citais		in consistency		Serious		6/188	11/192 (5.7%)		(from 5	⊕ООО	
							(3.2%)	11, 131 (31, 75)		fewer to 3	VERY LOW	
									,	more)		
eavin	g treatment e	early - lack o	of efficacy (data	by doses a	bove licensed	dose 60 mg) -	120 mg					
	randomised	no serious	no serious	serious ¹	very	none				4 fewer		
	trials	limitations	inconsistency		serious ²				RR 0.36	per 100	Φ000	
							4/196 (2%)	11/192 (5.7%)	(0.12 to	(from 5	⊕OOO VERY LOW	
									1.1)	fewer to 1	VERT LOW	
										more)		
avin	g treatment e	early - lack o	of efficacy (over	all): sensiti	vity analysis							
	randomised	no serious	no serious	serious ¹	no serious	none				5 fewer		
	trials	limitations	inconsistency		imprecision		48/1295		RR 0.34	per 100	⊕⊕⊕О	
							(3.7%)	71/878 (8.1%)	(0.22 to	(from 4	MODERATE	
							(3.770)		0.54)	fewer to 6	IVIODEIVATE	
										fewer)		
umb	er reporting s	ide effects (data by doses	above licens	sed dose 60 m	g) - 60 mg		l			I	
	randomised	no serious	serious ⁵	serious ¹	no serious	none				10 more		
	trials	limitations			imprecision		705/893	455/667	RR 1.14	per 100		
							(78.9%)	(68.2%)	(1.06 to	(from 4	⊕⊕OO LOW	
							(78.9%)	(68.2%)	1.23)	more to	LOW	
	1									16 more)		

3	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision	none	143/266 (53.8%)	122/262 (46.6%)	RR 1.12 (0.97 to 1.28)	6 more per 100 (from 1 fewer to 13 more)	⊕⊕⊕O MODERATE	
Numbe	er reporting s	ide effects (data by doses	above license	ed dose 60 m	ng) - 40 mg - 120	mg					
1	randomised trials		no serious inconsistency	serious ¹	serious ⁷	none	73/82 (89%)	55/75 (73.3%)	RR 1.21 (1.04 to 1.42)	15 more per 100 (from 3 more to 31 more)	⊕⊕OO LOW	
Numbe	er reporting s	ide effects (data by doses	above license	ed dose 60 m	g) - 80 mg	·				·	
4	randomised trials		no serious inconsistency	serious ¹	no serious imprecision	none	239/363 (65.8%)	188/371 (50.7%)	RR 1.27 (1.15 to 1.41)	14 more per 100 (from 8 more to 21 more)	⊕⊕⊕O MODERATE	
Numbe	er reporting s	ide effects (overall)	·		<u> </u>	Į.	<u> </u>	l		'	
10	randomised trials		no serious inconsistency	serious ¹	no serious imprecision	none	1098/1534 (71.6%)	698/1113 (62.7%)	RR 1.18 (1.12 to 1.24)	11 more per 100 (from 8 more to 15 more)	⊕⊕⊕O MODERATE	
Mean v	weight chang	e (kg) at end	dpoint (by dose	es above licer	nsed dose 60	mg) - 60 mg (m	easured wit	th: kg; Better ir	ndicated l	by lower va	alues)	
3	randomised	no serious	serious ⁵	serious ¹	no serious	none	479	364	-	MD 0.49 lower	⊕⊕ОО	

	trials	limitations			imprecision					(1.04 lower to 0.05 higher)	LOW	
/lean v	weight chang	e (kg) at end	lpoint (by dose	es above lice	nsed dose 60	mg) - 80 mg (m	easured wit	:h: kg; Better ir	ndicated I	oy lower va	lues)	
•	randomised trials	no serious limitations	serious ⁵	serious ¹	no serious imprecision	none	265	271	-	MD 0.70 lower (1.28 to 0.12 lower)	⊕⊕OO LOW	
/lean v	weight chang	e (kg) at end	lpoint (by dose	es above lice	nsed dose 60	mg) - 120 mg (ı	neasured w	ith: kg; Better	indicated	by lower v	alues)	
	randomised trials	no serious limitations	serious ⁵	serious ¹	serious ²	none	158	159	-	MD 0.61 lower (1.72 lower to 0.49 higher)	⊕OOO VERY LOW	
lean v	veight chang	e (kg) at end	point (by dose	es above lice	nsed dose 60	mg) - 40 mg - 1	20 mg (mea	sured with: kg	; Better in	ndicated by	lower value	es)
	randomised trials		no serious inconsistency	serious ¹	serious ⁵	none	81	72	-	MD 1.09 lower (1.71 to 0.47 lower)	⊕⊕OO LOW	
lean v	weight chang	e (kg) at end	lpoint (overall)) (measured	with: kg ; Bet	tter indicated by	lower value	es)				
	randomised	no serious	serious ⁵	serious ¹	no serious	none	890	773	-	MD 0.69 lower (1	⊕⊕ОО	

trials	limitations		imprecision			to 0.38	LOW	
						lower)		

¹ Selected outpatients from multiple sites

² Inconclusive effect size

Inconsistent effect size; single study
 Wide range of control group risks in individual studies (13% to 42%)
 Significant heterogeneity; random effects model used

⁶ Inconclusive effect size

⁷ Single study

Is one dose of duloxetine more effective than others for depression? (Acute phase efficacy data)

			Quality asses	ssment				Sum	mary of fi	ndings		
							No. of pa	tients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine at different doses	Control	Relative (95% CI)	Absolute	Quality	
Mean cl	hange scores	at endpoint	- 30 mg vs 60 r	mg (measure	d with: HAMI); Better indicat	ed by lower v	values)				
1	randomised trials		no serious inconsistency	serious ¹	very serious ²	none	202	198	-	MD 0.83 higher (0.43 lower to 2.09 higher)	⊕OOO VERY LOW	
Mean cl	hange scores	at endpoint	- 40 mg vs 80 r	mg (measure	d with: HAMI); Better indicat	ed by lower v	values)	,	!	!	
2	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ²	none	174	167	-	MD 0.58 higher (0.87 lower to 2.03 higher)	⊕OOO VERY LOW	
Mean cl	hange scores	at endpoint	- 80 mg vs 120	mg (measur	ed with: HAM	ID; Better indica	ited by lower	values)				
2	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ³	none	186	195	-	MD 0.7 higher (0.28 lower to 1.68 higher)	⊕OOO VERY LOW	

Non-re	sponse - 30 m	ng vs 60 mg										
1	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision ⁴	none	136/219 (62.1%)	278/428 (65%)	RR 0.96 (0.84 to 1.08)	3 fewer per 100 (from 10 fewer to 5 more)	⊕⊕⊕O	
Non-re	sponse - 40 m	ng vs 80 mg										
2	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ³	none	110/177 (62.1%)	103/175 (58.9%)	RR 1.05 (0.89 to 1.24)	3 more per 100 (from 6 fewer to 14 more)	⊕⊕OO LOW	
Non-re	sponse - 80 m	ng vs 120 mg	5									
2	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ³	none	66/188 (35.1%)	61/196 (31.1%)	RR 1.13 (0.85 to 1.5)	4 more per 100 (from 5 fewer to 16 more)		
Non-re	mission - 40 r	ng vs 80 mg		1	1							
2	randomised trials	no serious limitations	serious ⁵	serious ¹	serious ³	none	128/177 (72.3%)	109/175 (62.3%)	RR 1.15 (0.92 to 1.44)	9 more per 100 (from 5 fewer to 27 more)		
Non-re	mission - 30 r	ng vs 60 mg	_			'						
1	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision ⁴	none	125/219 (57.1%)	252/428 (58.9%)	RR 0.97 (0.84 to 1.11)	2 fewer per 100 (from 9 fewer to 6		

										more)	
Non-rer	nission - 80 n	ng vs 120 mg	5								
	randomised trials		no serious inconsistency	serious ¹	serious ⁴	none	104/188 (55.3%)	107/196 (54.6%)	RR 1.01 (0.83 to 1.23)	1 more per 100 (from 9 fewer to 13 more)	

¹ Selective outpatients from multiple sites
² Inconclusive effect size; single study
³ Inconclusive effect size

Unlikely to be a difference
 Significant heterogeneity; random effects model used

Is one dose of duloxetine more effective than others for depression? (Acute phase acceptability and tolerability data)

			Quality asses	ssment				Summ	ary of fin	dings		
							No. of pati	ents	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine at different doses - acceptability and tolerability	Control	Relative (95% CI)	Absolute	Quality	Importance
Leaving	treatment e	arly - any re	ason - 30 mg v	s 60 mg								
	randomised trials		no serious inconsistency	serious ¹	very serious ²	none	54/219 (24.7%)	129/428 (30.1%)	RR 0.82 (0.62 to 1.07)	5 fewer per 100 (from 11 fewer to 2 more)	⊕OOO VERY LOW	
Leaving	treatment e	arly - any re	ason - 40 mg v	s 80 mg								
	randomised trials		no serious inconsistency	serious ¹	very serious ²	none	31/86 (36%)	41.8%	RR 0.86 (0.6 to 1.25)	59 fewer per 1000 (from 167 fewer to 104 more)	⊕OOO VERY LOW	
Leaving	treatment e	arly - any re	ason - 80 mg v	s 120 mg		l						
	randomised trials		no serious inconsistency	serious ¹	serious ³	none	22/188 (11.7%)	20/196 (10.2%)	RR 1.15 (0.65 to 2.03)	2 more per 100 (from 4 fewer to	⊕⊕OO LOW	

	<u> </u>		1	1	1	1	1					
										11 more)		
Leaving	treatment e	arly - due to	adverse react	ion - 30 mg v	s 60 mg							
1	randomised	no serious	no serious	serious ¹	serious ⁴	none				5 fewer		
	trials	limitations	inconsistency					42/428	RR 0.47	per 100	⊕⊕OO	
							10/219 (4.6%)	(9.8%)	(0.24 to	(from 1	LOW	
								(3.070)	0.91)	fewer to 7	LOW	
										fewer)		
Leaving	treatment e	arly - due to	adverse react	 ion - 40 mg v	<u> </u> rs 80 mg							
_	·	_	1 .	I . 1	. 3	1	I					
	randomised			serious ¹	very serious ³	none				4 fewer		
	trials	limitations	inconsistency				,	27/175	RR 0.77	per 100	\oplus OOO	
							21/177 (11.9%)	(15.4%)	(0.45 to	-	VERY LOW	
									1.31)	fewer to 5		
										more)		
Leaving	treatment e	arly - due to	adverse react	ion - 80 mg v	rs 120 mg							
2	randomised	no serious	no serious	serious ¹	very serious ³	none			DD 4.2	1 more per		
	trials	limitations	inconsistency				0 (4 00 (4 20))	7/196	RR 1.2	100 (from	\oplus OOO	
							8/188 (4.3%)	(3.6%)	(0.44 to	2 fewer to	VERY LOW	
									3.24)	8 more)		
Leaving	treatment e	arly - lack of	 f efficacy - 30 n	ng vs 60 mg								
4				. 1	. 2	<u> </u>				0.6		
	randomised			serious ¹	very serious ²	none			DD 0 00	0 fewer		
	trials	limitations	inconsistency				2/240/4 40/	6/428	RR 0.98	per 100	\oplus OOO	
							3/219 (1.4%)	(1.4%)	(0.25 to	(from 1	VERY LOW	
									3.87)	fewer to 4		
										more)		
										1110101		

	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ¹	none	6/188 (3.2%)	2.1%	RR 1.56 (0.45 to 5.44)	12 more per 1000 (from 12 fewer to 93 more)	⊕OOO VERY LOW
lo rep	orting side ef	fects - 30 m	g vs 60 mg								
1	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ⁴	none	160/219 (73.1%)	315/428 (73.6%)	RR 0.99 (0.9 to 1.1)	1 fewer per 100 (from 7 fewer to 7 more)	⊕⊕OO LOW
lo rep	orting side ef	fects - 40 m	g vs 80 mg								
2	randomised trials	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision ⁵	none	151/177 (85.3%)	151/175 (86.3%)	RR 0.99 (0.91 to 1.07)	9 fewer per 1000 (from 78 fewer to 60 more)	⊕⊕⊕O MODERATE
No rep	orting side ef	fects - 80 m	g vs 120 mg								
2	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ³	none	88/188 (46.8%)	81/196 (41.3%)	RR 1.12 (0.9 to 1.4)	5 more per 100 (from 4 fewer to 17 more)	⊕⊕OO

	randomised	no serious	no serious	serious ¹	serious ⁴	none				MD 0.35	
	trials	limitations	inconsistency				168	155		lower (1	$\oplus \oplus OO$
							108	133	_	lower to	LOW
										0.3 higher)	
lean	weight chang	e (kg) at end	dpoint - 40 mg	vs 80 mg (n	neasured wit	h: kg; Better in	dicated by lower	values)			
	randomised	no serious	no serious	serious ¹	serious ³	none				MD 0.19	
	trials	limitations	inconsistency							lower	
							158	167	_	(0.69	⊕⊕OO
							156	107		lower to	LOW
										0.31	
										higher)	
1ean	weight chang	e (kg) at end	dpoint - 80 mg	vs 120 mg (measured wi	ith: kg; Better i	ndicated by lowe	r values)			
	randomised	no serious	no serious	serious ¹	serious ³	none				MD 0.08	
	trials	limitations	inconsistency							lower	
							93	93		(0.69	$\oplus \oplus OO$
							95	93	_	lower to	LOW
						1	1	I	1		
										0.53	

¹ Selected outpatients from multiple sites
² Inconclusive effect size; single study
³ Inconclusive effect size

Single studyUnlikely to be a difference

Is duloxetine more effective than other antidepressants for depression? (Acute phase efficacy data)

			Quality asse	ssment				Summar	y of findir	ngs		
			•				No. o	of patients	Eff	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Other antidepressants	Relative (95% CI)	Absolute	Quality	
Mean c	hange score	s at endpoir	it (all data) (m	easured with	n: HAMD; Bet	ter indicated by	lower valu	ies)				
		limitations			no serious imprecision ³		1601	1544	-	MD 0.19 higher (0.44 lower to 0.81 higher)	⊕⊕OO LOW	
Mean c	hange score	s at endpoir	it - paroxetine	(measured v	with: HAMD;	Better indicated	d by lower v	values)				
	randomised trials	no serious limitations	serious ¹		no serious imprecision	none	591	593	-	MD 0.2 lower (1.14 lower to 0.74 higher)	⊕⊕OO LOW	
Mean c	hange score	s at endpoir	t - fluoxetine	(measured w	vith: HAMD; I	Better indicated	by lower v	alues)				
	randomised trials		no serious inconsistency		very serious ⁴	none	147	70	-	MD 1.1 lower (3.03 lower to	⊕OOO VERY LOW	

										0.83		
										higher)		
Mean	change score	s at endpoir	l nt - escitalopra	m (measure	d with: HAMI); Better indica	ted by lowe	r values)				
3	randomised trials	no serious limitations	serious ¹	serious ²	no serious imprecision	none	545	551	-	MD 0.66 higher (0.61 lower to 1.93 higher)	⊕⊕OO LOW	
Mean	change score	s at endpoir	nt - venlafaxine	e (measured	with: HAMD	Better indicate	ed by lower	values)				
2	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	318	330	-	MD 1.06 higher (0.02 lower to 2.14 higher)	⊕⊕⊕O MODERATE	
Non-re	esponse (all d	ata)	<u> </u>			<u> </u>						
12	randomised trials	no serious limitations	serious ¹	serious ²	no serious imprecision	none	805/1645 (48.9%)	718/1563 (45.9%)	RR 1.05 (0.95 to 1.17)	2 more per 100 (from 2 fewer to 8 more)	⊕⊕OO LOW	
Non-re	esponse - par	oxetine										

5	randomised trials	no serious limitations	serious ¹	serious ¹	no serious imprecision	none	263/601 (43.8%)	257/599 (42.9%)	RR 1.01 (0.81 to 1.26)	0 more per 100 (from 8 fewer to 11 more)	⊕⊕OO LOW	
Non-re	sponse - fluo	extine										
2	randomised trials		no serious inconsistency	serious ²	serious ⁴	none	80/152 (52.6%)	37/70 (52.9%)	RR 0.99 (0.72 to 1.36)	1 fewer per 100 (from 15 fewer to 19 more)	⊕⊕OO LOW	
Non-re	sponse - esci	italopram			•							
3	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	331/562 (58.9%)	315/557 (56.6%)	RR 1.04 (0.94 to 1.16)	2 more per 100 (from 3 fewer to 9 more)	⊕⊕⊕O MODERATE	
Non-re	sponse - ven	lafaxine										
2	randomised trials	no serious limitations	serious ¹	serious ²	serious ⁴	none	131/330 (39.7%)	109/337 (32.3%)	RR 1.23 (0.92 to 1.64)	7 more per 100 (from 3 fewer to 21 more)	⊕OOO VERY LOW	
Non-re	mission (all o	data)	<u> </u>									
12	randomised	no serious	serious ¹	serious ²	no serious	none	948/1645	879/1563	RR 1.02 (0.94 to	1 more per 100	⊕⊕ОО	

	trials			2	imprecision		(57.6%)	(56.2%)	1.11)	(from 3 fewer to 6 more)	LOW	
5	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	334/601 (55.6%)	337/599 (56.3%)	RR 0.99 (0.9 to 1.1)	1 fewer per 100 (from 6 fewer to 6 more)	⊕⊕⊕O MODERATE	
Non-re	mission - flu	oxetine										
2	randomised trials	no serious limitations	very serious ¹	serious ²	very serious⁴	none	92/152 (60.5%)	51.8%	RR 1.21 (0.56 to 2.61)	109 more per 1000 (from 228 fewer to 834 more)	⊕OOO	
Non-re	mission - esc	citalopram										
3	randomised trials	no serious limitations	serious ¹	serious ²	no serious imprecision	none	345/562 (61.4%)	334/557 (60%)	RR 1.06 (0.89 to 1.26)	4 more per 100 (from 7 fewer to 16 more)	⊕⊕OO LOW	
Non-re	mission - ve	nlafaxine		<u>I</u>								
2	randomised trials	no serious limitations	serious ¹	serious ²	no serious imprecision	none	177/330 (53.6%)	171/337 (50.7%)	RR 1.06 (0.88 to	3 more per 100 (from 6	⊕⊕OO LOW	

				1.27)	fewer to	
					14 more)	

¹ Significant heterogeneity; random effects model used
² Selected outpatients from multiple sites
³ Unlikely to be a difference
⁴ Inconclusive effect size

Is duloxetine more effective than other antidepressants for depression? (Acute phase acceptability and tolerability data)

			Quality asses	ssment				Summary	of findir	ngs		
							No.	of patients	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Other antidepressants - acceptability and tolerability		Absolute	Quality	Importance
Leaving	treatment e	early - any ro	eason									
	randomised trials	no serious limitations	serious ¹		no serious imprecision	none	472/1494 (31.6%)	344/1420 (24.2%)	RR 1.27 (1.1 to 1.47)	7 more per 100 (from 2 more to 11 more)	⊕⊕OO LOW	
Leaving	treatment e	early - any ro	eason - paroxe	tine								
	randomised trials		no serious inconsistency		no serious imprecision	none	176/601 (29.3%)	145/599 (24.2%)	RR 1.21 (1.01 to 1.45)	5 more per 100 (from 0 more to	⊕⊕⊕O MODERATE	

										11 more)		
Leaving	treatment o	early - any r	 eason - fluoxet	ine								
	randomised trials		no serious inconsistency	serious ²	very serious ³	none	49/152 (32.2%)	26/70 (37.1%)	RR 0.87 (0.59 to 1.27)	•	VERY LOW	
Leaving	treatment e	early - any r	eason - escital	opram								
	randomised trials	no serious limitations	serious ¹	serious ²	no serious imprecision	none	131/411 (31.9%)	87/414 (21%)	RR 1.64 (0.97 to 2.78)	•	⊕⊕OO LOW	
Leaving	treatment e	early - any r	eason - venlafa	ixine								
	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	116/330 (35.2%)	86/337 (25.5%)	RR 1.37 (1.09 to 1.72)	9 more per 100 (from 2 more to 18 more)	⊕⊕⊕O MODERATE	
Leaving	treatment o	early - advei	rse reactions									
10	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	147/1412 (10.4%)	91/1383 (6.6%)	RR 1.54 (1.2 to 1.99)	(from 1	⊕⊕⊕O MODERATE	

	randomised	no corious	no serious	serious ²	serious ³	none				2 more	
			inconsistency	serious	serious	lione	55/601 (9.2%)	42/599 (7%)	RR 1.32 (0.9 to 1.93)	per 100 (from 1 fewer to 7 more)	⊕⊕OO LOW
eavin	g treatment o	early - adve	rse reactions -	fluoxetine	•						
	randomised trials		no serious inconsistency	serious ²	very serious ⁴	none	7/70 (10%)	1/33 (3%)	RR 3.3 (0.42 to 25.74)	7 more per 100 (from 2 fewer to 75 more)	⊕OOO VERY LOW
eavin	g treatment o	early - adve	rse reactions -	escitalopra	m						
	randomised trials	no serious limitations	serious ¹	serious ²	serious ³	none	37/411 (9%)	17/414 (4.1%)	RR 2.62 (0.67 to 10.3)	7 more per 100 (from 1 fewer to 38 more)	⊕OOO VERY LOW
eavin	g treatment o	early - adve	rse reactions -	venlafaxine	!		,				1
!	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	48/330 (14.5%)	31/337 (9.2%)	RR 1.58 (1.04 to 2.42)	5 more per 100 (from 0 more to 13 more)	⊕⊕⊕O MODERATE

7	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	40/1167 (3.4%)	37/1174 (3.2%)	RR 1.09 (0.7 to 1.68)	0 more per 100 (from 1 fewer to 2 more)	⊕⊕⊕O MODERATE	
Leaving	g treatment e	early - lack o	of efficacy - par	roxetine	,							
3	randomised trials		no serious inconsistency	serious ²	very serious ³	none	7/426 (1.6%)	3/423 (0.7%)	RR 2.29 (0.6 to 8.78)	1 more per 100 (from 0 fewer to 6 more)	⊕OOO VERY LOW	
Leaving	g treatment e	early - lack o	of efficacy - flu	oxetine - no	data							
0	no evidence available					none	0/0 (0%)	0%	not pooled	not pooled		
Leavin	g treatment e	early - lack o	of efficacy - esc	citalopram								
2	randomised trials		no serious inconsistency	serious ²	very serious ³	none	22/411 (5.4%)	25/414 (6%)	RR 0.88 (0.51 to 1.53)	1 fewer per 100 (from 3 fewer to 3 more)	⊕OOO VERY LOW	
Leaving	g treatment e	early - lack o	of efficacy - vei	nlafaxine								
2	randomised	no serious	no serious	serious ²	very	none	11/330	9/337 (2.7%)	RR 1.24 (0.52 to	1 more per 100	⊕000	

No. rep	orting side e	ffects no serious	no serious inconsistency	serious ²	no serious imprecision	none	(3.3%) 1010/1274 (79.3%)	949/1243 (76.3%)	2.95) RR 1.02 (0.98 to 1.07)	fewer to 5 more) 2 more per 100 (from 2	⊕⊕⊕O MODERATE	
No. rep	orting side e	ffects - parc	oxetine							, i		
	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	424/601 (70.5%)	389/599 (64.9%)	RR 1.07 (0.99 to 1.15)	5 more per 100 (from 1 fewer to 10 more)	⊕⊕⊕O MODERATE	
No. rep	orting side e	ffects - fluo	xetine									
	randomised trials		no serious inconsistency	serious ²	serious ⁵	none	62/70 (88.6%)	30/33 (90.9%)	RR 0.97 (0.85 to 1.12)	3 fewer per 100 (from 14 fewer to 11 more)	⊕⊕OO LOW	
No. rep	orting side e	ffects - esci	talopram									
	randomised trials		no serious inconsistency	serious ²	serious ⁵	none	241/273 (88.3%)	237/274 (86.5%)	RR 1.02 (0.96 to 1.09)	2 more per 100 (from 3 fewer to	⊕⊕OO LOW	

										8 more)		
No. rep	orting side e	ffects - ven	lafaxine									
		limitations		serious ²	imprecision	none	283/330 (85.8%)	293/337 (86.9%)	RR 0.99 (0.88 to 1.11)	1 fewer per 100 (from 10 fewer to 10 more)	⊕⊕OO LOW	
Mean w	veight chang	e (kg) at en	dpoint (sensiti	vity analysis) (measured	with: kg; Better	indicated b	y lower values)				
	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	1042	1016	-	MD 0 higher (0.03 lower to 0.03 higher)	⊕⊕⊕O MODERATE	
Mean w	veight chang	e (kg) at en	dpoint - parox	etine (meası	red with: kg	; Better indicate	ed by lower	values)		l .	1	
	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	422	412	-	MD 0 higher (0.03 lower to 0.03 higher)	⊕⊕⊕O MODERATE	
Mean w	veight chang	e (kg) at en	dpoint - fluoxe	tine (measu	red with: kg;	Better indicate	d by lower	values)				
	randomised trials		no serious inconsistency	serious ²	serious ⁵	none	65	33	-	MD 0.01 lower (0.74 lower to	⊕⊕OO LOW	

lean w	veight chang	e (kg) at end	dpoint - escita	lopram (mea	asured with:	kg; Better indica	ated by low	er values)	0.72 higher)	
	randomised trials		no serious inconsistency		serious ⁵	none	273	274	MD 0.06 higher (1.08 lower to 1.2 higher)	⊕⊕OO LOW
ean w	eight chang	e (kg) at en	dpoint - venlaf	axine (meas	ured with: kខ្	g; Better indicat	ed by lower	r values)	,	
	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	282	297	MD 0.39 higher (0.09 lower to 0.86 higher)	⊕⊕⊕O MODERATE

¹ Significant heterogeneity; random effects model used
² Selected outpatients from multiple sites
³ Inconsistent effect size

⁴ Inconsistent effect size; single study

⁵ Single study

Is duloxetine effective as a continuation treatment following a 30% improvement in baseline (HAMD-17) symptoms of depression?

			Quality asses	ssment				Summa	ry of find	ings		
			ζ,				No. of patie	nts	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation phase for those with 30% improvement in baseline HAMD- 17 scores: duloxetine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mean c	hange scores	from end o	f acute phase	- 80 mg (mea	sured with:	HAMD; Better in	ndicated by lower	values)				
	randomised trials		no serious inconsistency	serious ¹	serious ¹	none	70	70	-	MD 1 lower (2.5 lower to 0.5 higher)	⊕⊕OO LOW	
Mean c	hange scores	s from end o	f acute phase	- 120 mg (me	asured with:	: HAMD; Better	indicated by lowe	er values)				
	randomised trials		no serious inconsistency	serious ²	serious ¹	none	80	70	-	MD 0.2 lower (1.78 lower to 1.38 higher)	⊕⊕OO LOW	

	randomised	no serious	no serious	serious ²	serious ¹	none				5 fewer	
_			inconsistency	serious	serious	none	58/71 (81.7%)	62/71 (87.3%)	RR 0.94 (0.81 to 1.08)	per 100	⊕⊕OO LOW
eaving	g treatment e	early - for an	y reason - 120	mg							
1	randomised trials		no serious inconsistency	serious ²	serious ¹	none	62/81 (76.5%)	62/71 (87.3%)	RR 0.88 (0.75 to 1.02)	· ·	⊕⊕OO LOW
.eavin	g treatment e	early - adver	se reactions - 8	0 mg							
2	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	7/146 (4.8%)	6/129 (4.7%)	RR 0.96 (0.34 to 2.73)	(from 3	⊕⊕⊕O MODERATE
Leaving	g treatment e	early - adver	se reactions - 1	.20 mg							
2	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	6/151 (4%)	6/129 (4.7%)	RR 0.84 (0.28 to 2.54)	(from 3	⊕⊕⊕O MODERATE

Leaving	treatment e	arly - lack o	f efficacy - 80 r	ng										
		limitations	inconsistency		serious ¹	none	1/71 (1.4%)	1/71 (1.4%)	RR 1 (0.06 to 15.68)	0 fewer per 100 (from 1 fewer to 21 more)	⊕⊕OO LOW			
Leaving treatment early - lack of efficacy - 120 mg														
	randomised trials		no serious inconsistency	serious ²	serious ¹	none	4/81 (4.9%)	1/71 (1.4%)	RR 3.51 (0.4 to 30.65)	4 more per 100 (from 1 fewer to 42 more)	⊕⊕OO LOW			

¹ Single study
² Selective patients from multiple sites

Is one dose of duloxetine more effective than another as a continuation treatment following a 30% improvement in baseline (HAMD-17) symptoms of depression?

			Quality asses	sment			Sı	ummary	of finding	S		
			Quality usses	Silicit			No. of patien	ts	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Continuation phase for those with 30% improvement in baseline HAMD-17 scores: duloxetine at different doses		Relative (95% CI)	Absolute	Quality	Importance
Mean c	hange scores	from end of	facute phase -	80 mg vs 120	0 mg (measu	red with: HAMI); Better indicated b	y lower \	ralues)		ļ	
1	randomised trials		no serious inconsistency	serious ¹	serious ²	none	70	80	-	MD 0.8 lower (2.18 lower to 0.58 higher)	⊕⊕OO LOW	
Leaving	treatment e	arly - for any	reason - 80 m	ng vs 120 mg								
1	randomised trials		no serious inconsistency	serious ¹	serious ²	none	58/71 (81.7%)	62/81 (76.5%)	RR 1.07 (0.91 to 1.26)	5 more per 100 (from 7 fewer to 20 more)	⊕⊕ОО	
Leaving	treatment e	arly - advers	e reactions - 8	0 mg vs 120 i	mg			1			l	
1	randomised	no serious	no serious	serious ¹	very	none	2/71 (2.8%)	3/81	RR 0.76	1 fewer	⊕OOO	

trials	limitations	inconsistency		serious ³			(3.7%)	(0.13 to 4.42)	per 100 (from 3 fewer to 13 more)	VERY LOW	
Leaving treatment eads 1 randomised trials	no serious	, T	serious ¹	very serious ³	none	1/71 (1.4%)	4/81 (4.9%)	RR 0.29 (0.03 to 2.49)	-	⊕OOO VERY LOW	

¹ Selected patients from multiple sites
² Single study
³ Single study + inconsistent effect size

Is duloxetine more effective than other antidepressants as a continuation treatment following a 30% improvement in baseline (HAMD-17) symptoms of depression?

			Quality asses	sment			S	ummary	of finding	gs		
							No of patien	ts	Ef	ffect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation phase for those with 30% improvement in baseline HAMD-17 scores: duloxetine	drugs	Relative (95% CI)	Absolute	Quality	Importance
Mean c	hange scores	from end of	f acute phase -	80 mg vs par	roxetine (me	asured with: HA	AMD; Better indicate	ed by lov	ver values	;)		
	randomised trials		no serious inconsistency	serious ¹	serious ²	none	70	70	-	MD 0.3 higher (1.06 lower to 1.66 higher)	⊕⊕OO LOW	
Leaving	treatment e	arly - for any	reason - paro	xetine								
	randomised trials		no serious inconsistency	serious ²	serious ¹	none	58/71 (81.7%)	61/70 (87.1%)	RR 0.94	5 fewer per 100 (from 17 fewer to 7 more)	⊕⊕00	
Leaving	treatment e	arly - advers	e reactions - pa	aroxetine								
	randomised trials		no serious inconsistency	serious ²	very serious ³	none	7/146 (4.8%)	2/140 (1.4%)	RR 2.84 (0.7 to	3 more per 100 (from	⊕OOO VERY	

									11.6)	0 fewer to 15 more)	LOW	
Leaving	treatment e	arly - lack of	efficacy - paro	xetine								
	randomised trials		no serious inconsistency		very serious ⁴	none	1/71 (1.4%)	2/70 (2.9%)	RR 0.49 (0.05 to 5.31)	100 (trom	⊕OOO VERY	

Is duloxetine more effective than other antidepressants following response to acute phase treatment?

			Quality assess	sment				Summa	ry of findii	ngs		
							No of patie	nts	E	ffect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation phase no entry criteria: duloxetine	Other drugs	Relative (95% CI)	Absolute	Quality	Importance
Mean so	cores at endp	oint - escital	opram (measu	red with: HA	MD; Better i	ndicated by low	er values)					
	randomised trials		no serious inconsistency	serious ¹	serious ²	none	146	141	-	MD 1.34 higher (0.25 lower to 2.93 higher)	LOW	

¹ Single study
² Selective outpatients from multiple sites
³ Inconsistent effect size
⁴ Single study + inconsistent effect size

Non-re	esponse - escit	alopram										
L	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ³	none	49/151 (32.5%)	40/143 (28%)	RR 1.16 (0.82 to 1.65)	4 more per 100 (from 5 fewer to 18 more)	⊕OOO VERY LOW	
lon-re	emission - esci	talopram										
L	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ²	none	39/151 (25.8%)	28/143 (19.6%)	RR 1.32 (0.86 to 2.02)	6 more per 100 (from 3 fewer to 20 more)	⊕⊕OO LOW	
eavin	g treatment e	arly - any rea	ason - escitalop	ram								
	randomised trials	no serious limitations	no serious inconsistency	serious ¹	very serious ³	none	37/151 (24.5%)	31/143 (21.7%)	RR 1.13 (0.74 to 1.72)	3 more per 100 (from 6 fewer to 16 more)	⊕OOO VERY LOW	
eavin	g treatment e	arly - advers	e reactions - es	citalopram								
	randomised trials	no serious limitations	no serious inconsistency	serious ¹	serious ²	none	26/151 (17.2%)	13/143 (9.1%)	RR 1.89 (1.01 to 3.54)	8 more per 100 (from 0 more to 23 more)	⊕⊕OO LOW	
eavin	g treatment e	arly - lack of	efficacy - escita	alopram								
	randomised	no serious	no serious	serious ¹	very	none	2/151 (1.3%)	7/143	RR 0.27 (0.06 to	4 fewer per 100 (from 5		

trials	limitations	inconsistency	serious ³		(4.9%)	1.28)	fewer to 1	LOW	
							more)		

¹ Selected patients from multiple sites

Light therapy

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

			Quality asses	ssment				S	ummary o	f findings		
			Z ,				No. of p	patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Waitlist	Relative (95% CI)	Absolute	Quality	
Leaving	study early f	or any reaso	n (overall) (tota	l number not	completing st	udy)						
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	0 fewer per 100 (from 6 fewer to 25 more)	⊕⊕OO LOW	
								8.7%	4.32)	0 fewer per 100 (from 7 fewer to 29 more)		
Leaving	study early d	lue to side ef	fects - Light box	vs waitlist co	ontrol							
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	⊕⊕⊕О	

² Single study ³ Single study + inconsistent effect size

								0%		not pooled	MODERATE
eaving	study early -	Light room v	s waitlist contr	ol							
	randomised trials	limitations	no serious inconsistency	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
laan a								0%		0 fewer per 100 (from 0 fewer to 0 more)	I lawar valva)
ean s	en rated SAD	depression	scores at enopo	int - Light roo		control (measure	a with: 3	olun-sal	-sk; belle	r indicated by	riower values)
	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
ean c	linician rated	SAD depress	sion scores at e	ndpoint - Ligh	t box vs waitli	st control (meas	ured witl	h: SIGH-S	SAD; Bette	r indicated by	lower values)
	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
lean c	linician rated	typical depr	ession scores at	: endpoint - Li	ght box vs wa	itlist control (me	easured w	vith: HRS	5D-21; Bett	er indicated k	oy lower 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	⊕⊕⊕⊕ HIGH

										lower)	
lean se	elf-rated dep	ression score	- overall (Bette	er indicated by	y lower values	s)					
	randomised	no serious	no serious	no serious	no serious	none				MD 1.15	
	trials	limitations	inconsistency	indirectness	imprecision		40	39	_	to 0.67	⊕⊕⊕ HIGH
lean se	elf rated depr	ression score	s at endpoint -	Light room vs	waitlist contr	ol (measured w	ith: HRSD)-21-SR; B	Better indi	lower)	r values)
			•			•	T	·		-	ŕ
	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 se	elf rated depr	ression score	s at endpoint -	Light box vs w	aitlist contro	l (measured wit	h: BDI; Be	tter indi	cated by lo	wer 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 cl	linician rated	atypical dep	ression scores	at endpoint - L	ight box vs w	raitlist control (r	neasured	with: SA	D subscale	; Better indica	ated by lower va
	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
lean se		ical depressi	on scores at en	dpoint - Light	room vs wait	list control (mea	asured wi	th: SAD-S	iR subscale	e of SIGH-SAD); Better indicate
	randomised	no serious	no serious	no serious	serious ²	none	24	24	-	MD 5.2 lower (7.39	⊕⊕⊕О

	trials	limitations	inconsistency	indirectness						to 3.01 lower)	MODERATE
Non rei	mission (SIGH	-SAD-SR) (ov	erall)	'			·		·		,
2	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)	
								88%	0.74)	41 fewer per 100 (from 23 fewer to 55 fewer)	
Non rei	mission (SIGH	-SAD-SR) - Li	ght room vs wa	itlist control							
1	randomised trials		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)	
								96%		50 fewer per 100 (from 26 fewer to 66 fewer)	
Non rei	mission (SIGH	-SAD-SR) - Li	ght box vs wait	list control							
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)	more)	⊕⊕⊕O MODERATE
								80%		30 fewer per	

										100 (from 51 fewer to 6 more)		
Non res	ponse (SIGH-	SAD) - Light i	room vs waitlist	t control								
1	randomised trials			no serious indirectness	serious ²	none	13/26 (50%)	25/25 (100%)	RR 0.50 (0.34 to 0.73)		⊕⊕⊕O MODERATE	
								100%		50 fewer per 100 (from 27 fewer to 66 fewer)		

¹ Inconclusive effect size ² Single study

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

			Quality asse	ssment				Sun	nmary of f	indings		
							No. o	f patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	_	Attentional control	Relative (95% CI)	Absolute	Quality	
Leaving	study early f	or any reaso	on (overall)									
	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	18/134 (13.4%)	18/124 (14.5%)	RR 0.92 (0.51 to	1 fewer per 100 (from 7 fewer to 9 more)	⊕⊕OO LOW	
								13.1%	1.64)	1 fewer per 100 (from 6 fewer to 8 more)	LOW	
			on - Light box vs						1			
	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)		
Leaving	study early f	or any reaso	n - Low dose (<	5000lux hour	rs/day) LED li	ght vs negative i	ion gene	rator				

	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	1/15 (6.7%)	2/11 (18.2%)	RR 0.37 (0.04 to 3.55)	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)		
eaving	study early f	or any reaso	on - Light box vs	s high dose (>	300lux) dim re	ed light box						
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	6/33 (18.2%)	5/26 (19.2%)	RR 0.95 (0.32 to 2.76)	1 fewer per 100 (from 13 fewer to 34 more)	⊕⊕OO LOW	
								19.2%	2.76)	1 fewer per 100 (from 13 fewer to 34 more)		
eaving	study early f	or any reaso	n - Light box vs	low-density	ionisation						·	
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	2/23 (8.7%)	2/25 (8%)	RR 1.09 (0.17 to	1 more per 100 (from 7 fewer to 49 more)	⊕⊕OO LOW	
							(8.7%)	8%	7.1)	1 more per 100 (from 7 fewer to 49 more)		

1	randomised trials		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)	⊕⊕OO LOW	
								0%	78.30)	0 more per 100 (from 0 fewer to 0 more)		
Leaving	study early f	or any reaso	n - Low dose (<	5000lux hour	rs/day) light v	visor vs no light	visor					
1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	0/12 (0%)	0/10 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE	
Leaving	study early o	due to lack o	l f efficacy - Low	dose (<5000l	ux hours/day) LED light vs ne	egative io			not pooled		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	0/15 (0%)	9.1%	RR 0.25 (0.01 to 5.62)	7 fewer per 100 (from 9 fewer to 42 more) 7 fewer per 100 (from 9 fewer to 42	⊕⊕OO LOW	
Reporte	ed side effect	s (overall)								more)		
2	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	25/45 (55.6%)	21/36 (58.3%) 44.6%	RR 0.98 (0.73 to 1.32)	1 fewer per 100 (from 16 fewer to 19 more) 1 fewer per 100 (from 12 fewer to	⊕⊕OO LOW	

			(<5000lux hou	., , ,							
	randomised trials		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%	121	4 more per 100 (from 8 fewer to 120 more)	
eporte	ed side effect	s - Light viso	r vs dim light v	isor							
-	rted side effects randomised n trials		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	⊕⊕OO LOW
								80%		100 (from 22 fewer to 22 more)	
Aean c	linician rated	SAD depres	sion scores at e	endpoint (ove	rall) (measur	ed with: SIGH	-SAD; Bette	er indicated k	y lower v	alues)	
i	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

1	randomised trials	limitations	no serious inconsistency	indirectness	serious ³	none	14	9	-	lower to 0.94 higher)		
Mean c	linician rated	SAD depres	sion scores at e	endpoint - Ligh	nt visor vs dir	n light visor (me	asured w	vith: SIGH-SA	D; Better	indicated by	lower value	es)
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)	LOW	
Mean c	linician rated	SAD depres	sion scores at e	endpoint - Ligh	nt box vs low	-density ionisation	on (meas	sured with: S	IGH-SAD;	Better indica	ated by lowe	er values)
2	randomised trials	no serious limitations	serious ²		no serious imprecision	none	40	42	-	MD 8.56 lower (14.73 to 2.39 lower)	⊕⊕⊕O MODERATE	
	linician rateded	-	sion scores at e	endpoint - Lov	v dose (<5000	Dlux hours/day)	light box	vs no light b	ox (meas	ured with: SI	GH-SAD; Be	tter
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	9	12	-	MD 1.4 higher (4.93 lower to 7.73 higher)	LOW	
	linician rated ed by lower v	-	sion scores at e	endpoint - Lov	v dose (<5000	Dlux hours/day)	light viso	r vs no light	visor (me	asured with:	SIGH-SAD; I	Better
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	12	10	-	MD 0.2 lower (6.22 lower to	⊕⊕OO LOW	

										5.82 higher)	
ean c	clinician rated	typical dep	ression scores a	at endpoint (n	neasured wi	th: HAMD-17/HI	RSD-21; B	etter indicat	ed by low	er values)	
,	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
lean (alues)		typical dep	ression scores a	at endpoint - I	Light visor vs	dim light visor	(measure	d with: HAM	D-17/HR	SD-21; Better	indicated by low
2	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)	LOW
	clinician rated values)	typical dep	ression scores a	at endpoint - I	Light box vs	ow-density ioni	sation (mo	easured with	n: HAMD-	17/HRSD-21;	Better indicated
L	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	none	21	23	-	SMD 0.81 lower (1.43 to 0.19 lower)	⊕⊕⊕O MODERATE
Better	indicated by I	ower values)	•	Low dose (</td <td></td> <td>ay) light b</td> <td>ox vs no ligh</td> <td>nt box (me</td> <td></td> <td>HAMD-17/HRSC</td>		ay) light b	ox vs no ligh	nt box (me		HAMD-17/HRSC
1	randomised trials	limitations	no serious inconsistency	no serious indirectness	serious	none	9	12	-	SMD 0.26 higher (0.61 lower to	⊕⊕⊕O MODERATE

										1.13 higher)		
	clinician rated			at endpoint - I	Low dose (<5	 000lux hours/da	ay) light v	isor vs no lig	tht visor (measured wi	th: HAMD-17	7/HRSD-21
1 Mean		limitations	no serious inconsistency	no serious indirectness	serious ⁴	none th: SAD subscal	12	10	lower va	SMD 0.2 higher (0.64 lower to 1.04 higher)	MODERATE	
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	55	-	MD 1.25 lower (2.77 lower to 0.27 higher)		
Mean 1	randomised		no serious	no serious indirectness	serious ⁴	none	34	33	- -	MD 2.1 lower (4.31 lower to 0.11 higher)	⊕⊕⊕O MODERATE	er values)
Moan	clinician rated	l atypical dep	pression scores	at endpoint -	· Low dose (<	5000lux hours/o	day) light	box vs no lig	tht box (m	neasured witl	n: SAD subsc	ale; Better

										4.88 higher)	
	linician rated			at endpoint -	Low dose (<	l 5000lux hours/d	lay) light	visor vs no li	ght visor	l (measured w	rith: SAD subscale;
l	randomised trials	limitations	no serious inconsistency	indirectness	serious ⁴	none	12	10	-	1.24 higher)	MODERATE
lean s	elf rated dep	ression score	es at endpoint -	- Light box vs	deactivated r	negative ion gen	erator (m	neasured wit	h: BDI; Be	etter indicate	ed by lower values)
L	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	33	31	-	MD 2.6 lower (6.72 lower to 1.52 higher)	⊕⊕⊕O MODERATE
lon rei	l mission (SIGH	 -SAD or SIGI	 H-SAD-SR or HD	DRS) (overall)							
j	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	7 fewer per 100 (from 21 fewer to 12 more)	⊕⊕OO LOW
								70.5%	1.2)	8 fewer per 100 (from 24 fewer to 14 more)	
Non rei	mission (SIGH	-SAD or SIGI	H-SAD-SR or HD	RS) - Low dos	se (<5000lux	hours/day) LED	light vs n	egative ion g	enerator		
-	randomised trials		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	⊕⊕⊕O MODERATE

										fewer)		
								90.9%		45 fewer per 100 (from 8 fewer to 65 fewer)		
n rer	nission (SIGH	I-SAD or SIGI	H-SAD-SR or HD	ORS) - Light bo	x vs deactiva	ted negative ior	n generat	tor				
	randomised trials	no serious limitations		no serious indirectness	serious ³	none	21/41 (51.2%)	30/40 (75%)	RR 0.68 (0.48 to	24 fewer per 100 (from 2 fewer to 39 fewer)	⊕⊕⊕O MODERATE	
								75%	0.97)	24 fewer per 100 (from 2 fewer to 39 fewer)		
n rer	nission (SIGH	l-SAD or SIGI	H-SAD-SR or HE	DRS) - Light vis	sor vs dim lig	ht visor						
	randomised trials	no serious limitations		no serious indirectness	serious ⁴	none	33/64 (51.6%)	22/58 (37.9%)	RR 1.34 (0.79 to 2.27)	13 more per 100 (from 8 fewer to 48 more)	⊕⊕OO LOW	
								38.7%		13 more per 100 (from 8		

										fewer to 49		
Non rer	nission (SIGH	 -SAD or SIGI	 H-SAD-SR or HD	 DRS) - Light bo	x vs high dos	 e (>300lux) dim	red light	box		more)		
			1					T		T T	T	
	randomised trials		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	
								73.1%	1.4)	3 more per 100 (from 17 fewer to 29 more)		
lon rer	nission (SIGH	-SAD or SIGI	H-SAD-SR or HD	ORS) - Light bo	x vs low-den	sity ionisation						
	randomised trials		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)	12 fewer per 100 (from 32 fewer to 20 more)	⊕⊕OO LOW	
								68%		per 100 (from 32 fewer to 20 more)		
lon res	ponse (SIGH	-SAD) (overa	II)									
,	randomised trials	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	
								58.3%		8 fewer per 100 (from		

										21 fewer to 9 more)		
Non res	sponse (SIGH	-SAD) - Light	box vs deactive	ated negative	ion generat	or						
1	randomised trials		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)	⊕⊕⊕O MODERATE	
								62.5%	1.11)	16 fewer per 100 (from 32 fewer to 7 more)		
Non res	sponse (SIGH	-SAD) - Light	visor vs dim lig	tht visor								
2	randomised trials	no serious limitations	serious ³	no serious indirectness	serious ⁴	none	30/64 (46.9%)	22/58 (37.9%)	RR 1.24 (0.56 to	9 more per 100 (from 17 fewer to 66 more)		
								37.2%	- 2.75)	9 more per 100 (from 16 fewer to 65 more)		
Non res	sponse (SIGH	-SAD) - Light	box vs high do	se (>300lux) d	lim red light	box						
1	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	none	13/33 (39.4%)	14/26 (53.8%)	RR 0.73 (0.42 to 1.27)	15 fewer per 100 (from 31 fewer to 15 more)	⊕⊕⊕O MODERATE	

(5)							53.9%		15 fewer per 100 (from 31 fewer to 15 more)		
esponse (SIGH	-SAD) - Light	box vs low-dei	•								
randomised trials	no serious limitations	no serious inconsistency		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)		
response (SIGH-	-	-							fewer)		
randomised	-	no serious inconsistency		ght box vs n	o light box	7/10 (70%)	7/12 (58.3%)	RR 1.2 (0.64 to 2.25)		⊕⊕⊕O MODERATE	

5/12 (41.7%) 6/10 (60%) RR 0.69 fewer to more)	1	randomised no serious	no serious no serious	serious ⁴ none			19 fewer		
(41.7%) (0.3 to 1.61)		trials limitations	inconsistency indirectness		5/10 (60%)	RR 0.69	per 100 (from 42 fewer to 37		
						•		⊕⊕⊕O MODERATE	
60% per 100 (from 4 fewer to					60%		19 fewer per 100 (from 42 fewer to 37 more)		

¹ Inconclusive effect size
² Single study; inconclusive effect size
³ Significant heterogeneity; random effects model used
⁴ Single study

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

			Quality asses	ssment				Sur	nmary of	findings		
			Quality asset	oomene			No. o	f patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Active treatment control	Relative (95% CI)	Absolute	Quality	
Leaving	study early f	or any reaso	on - Light box vs	group CBT								
	randomised trials	no serious limitations		no serious indirectness	serious ¹	none	2/25 (8%)	4/24 (16.7%)	RR 0.53 (0.12 to	8 fewer per 100 (from 15 fewer to 22 more)	⊕⊕⊕O MODERATE	
								17.8%	2.31)	8 fewer per 100 (from 16 fewer to 23 more)		
Leaving	study early f	or any reaso	on - Light box +	placebo pill v	s dim light bo	x + fluoxetine						
	randomised trials	no serious limitations		no serious indirectness	serious ¹	none	12/68 (17.6%)	8/68 (11.8%)	RR 1.5 (0.65 to	6 more per 100 (from 4 fewer to 29 more)	⊕⊕⊕O MODERATE	
								9.8%	3.44)	5 more per 100 (from 3 fewer to 24 more)		

ľ	andomised	no serious	no serious	no serious	no serious	none	0/10	0/10 (0%)	not	not pooled	$\oplus \oplus \oplus \oplus$
t	rials	limitations	inconsistency	indirectness	imprecision		(0%)		pooled		HIGH
								0%	•	not pooled	
ng s	tudy early o	lue to side e	ffects - Light bo	x + placebo p	ill vs dim ligh	t box + fluoxeti	ne				
			ı	ı	1 2		1	I		1 -	
	andomised		no serious	no serious	very serious ²	none				2 fewer per	
t	rials	limitations	inconsistency	indirectness				2/48 (4.2%)		100 (from 4	
								2, 10 (11270)	RR 0.5	fewer to 18	
							1/48		(0.05 to	more)	⊕⊕ОО
							(2.1%)		5.33)	_	LOW
										2 fewer per	
								4.2%		100 (from 4 fewer to 18	
										more)	
ing s	tudv early o	lue to side e	ffects - Light bo	ox vs group CE	BT					,	
	,, .		G								
r	andomised	no serious	no serious	no serious	serious ³	none	0/16	0/15 (0%)	not	not pooled	⊕⊕⊕О
		no serious limitations		no serious indirectness	serious ³	none	0/16 (0%)		not pooled		⊕⊕⊕O MODERATE
					serious ³	none	,	0/15 (0%)		not pooled	
t	rials	limitations	inconsistency	indirectness		none light box + fluo	(0%)				
ring s	rials tudy early c	limitations	inconsistency f efficacy - Ligh	indirectness t box + placel	oo pill vs dim	light box + fluo	(0%)			not pooled	
ing s	rials tudy early c andomised	limitations lue to lack o	inconsistency f efficacy - Ligh no serious	indirectness t box + placel no serious		light box + fluo	(0%)			not pooled 0 more per	
ring s	rials tudy early c andomised	limitations	inconsistency f efficacy - Ligh	indirectness t box + placel	oo pill vs dim	light box + fluo	(0%)			not pooled 0 more per 100 (from 0	
ring s	rials tudy early c andomised	limitations lue to lack o	inconsistency f efficacy - Ligh no serious	indirectness t box + placel no serious	oo pill vs dim	light box + fluo	(0%)	0%		not pooled 0 more per 100 (from 0 fewer to 0	
ing s	rials tudy early c andomised	limitations lue to lack o	inconsistency f efficacy - Ligh no serious	indirectness t box + placel no serious	oo pill vs dim	light box + fluo	(0%) xetine 2/43	0%	pooled	not pooled 0 more per 100 (from 0	
ing s	rials tudy early c andomised	limitations lue to lack o	inconsistency f efficacy - Ligh no serious	indirectness t box + placel no serious	oo pill vs dim	light box + fluo	(0%)	0%	pooled RR 5.57	0 more per 100 (from 0 fewer to 0 more)	
ring s	rials tudy early c andomised	limitations lue to lack o	inconsistency f efficacy - Ligh no serious	indirectness t box + placel no serious	oo pill vs dim	light box + fluo	(0%) xetine 2/43	0%	pooled RR 5.57 (0.27 to	not pooled 0 more per 100 (from 0 fewer to 0 more) 0 more per	
ing s	rials tudy early c andomised	limitations lue to lack o	inconsistency f efficacy - Ligh no serious	indirectness t box + placel no serious	oo pill vs dim	light box + fluo	(0%) xetine 2/43	0%	pooled RR 5.57 (0.27 to	0 more per 100 (from 0 fewer to 0 more)	

	no serious	no serious	no serious	serious ³	none				22 more per		
trials	limitations	inconsistency	indirectness			37/48		RR 1.03	1000 (from		
						(77.1%)	75%	(0.82 to	135 fewer		
						(//.1/0)		1.29)	to 217		
									more)		
ean clinician rate	d SAD depres	ssion scores at e	endpoint - Ligi	nt box vs grou	up CBT (measure	ed with: S	SIGH-SAD; B	etter indic	cated by lowe	r values)	
randomised	no serious	no serious	no serious	very serious ²	none				MD 0.2		
trials	limitations	inconsistency	indirectness						lower (6.5	$\oplus \oplus OO$	
						16	15	-	lower to 6.1	LOW	
									higher)		
									,		
randomised	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	68	-	MD 0.49 lower (3.72	$\oplus \oplus \oplus \oplus$	
	limitations	inconsistency	indirectness	imprecision		68	68	-			
trials	IIIIIIIIIIII	,									
trials	Initiations								lower to	HIGH	
trials	iiiiitations	·							2.74 higher)	пібп	
ean clinician rate	d typical dep	T	t endpoint - L			ured with	ո։ HAMD-17	/HRSD-21	2.74 higher) ; Better indica		er valu
	d typical dep	no serious	no serious	eight box vs gr		ured with	n: HAMD-17	/HRSD-21	2.74 higher) ; Better indica	ated by low	er valu
lean clinician rate	d typical dep	no serious	, T					/HRSD-21	2.74 higher) ; Better indica	eted by low ⊕⊕OO	er valu
randomisec	d typical dep	no serious	no serious			ured with	15	/HRSD-21	2.74 higher) ; Better indication SMD 0.13 lower (0.83 lower to	ated by low	er valu
lean clinician rate	d typical dep	no serious	no serious					/HRSD-21	2.74 higher) ; Better indication SMD 0.13 lower (0.83)	eted by low ⊕⊕OO	er valu

	randomised	no serious	no serious	no serious	no serious	none				SMD 0.04		
	trials	limitations	inconsistency		imprecision					lower (0.38	$\oplus \oplus \oplus \oplus$	
			,		'		68	68	-	lower to	HIGH	
										0.29 higher)		
			ression scores a	ıt endpoint - l	light box + hy	pericum vs dir	m light + h	ypericum (m	l leasured	with: HAMD-1	.7/HRSD-21;	Bett
dica	ted by lower v	alues)										
	randomised	no serious	no serious	no serious	very serious ²	none				SMD 0.32		
	trials	limitations	inconsistency	indirectness			10	10		lower (1.2	$\oplus \oplus OO$	
							10	10	_	lower to	LOW	
										0.57 higher)		
ean	clinician rated	atypical de	pression scores	at endpoint -	Light box vs	group CBT (me	easured wi	th: SAD sub	scale; Bet	ter indicated l	by lower val	ues)
	randomised	no serious	no serious	no serious	serious ³	none				MD 0.4		
	randomised trials	no serious limitations		no serious indirectness	serious ³	none	16	15		MD 0.4 higher (2.68	⊕⊕⊕О	
					serious ³	none	16	15	-	higher (2.68	⊕⊕⊕O MODERATE	
					serious ³	none	16	15	-	higher (2.68		
ean	trials	limitations		indirectness					- ine (meas	higher (2.68 lower to 3.48 higher)	MODERATE	Bette
	trials	limitations	inconsistency	indirectness					ine (meas	higher (2.68 lower to 3.48 higher)	MODERATE	Betto
	trials clinician rated	limitations latypical department	inconsistency	indirectness		lacebo pill vs (ine (meas	higher (2.68 lower to 3.48 higher)	MODERATE	Betto
	trials clinician rated ted by lower v	limitations latypical department	inconsistency pression scores	indirectness at endpoint -	Light box + p	lacebo pill vs (dim light b	ox + fluoxet	ine (meas	higher (2.68 lower to 3.48 higher) sured with: SA	MODERATE	Bette
	trials clinician rated ted by lower v	limitations atypical departments alues)	pression scores	at endpoint -	Light box + p	lacebo pill vs (- ine (meas	higher (2.68 lower to 3.48 higher) sured with: SA	MODERATE D subscale;	Betto
	trials clinician rated ted by lower v	limitations atypical departments alues)	pression scores	at endpoint -	Light box + p	lacebo pill vs (dim light b	ox + fluoxet	ine (meas	higher (2.68 lower to 3.48 higher) sured with: SA MD 0.3 lower (1.75	MODERATE D subscale; ⊕⊕OO	Betto

Mean s	elf rated dep	limitations	no serious	- Light box + p no serious	very serious ² lacebo pill vs	dim light box +	16	15 ne (measure		MD 0.7 lower (7.16 lower to 5.76 higher) DI; Better indi MD 1.6 lower (5.68	cated by lov ⊕⊕OO	wer values)
Non ror			inconsistency		evetine		48	48	-	lower to 2.48 higher)	FOM	
Non rei	ilissioii - Ligii	t box + place	soo piii vs aiiii i	igiit box + iiu	oxetine							
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	4 fewer per 100 (from 18 fewer to 15 more)	⊕⊕OO LOW	
								60.4%	1.27)	5 fewer per 100 (from 20 fewer to 16 more)		
Non rer	nission - Ligh	t box vs grou	ир 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	
								63.3%		15 fewer per 100 (from 34		

										fewer to 18 more)		
Non re	sponse - Light	box + place	bo pill vs dim li	ght box + fluo	exetine							
2	randomised trials	no serious limitations		no serious indirectness	very serious ¹	none	22/68 (32.4%)	23/68 (33.8%)	RR 0.96 (0.59 to	1 fewer per 100 (from 14 fewer to 18 more)	⊕⊕OO LOW	
								34.2%	1.34)	1 fewer per 100 (from 14 fewer to 18 more)		

¹ Inconclusive effect size
² Inconclusive effect size/single study
³ Single study
⁴ Significant heterogeneity; random effects model used

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

			Quality asses	ssment				9	Summary o	of findings		
			Launi, 2000				No. of	patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light	Light + CBT combo	Relative (95% CI)	Absolute	Quality	importunee
Leaving	study early f	or any reasor	1									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	2/25 (8%)	2/23 (8.7%)	RR 0.92 (0.17 to	1 fewer per 100 (from 7 fewer to 34 more)	⊕⊕⊕O MODERATE	
								9.6%	4.91)	1 fewer per 100 (from 8 fewer to 38 more)		
Leaving	study early d	lue to side ef	fects									
1	randomised trials	no serious limitations		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)		

	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)	⊕⊕⊕O MODERATE
ean	clinician rated	typical depr	ession scores at	endpoint (me	asured with:	HAMD-17/HRSD	-21; Bet	tter indic	ated by lov	ver values)	
	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
lean (clinician rated	atypical dep	ression scores a	it endpoint (m	easured with	: SAD subscale; E	Better ir	ndicated I	oy lower va	alues)	
	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
/lean	self rated dep	ression score	s at endpoint (r	neasured with	: BDI; Better i	indicated by low	er value	es)			
	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)	⊕⊕OO LOW
on re	mission (SIGH	-SAD)									
	randomised	no serious	no serious	no serious	no serious	none	12/25	5/23	RR 2.22	27 more per	$\oplus \oplus \oplus \oplus$

trials	limitations	inconsistency	indirectness	imprecision	(48%)	(21.7%)	5.32)	fewer to 94	HIGH	
								more)		
								24		
								24 more per 100 (from 2		
						19.6%		fewer to 85		
								more)		

Does the time of day increase the effectiveness of bright light box therapy?

			Quality asse	ssment				Summary	of findin	ıgs		
			•				N	o. of patients	Ef	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Morning	Afternoon/evening bright light box	Relative (95% CI)	Ahsolute	Quality	
Leaving	study early	for any reas	son (overall)									
3	randomised trials		no serious inconsistency			none	8/66 (12.1%)	8/64 (12.5%)	RR 0.98 (0.41 to 2.35)	0 fewer per 100 (from 7 fewer to 17 more)	⊕⊕⊕O MODERATE	
								0%	2.33)	0 fewer per 100 (from 0 fewer to 0 more)		

¹ Inconclusive effect size
² Inconclusive effect size; single study
³ Single study

Leaving	g study early	for any rea	son - SAD								
2	randomised trials		no serious inconsistency		serious ¹	none	8/50 (16%)	8/49 (16.3%)	RR 0.98 (0.41 to 2.35)	22 more)	⊕⊕⊕O MODERATE
						10%	2.33)	0 fewer per 100 (from 6 fewer to 13 more)			
eaving	g study early	for any rea	son - Subsyndr	omal SAD							
	randomised trials		no serious inconsistency			none	0/16 (0%)	0/15 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
							(0%)	0%		not pooled	
eaving	g study early	due to side	effects - Subsy	ndromal SAI	D	,	1		'		1
	randomised trials		no serious inconsistency		serious ²	none	0/16 (0%)	0/15 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
								0%		not pooled	
eport	ed side effec	ts - Subsync	dromal SAD			•					<u> </u>
	randomised trials		no serious inconsistency		very serious ³	none	1/16 (6.3%)	2/15 (13.3%)	RR 0.47 (0.05 to 4.65)	7 fewer per 100 (from 13 fewer to	⊕⊕OO LOW

	1	ı	1	1		1		,		1	
									49 more)		
									7 fewer		
								42.20/	per 100		
								13.3%	(from 13 fewer to		
									49 more)		
Maan	linisian vata	d CAD done		t andmaint (a	verall\ /mea		II CAD. B	l Setter indicated by lo	<u> </u>		
iviean	iinician rate	a SAD depre	ession scores a	t enapoint (o	verall) (mea	isurea with: 31G	п-зар; в	etter indicated by ic	ower values)		
2	randomised	no serious	no serious	no serious	very	none			MD 1.38		
	trials	limitations	inconsistency	indirectness	serious ¹				lower		
							25	22	(5.49	⊕⊕OO	
							35	33	- lower to	LOW	
									2.73		
									higher)		
									,		
Mean o	linician rate	d SAD depre	ession scores a	t endpoint - S	Subsyndrom	al SAD (measur	ed with:	SIGH-SAD; Better inc	dicated by lower va	alues)	
1	randomised	no serious	no serious	no serious	very	none			MD 0.6		
	trials	limitations	inconsistency	indirectness	serious ³				higher		
									(3.89	⊕⊕OO	
							16	14	- lower to	LOW	
									5.09		
									higher)		
Mean	linician rate	d SAD depre	ession scores a	t endpoint - S	SAD (measu	red with: SIGH-	SAD; Bett	er indicated by lowe	er values)		
1	randomised	no serious	no serious	no serious	very	none			MD 3.6		
	trials	limitations	inconsistency	indirectness	serious ³				lower		
									(8.5	⊕⊕OO	
							19	19	- lower to	LOW	
									1.3		
									higher)		
	1	l	1	1		ı		l .	l	l	

randomised no serious inconsistency indirectness serious randomised no serious inconsistency indirectness randomised no serious randomised no serious randomised no serious inconsistency indirec			no serious limitations	no serious inconsistency		serious ¹	none	25	22	SMD 0.05 lower (0.63 lower to 0.52 higher)	⊕⊕⊕O MODERATE
trials limitations inconsistency indirectness serious ³ 16 14 - lower (0.87 lower to 0.57 higher) Franchinician rated typical depression scores at endpoint - SAD (HRSD-31) (measured with: HAMD-17/HRSD-21; Better indicated by lower value trials limitations inconsistency indirectness serious ³ 18 19 19 10 10 10 10 10 10 10 10	an clini	ician rated	d typical de	pression score	s at endpoint	t - Subsynd	romal SAD (mo	easured with:	: HAMD-17/HRSD	D-21; Better indicate	d by lower va
trials limitations inconsistency indirectness serious ³ higher (0.83 $\oplus \oplus$ OO							none	16	14	lower (0.87 lower to 0.57	⊕⊕OO
trials limitations inconsistency indirectness serious ³ higher (0.83 $\oplus \oplus$ OO		ician rate	d typical de	pression score	s at endpoint	- SAD (HR	SD-31) (measu	red with: HAI	MD-17/HRSD-21;	Better indicated by	lower values
1.07 higher)	iean ciini					vorv	none			SMD 0.13	
	rar tria	als	limitations	inconsistency	indirectness	serious ³				higher (0.83 lower to 1.07	⊕⊕OO LOW

Mean s	self rated de	pression sco	res at endpoir	it - SAD (mea	sured with:	BDI; Better ind	icated by	lower values)		lower to 3.72 higher)	
1	randomised trials		no serious inconsistency		very serious ³	none	33	32	-	MD 0.9 lower (4.66 lower to 2.86 higher)	⊕⊕OO LOW
Non re	mission - SA	D									<u>.</u>
2	randomised trials	no serious limitations	serious ⁴	no serious indirectness	serious ¹	none	27/50 (54%)	26/48 (54.2%)		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)	
Non re	sponse (ove	rall)									
3	randomised trials	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	⊕⊕OO LOW

							40%		42 more) 0 fewer per 100 (from 20 fewer to 39 more)		
Non re	sponse - SAD)									
2	randomised trials		no serious inconsistency	serious ¹	none	24/50 (48%)	18/48 (37.5%)		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)		
Non re	sponse - Sub	syndromal S	SAD								
1	randomised trials		no serious inconsistency	serious ³	none	5/16 (31.3%)	9/15 (60%)		29 fewer per 100 (from 46 fewer to 12 more)	⊕⊕⊕O MODERATE	
							60%	- 1.2)	29 fewer per 100 (from 46 fewer to 12 more)		

¹ Inconclusive effect size ² Single study

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

			Quality asse	ssment				Summ	nary of fin	dings		
							No. of	patients	Ef	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dawn simulation	Attentional control	Relative (95% CI)	Absolute	Quality	
Leaving	study early	for any reas	on									
	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	2/70 (2.9%)	10/71 (14.1%)	RR 0.33 (0.05 to 2.22)	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	study early	due to side 6	effects									
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	0/31 (0%)	1/31 (3.2%)	RR 0.33 (0.01 to 7.88)	2 fewer per 100 (from 3 fewer to	⊕⊕OO LOW	

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

										22 more)	
								3.2%		2 fewer per 100 (from 3 fewer to 22 more)	
aving	study early (due to lack o	of efficacy								
	randomised trials		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%	1.1)	10 fewer per 100 (from 12 fewer to 1 more)		
eport											
	randomised I		no serious inconsistency	no serious indirectness	very serious ²	none	6/14 (42.9%)	1/13 (7.7%)	RR 5.57 (0.77 to 40.26)	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)	

2 Mean c		limitations	serious ³ pression score	indirectness	·	none vith: SAD subsca	37 le; Better in	36 Indicated by I	- ower valu	0.15 higher)	⊕⊕⊕O MODERATE	
2 Non rei	randomised trials mission (SIGF	limitations	serious ³	no serious indirectness	very serious ²	none	37	36	-	MD 2.20 lower (7.52 lower to 3.11 higher)	⊕OOO VERY LOW	
2	randomised trials	no serious limitations	serious ³	no serious indirectness	serious ¹	none	25/56 (44.6%)	29/58 (50%) 49.9%	RR 0.9 (0.46 to 1.78)	5 fewer per 100 (from 27 fewer to 39 more) 5 fewer per 100 (from 27 fewer to 39 more)	⊕⊕OO LOW	
Non res	randomised trials	no serious	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	⊕⊕⊕O MODERATE	

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

¹ Inconclusive effect size
² Inconclusive effect size; single study
³ Significant heterogeneity; random effects model used

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

			Quality asse	ssment				Sun	nmary of	findings		
			,				No. of	f patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bright light box	Dawn simulation	Relative (95% CI)	Absolute	Quality	
Leaving	study early f	or any reaso	n									
	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	study early o	due to side e	ffects									
	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	study early c	due to lack o	f efficacy									

1	randomised	no serious	no serious	no serious	no serious	none	0/31	0/31 (0%)	not	not pooled	$\oplus \oplus \oplus \oplus$
	trials	limitations	inconsistency	indirectness	imprecision		(0%)		pooled		HIGH
								0%		not pooled	
lon re	emission (SIGH	-SAD)									
)	randomised	no serious	serious ³	no serious	very serious ¹	none				8 more per	
	trials	limitations		indirectness				25/56		100 (from	
								(44.6%)		13 fewer to	
							30/56 (53.6%)		RR 1.19 (0.7 to 2)	45 more)	⊕OOO VERY LOW
								46.1%		9 more per 100 (from 14 fewer to 46 more)	
lon re	sponse (SIGH-	SAD)									
	randomised	no serious	no serious	no serious	serious ¹	none				11 more per	
	trials	limitations	inconsistency	indirectness				14/56		100 (from 5	
							20/56 (35.7%)	(25%)	RR 1.45 (0.82 to	fewer to 39 more)	⊕⊕⊕O MODERATE
							(33.770)		2.58)	12 more per	
								26.40/		100 (from 5	
								26.1%		fewer to 41	
										more)	
epres	ssion: mean er	ndpoint scor	es (Better indic	ated by lower	values)						
	randomised	no serious	no serious	no serious	very serious ²	none				MD 0.9	
	trials	limitations	inconsistency	indirectness			21	24	_	lower (4	⊕⊕OO
							21	24	_	lower to 2.2	LOW
										higher)	
AD: m	l nean endpoint	scores (Bett	 ter indicated by	l lower values)						
		12.20		, , , , , , , , , , , , , , , , , , , ,	•						

1	randomised	no serious	no serious	no serious	very serious ²	none				MD 1.8		
	trials	limitations	inconsistency	indirectness			21	24		lower (6.98	$\oplus \oplus OO$	
							21	24	-	lower to	LOW	
										3.38 higher)		

Which therapy is most effective for relapse prevention of depression with a seasonal pattern/SAD?

Quality assessment												
							No. of patients		Effect			Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Relapse prevention	Control	Relative (95% CI)	Absolute	Quality	
Leaving study early for any reason - Bright white light visor vs no treatment control												
	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	4/18 (22.2%)	1/10 (10%)	RR 2.22 (0.29 to - 17.27)	12 more per 100 (from 7 fewer to 163 more)	⊕⊕OO LOW	
								10%		12 more per 100 (from 7 fewer to 163 more)		
Leaving	study early f	or any reaso	n - Bright white	e light visor vs	dim red ligh	t visor						
	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	4/18 (22.2%)	3/18 (16.7%)	RR 1.33 (0.35 to	6 more per 100 (from 11 fewer to	⊕⊕OO LOW	

¹ Inconclusive effect size
² Inconclusive effect size; single study
³ Significant effect size - random effects model used

Relapse	during cours	se of study (E	BDI>=13 for 2 co	onsecutive wk	s) - Bright w	hite light visor v	s no treatme	16.7% ent contr	5.13) ol	69 more) 6 more per 100 (from 11 fewer to 69 more)		
	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	9/18 (50%)	8/10 (80%)	RR 0.63 (0.36 to 1.09)	30 fewer per 100 (from 51 fewer to 7 more) 30 fewer per 100 (from 51 fewer to 7 more)	⊕⊕⊕O MODERATE	
1	randomised trials	no serious limitations	no serious inconsistency		s) - Bright w	none	9/18 (50%)	4/18 (22.2%) 22.2%	RR 2.25 (0.84 to 5.99)	28 more per 100 (from 4 fewer to 111 more) 28 more per 100 (from 4 fewer to 111 more)	⊕⊕⊕O MODERATE	

Inconclusive effect size; single study
² Single study

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 find	lings		
			Quality asse	Sincin			No. of pati	ents	Ef	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acute phase treatment: antidepressants	Control	Relative (95% CI)	Absolute	Quality	
Numbe	r not achievi	ng =/> 50%	reduction in SI	GH-SAD score	at endpoint	: (overall)						l
2	randomised trials		no serious inconsistency			none	57/129 (44.2%)	68/126 (54%)	RR 0.82 (0.63 to	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)		
Numbe	r not achievi	ng =/> 50% i	reduction SIGH	-SAD score								
1	randomised trials		no serious inconsistency		very serious ¹	none	41/93 (44.1%)	47/94 (50%)	RR 0.88 (0.65 to 1.2)	6 fewer per 100 (from 18 fewer to 10 more)	⊕⊕OO LOW	
								50%		6 fewer		

Numbe	r not achievi	ng =/> 50% ເ	reduction in ou	tcome score	at endpoint	- Fluoxetine vs F	Placebo			per 100 (from 18 fewer to 10 more)	
1	randomised trials		no serious inconsistency		very serious ¹	none	16/36 (44.4%)	21/32 (65.6%)	RR 0.68 (0.43 to 1.05)	21 fewer per 100 (from 37 fewer to 3 more)	⊕⊕OO LOW
Mean e	ndpoint SIGI	-SAD (clinic	ian rated) (ant	idenressants	(Better indi	cated by lower	values)	65.6%	1.03)	21 fewer per 100 (from 37 fewer to 3 more)	
2	randomised		serious ²	no serious indirectness		none	52	47	-	SMD 0.11 lower (0.65 lower to 0.42 higher)	⊕⊕OO LOW
Mean e	ndpoint (clin	ician rated)	(antidepressai	nts) - Moclob	emide vs Plac	cebo (Better ind	icated by lower	values)			
1	randomised trials		no serious inconsistency		very serious ¹	none	16	15	-	SMD 0.23 higher (0.48 lower to 0.94	⊕⊕OO LOW

										higher)		
Mean e	ndpoint (clin	ician rated)	(antidepressa	nts) - Fluoxet	ine vs Placeb	o (Better indica	ted by lower val	ues)				
1	randomised trials		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	
Mean e	ndpoint BDI	(self rated)	- Fluoxetine vs	Placebo (Bet	ter indicated	by lower value	s)					
1	randomised trials	no serious limitations	no serious inconsistency		very serious ¹	none	36	32	-	MD 1.7 lower (6.53 lower to 3.13 higher)	⊕⊕OO LOW	
Mean c	hange (clinic	ian rated) -	Sertraline vs Pl	acebo (Bette	r indicated b	y lower values)						
1	randomised trials	no serious limitations	no serious inconsistency		serious ³	none	93	93	-	MD 4.51 lower (8.23 to 0.79 lower)	⊕⊕⊕O MODERATE	
Relapse	Prevention	- Number of	f patients expe	riencing a rec	urrence							
3	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 0.72)		⊕⊕⊕⊕ HIGH	

					16 fewer)	
					13 fewer	
				31.9%	per 100 (from 9	
					fewer to 17 fewer)	

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

			Quality asses	ssment				Summar	y of findi	ngs		
							No. of patier	nts	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acute phase acceptability and tolerability (antidepressants)	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Numbe	r leaving the	study early	for any reason	n (overall)	'							
2	randomised trials	no serious limitations		no serious indirectness	very serious ²	none	20/109 (18.3%)	23/112 (20.5%)	RR 0.7 (0.16 to 3.05)	6 fewer per 100 (from 17 fewer to 42 more)	⊕OOO VERY LOW	
								19%	5.05)	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

Numbe	r leaving the	study early	for any reason	n - Sertraline	vs Placebo							
	randomised trials		no serious inconsistency		very serious ³	none	20/93 (21.5%)	20/94 (21.3%)	RR 1.01 (0.58 to	0 more per 100 (from 9 fewer to 16 more)	⊕⊕OO LOW	
								21.3%	1.73)	0 more per 100 (from 9 fewer to 16 more)		
lumbe	r leaving the	study early	for any reaso	n - Mocloben	nide vs Place	ebo						
	randomised trials		no serious inconsistency		very serious ³	none	0/16 (0%)	3/18 (16.7%)	RR 0.16 (0.01 to 2.87)	14 fewer per 100 (from 17 fewer to 31 more) 14 fewer per 100 (from 17 fewer to	⊕⊕OO LOW	
lumbo	r leaving the	study parly	due to side ef	focts						31 more)		
unibe	i leaving the	study carry	due to side ei	1003								
	randomised trials		no serious inconsistency		very serious ²	none	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)	⊕⊕OO LOW	
								5.3%		3 more		

	1	ı	1	1	ı		T			· · · · · · · · · · · · · · · · · · ·		
								1		per 100		
										(from 2		
										fewer to		
										13 more)		
Numbe	r leaving the	study early	due to side ef	fects - Sertra	line vs Place	bo						
1	randomised	no serious	no serious	no serious	very	none				5 more		
	trials	limitations	inconsistency	indirectness	serious ²			F /0.4		per 100		
								5/94		(from 1		
								(5.3%)	RR 2.02	fewer to		
							40/03/40.00()			25 more)	$\oplus \oplus OO$	
							10/93 (10.8%)		(0.72 to 5.69)	23 1110107	LOW	
									3.037	5 more		
										per 100		
								5.3%		(from 1		
										fewer to 25 more)		
										25 111016)		
	T		due to side ef	T		T		I				
	randomised				very	none				9 fewer		
	trials	limitations	inconsistency	indirectness	serious³			2/18		per 100		
								(11.1%)		(from 11		
								(11.1%)	RR 0.22	fewer to		
							0/16 (0%)		(0.01 to	37 more)	$\oplus \oplus OO$	
							0/10 (0%)		4.34)	,	LOW	
									4.34)	9 fewer		
										per 100		
								11.1%		(from 11		
										fewer to		
										37 more)		
Numbe	r leaving the	study early	due to side ef	fects - Fluoxe	tine vs Plac	ebo						
1	randomised	no serious	no serious	no serious	very	none	- / : ::	1/32	RR 1.78	2 more	⊕⊕ОО	
	trials	limitations	inconsistency	indirectness	serious ³		2/36 (5.6%)	(3.1%)		per 100	LOW	
								(3.2,2)	(0.17 to	(from 3		
			1							,		

Numbe	r reporting s	ide effects -	Sertraline vs F					3.1%	18.69)	fewer to 55 more) 2 more per 100 (from 3 fewer to 55 more)		
	randomised trials		no serious inconsistency		serious ⁴	none	76/93 (81.7%)	47/94 (50%)	RR 1.63 (1.31 to 2.04)	31 more per 100 (from 15 more to 52 more)	⊕⊕⊕O MODERATE	
Numbo	r reporting s	ida offacts	Fluoxetine vs	Placobo				50%		per 100 (from 15 more to 52 more)		
Numbe	r reporting s	ide effects -	riuoxetiile vs	riacebo								
	randomised trials		no serious inconsistency		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%	1.21)	6 more per 100 (from 5 fewer to 19 more)		

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

			Quality asses	ssment				Summa	ary of find	lings			
			Z,				No. of patie	nts	Ef	fect		Importance	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acute phase treatment: antidepressants		Relative (95% CI)	Absolute	Quality		
Numbe	r not achievi	ng =/> 50%	reduction in SI	 GH-SAD score	at endpoin	t - High ion dens	ity vs Low ion de	nsity					
1	randomised trials		no serious inconsistency		serious ¹	none	5/12 (41.7%)	11/13 (84.6%)	RR 0.49 (0.24 to	43 fewer per 100 (from 64 fewer to 0 more)	⊕⊕⊕O MODERATE		
								84.6%	- 1)	43 fewer per 100 (from 64 fewer to 0 more)			
Mean e	Mean endpoint SIGH-SAD (clinician rated) - Moclobemide vs Fluoxetine (Better indicated by lower values)												
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	11	18	-	MD 1.6 lower	⊕⊕OO LOW		

¹ Significant heterogeneity - random effects model used ² Inconclusive effect size

Single study; inconclusive effect size
 Single study

					(7.01	
					lower to	
					3.81	
					higher)	

¹ Single study; inconclusive effect size

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

			Quality asses	ssment				Sum	mary of fi	ndings		
			1				No. of pati	ents	Ef	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation treatment	Control	Relative (95% CI)	Absolute	Quality	
Mean e	ndpoint HAN	I 1D-21 (clinici	ian-rated) - Pro	panolol vs Pla	acebo (Bette	r indicated by lo	wer values)					
1	randomised trials		no serious inconsistency		serious ¹	none	12	11	-	MD 7 lower (11.24 to 2.76 lower)	⊕⊕⊕O MODERATE	
Numbe	r leaving the	study early f	or any reason	- Propanolol v	s Placebo							
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	1/13 (7.7%)	0/11 (0%)	RR 2.57 (0.12 to 57.44)	0 more per 100 (from 0 fewer to 0 more)		
								0%	37.44)	0 more per 100 (from 0 fewer to 0 more)		

¹ Single study ² Single study; inconclusive effect size

Is relapse prevention effective for depression with a seasonal pattern/SAD? (Buspirone versus placebo)

			Quality asses	sement				Sumr	nary of fi	ndings		
			Quality asses				No. of pa	tients	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	()TDAT	Buspirone- preven- tion	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse	Prevention	- Number of	patients experi	encing a recu	rrence							
11 1	randomised trial		no serious inconsistency		no serious imprecision	none	92/542 (17%)	153/519 (29.5%) 31.9%	0.50	12 fewer per 100 (from 8 fewer to - 16 fewer) 13 fewer per 100	⊕⊕⊕⊕HIGH	

Next-step treatments

Is dose escalation effective for depression that has not adequately responded to treatment?

			Quality asse	ssment				Sur	mmary of f	findings		
			,				No. of pa	atients	E ⁻	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dose escalation	Control	Relative (95% CI)	Absolute	Quality	
Mean d	epression sco	ores (overall)	(Better indicat	ted by lower v	values)	<u>I</u>						
2	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	228	215	-	SMD 0.11 lower (0.29 lower to 0.08 higher)	HIGH	
Mean d	epression sco	ores - Same o	or increased-do	se duloxetine	60mg vs high	n-dose duloxetir	ne 120mg (E	Better ind	icated by	lower values)	
1	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	130	118	-	SMD 0.01 lower (0.26 lower to 0.24 higher)	MODERATE	
Mean d	epression sco	ores - Same-o	dose sertraline	(100mg) vs hi	igh-dose serti	raline (200mg) (I	Better indic	ated by lo	ower value	es)		
1	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	98	97	-	SMD 0.22 lower (0.51 lower to	⊕⊕⊕O MODERATE	

										0.06 higher)	
Numbe	r not achievir	ng remission	(overall)								
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/230 (67%)	158/222 (71.2%)	RR 0.94 (0.83 to 1.06)	4 fewer per 100 (from 12 fewer to 4 more)	
								71.2%	1.00)	4 fewer per 100 (from 12 fewer to 4 more)	
Numbe	r not achievir	ng remission	- Same or incre	eased-dose du	lloxetine 60m	ng vs high-dose d	luloxetine :	120mg			
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	92/131 (70.2%)	88/124 (71%)	RR 0.99 (0.84 to	1 fewer per 100 (from 11 fewer to 11 more)	⊕⊕⊕O MODERATE
								71%	1.16)	1 fewer per 100 (from 11 fewer to 11 more)	
Numbe	r not achievir	ng remission	- Same-dose se	ertraline (100)	mg) vs high-d	ose sertraline (2	00mg)				
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	62/99 (62.6%)	70/98 (71.4%)	RR 0.88 (0.72 to	9 fewer per 100 (from 20 fewer to 5 more)	
								71.4%	1.07)	9 fewer per 100 (from 20 fewer to 5 more)	

Numbe	r not achievir	ng response	(overall)									
2	randomised trials	no serious limitations	serious ³	no serious indirectness	serious ⁴	none	103/230 (44.8%)	121/222 (54.5%)	RR 0.8 (0.59 to	11 fewer per 100 (from 22 fewer to 5 more)	⊕⊕OO LOW	
							·	53.6%	1.1)	11 fewer per 100 (from 22 fewer to 5 more)		
Numbe	r not achievir	ng response	- Same or incre	ased-dose du	loxetine 60m	g vs high-dose d	uloxetine 1	20mg				
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	73/131 (55.7%)	76/124 (61.3%)	RR 0.91 (0.74 to	6 fewer per 100 (from 16 fewer to 7 more)	⊕⊕OO LOW	
								61.3%	1.12)	6 fewer per 100 (from 16 fewer to 7 more)		
Numbe	r not achievir	ng response	- Same-dose se	rtraline (100n	ng) vs high-do	ose sertraline (20	00mg)	•	'			
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	30/99 (30.3%)	45/98 (45.9%)	RR 0.66 (0.46 to 0.95)	16 fewer per 100 (from 2 fewer to 25 fewer)	⊕⊕⊕O MODERATE	
								45.9%		16 fewer per 100 (from 2		

			1		1			1		1	1	
										fewer to 25		
										fewer)		
Leaving	treatment e	arly for any i	reason (overall)									
2	randomised	no serious	no serious	no serious	serious ⁴	none				7 fewer per		
	trials	limitations	inconsistency	indirectness				49/222		100 (from		
								(22.1%)	RR 0.7	11 fewer to		
							36/230		(0.48 to	1 more)	⊕⊕⊕О	
							(15.7%)		1.04)		MODERATE	
									1.04)	6 fewer per		
								21.4%		100 (from		
										11 fewer to		
			_	L	<u> </u>					1 more)		
Leaving	treatment e	arly for any i	reason - Same o	or increased-d	ose duloxetir	ne 60mg vs high-	dose dulox	etine 120	ımg			
1	randomised	no serious	no serious	no serious	serious ⁴	none				8 fewer per		
	trials	limitations	inconsistency	indirectness				34/124		100 (from		
								(27.4%)	RR 0.72	15 fewer to		
							26/131		(0.46 to	4 more)	⊕⊕⊕О	
							(19.8%)		1.13)		MODERATE	
									1.13)	8 fewer per		
								27.4%		100 (from		
								271170		15 fewer to		
										4 more)		
Leaving	treatment e	arly for any i	reason - Same-	dose sertralin	e (100mg) vs	high-dose sertra	line (200m	g)				
1	randomised	no serious	no serious	no serious	very serious ³	none				5 fewer per		
	trials	limitations	inconsistency	indirectness				15/98		100 (from		
								(15.3%)	RR 0.66	11 fewer to		
							10/99		(0.31 to	6 more)	⊕⊕OO	
							(10.1%)		1.4)		LOW	
									1.4)	5 fewer per		
								15.3%		100 (from		
										11 fewer to		
										6 more)		

	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	12/230 (5.2%)	12/223 (5.4%)	RR 0.97 (0.45 to 2.11)	0 fewer per 100 (from 3 fewer to 6 more)	⊕⊕OO LOW
								5.4%	2.11)	0 fewer per 100 (from 3 fewer to 6 more)	
avin	g treatment e	arly due to s	ide effects - Sa	me or increase	ed-dose dulo	cetine 60mg v	s high-dose d	uloxetine	120mg		
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	6/131 (4.6%)	7/124 (5.6%)	RR 0.81 (0.28 to 2.35)	1 fewer per 100 (from 4 fewer to 8 more)	⊕⊕OO LOW
								5.7%	2.33)	1 fewer per 100 (from 4 fewer to 8 more)	
eavin	g treatment e	arly due to s	ide effects - Sa	me-dose sertr	aline (100mg) vs high-dose	sertraline (20	00mg)			
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	6/99 (6.1%)	5/99 (5.1%)	RR 1.2 (0.38 to	1 more per 100 (from 3 fewer to 14 more)	⊕⊕OO LOW
								5.1%	3.8)	1 more per 100 (from 3 fewer to 14	

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	5/131 (3.8%)	10/124 (8.1%)	RR 0.47 (0.17 to	4 fewer per 100 (from 7 fewer to 3 more)	⊕⊕OO LOW	
								8.1%	1.35)	4 fewer per 100 (from 7 fewer to 3 more)		
Numbe	r reporting si	de effects - S	Same-dose sert	raline (100mg) vs high-dose	e sertraline (200	mg)					
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	45/99 (45.5%)	54/98 (55.1%)	RR 0.82 (0.62 to 1.09)	10 fewer per 100 (from 21 fewer to 5 more)	⊕⊕OO LOW	
								55.1%	1.03)	10 fewer per 100 (from 21 fewer to 5 more)		

Is switching antidepressants effective for depression that has not adequately responded to treatment?

				Quality asses	sment				Sumr	mary of fi	ndings		
				•				No. of p	atients	Ef	fect	Quality	Importance
N	lo. of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Switching:	Switching	Relative	Absolute		

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

⁴ Single study; inconclusive effect size

studies						considerations	continuing AD		(95% CI)			
Numbe	r not achievir	ng response	- Nortriptyline	vs fluoxetine								
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	21/68 (30.9%)	41/142 (28.9%)	RR 1.07 (0.69 to 1.66)	2 more per 100 (from 9 fewer to 19 more)		
								28.9%	1.00)	2 more per 100 (from 9 fewer to 19 more)		
Numbe	r not achievir	ng response	- Fluoxetine vs	mianserin								
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	24/38 (63.2%)	18/34 (52.9%)	RR 1.19 (0.8 to	10 more per 100 (from 11 fewer to 41 more)	⊕⊕OO LOW	
								52.9%	- 1.78)	10 more per 100 (from 11 fewer to 41 more)		
Numbe	r not achievir	ng response	- Venlafaxine v	s fluoxetine								
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	46/59 (78%)	50/60 (83.3%)	RR 0.94 (0.78 to 1.12)	5 fewer per 100 (from 18 fewer to 10 more)	⊕⊕⊕O MODERATE	

Numbe	r not achievin	ng remission	- Nortriptyline	vs fluoxetine				83.3%		5 fewer per 100 (from 18 fewer to 10 more)		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	12/68 (17.6%)	19/142 (13.4%)	RR 1.32 (0.68 to 2.56)	4 more per 100 (from 4 fewer to 21 more)		
								13.4%	2.30)	4 more per 100 (from 4 fewer to 21 more)		
Numbe	r not achievir	ng remission	- Fluoxetine vs	mianserin								
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	31/38 (81.6%)	22/34 (64.7%)	RR 1.26 (0.94 to	17 more per 100 (from 4 fewer to 45 more)	⊕⊕OO LOW	
								64.7%	1.69)	17 more per 100 (from 4 fewer to 45 more)		
Numbe	r not achievir	ng remission	- Venlafaxine	vs fluoxetine								
1	randomised trials		no serious inconsistency		serious ²	none	30/59 (50.8%)	41/60 (68.3%)	RR 0.74 (0.55 to 1.01)	18 fewer per 100 (from 31 fewer to 1	⊕⊕⊕O MODERATE	

			1	•	1			1		,	
										more)	
								68.3%		18 fewer per 100 (from 31 fewer to 1 more)	
Other c	omparisons:	mean endpo	oint scores (self	f-rated) - Nort	riptyline vs	fluoxetine (Bette	er indicated	by lower va	alues)		
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	68	142	-	MD 1.05 higher (1.31 lower to 3.41 higher)	⊕⊕⊕O MODERATE
Other o	comparisons:	mean endpo	oint scores (self	-rated) - Fluo	xetine vs mi	anserin (Better i	ndicated by	lower valu	es)		
1	randomised trials	no serious limitations		no serious indirectness	very serious ¹	none	38	33	-	MD 1.8 higher (1.63 lower to 5.23 higher)	⊕⊕OO LOW
Other c	comparisons:	mean endpo	pint scores (self	f-rated) - Venl	afaxine vs f	luoxetine (Better	r indicated b	y lower val	lues)		
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	59	60		MD 2.03 lower (5.22 lower to 1.16 higher)	⊕⊕OO LOW
Other c	comparisons:	number leav	ving treatment	early for any	reason - No	rtriptyline vs fluc	oxetine				

			inconsistency				(11.8%)	19.7%)	(0.29 to 1.24)	100 (from 14 fewer to 5 more) 8 fewer per 100 (from 14 fewer to 5 more)	LOW	
Other co	omparisons:	number leav	ing treatment	early for any	reason - Ver	nlafaxine versus	fluoxetine					
	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	15/59 (25.4%)	12/60 (20%)	RR 1.27 (0.65 to 2.48)	5 more per 100 (from 7 fewer to 30 more)	⊕⊕OO LOW	
Other	omnarisons:	number leav	ing treatment	aarly bacause	of side offe	cts - Nortriptylii	ne vs fluovet	20%	2.40)	5 more per 100 (from 7 fewer to 30 more)		
Other Co			ing treatment	earry because	or side erre	cts - North ptylli	ile vs iluoxet	ille				
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	2/68 (2.9%)	4/142 (2.8%)	RR 1.04 (0.2 to	0 more per 100 (from 2 fewer to 13 more)	⊕⊕OO LOW	
								2.9%	5.56)	0 more per 100 (from 2 fewer to 13 more)		
Other co	omparisons:	number leav	ing treatment	early because	of side effe	cts - Fluoxetine	continuation	vs mianse	erin			
	randomised trials		no serious inconsistency		very serious ¹	none	7/38 (18.4%)	12/34 (35.3%)	RR 0.52 (0.23 to	17 fewer per 100	⊕⊕OO	

									1.17)	(from 27 fewer to 6 more)	LOW
011							<u> </u>	35.3%		17 fewer per 100 (from 27 fewer to 6 more)	
Otner c	omparisons:	number leav	ing treatment	early because	e ot side ette	cts - Venlafaxin	e vs fluoxetii	1e			
1	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	1/59 (1.7%)	3/60 (5%)	RR 0.34 (0.04 to 3.17)	3 fewer per 100 (from 5 fewer to 11 more)	⊕⊕OO LOW
								5%		3 fewer per 100 (from 5 fewer to 11 more)	
Other c	omparisons:	number repo	orting side effe	cts - Nortript	yline vs fluo	etine					
1	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	58/68 (85.3%)	119/142 (83.8%)	RR 0.98 (0.87 to	2 fewer per 100 (from 11 fewer to 9 more)	⊕⊕⊕O MODERATE
								85.3%	1.11)	2 fewer per 100 (from 11 fewer to 9 more)	

¹ Single study; inconclusive effect size ² Single study

Which switching regimen is most effective – switching to single or combination drugs?

			Quality asse	ssment				Summ	ary of fin	dings		
							No. of pat	ients	Ef	fect		=
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Switching: switching to single or combination drugs	Control	Relative (95% CI)	Absolute	Quality	Importance
Switch	to venlafaxin	e vs switch	to another ant	idepressant (efficacy) - No	on-response		-				
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	157/255 (61.6%)	173/264 (65.5%) 67.4%	RR 0.91 (0.73 to 1.14)	6 fewer per 100 (from 18 fewer to 9 more) 6 fewer per 100 (from 18 fewer to 9	⊕⊕OO LOW	
Switch	to venlafaxin	e vs switch	to another ant	idepressant (efficacy) - No	on-remission				more)		
2	randomised	no serious	serious ¹	no serious	serious ²	none	133/255	144/264	RR 0.91	5 fewer	⊕⊕ОО	

	1	ı	1	1	ı	T		Ι	I .		I I	
	trials	limitations		indirectness			(52.2%)	(54.5%)	(0.67 to	per 100	LOW	
									1.24)	(from 18		
										fewer to		
										13 more)		
										6 fewer		
										per 100		
								64.2%		(from 21		
										fewer to		
										15 more)		
Switch 1	to venlafaxin	e vs switch	to another ant	idepressant (efficacy) - ve	rsus SSRI (Bette	r indicated by lo	ower valu	es)			
2	randomised	no serious	no serious	no serious	serious ²	none				MD 0.5		
	trials	limitations	inconsistency	indirectness						lower		
										(2.09	⊕⊕⊕О	
							194	202	-	•	MODERATE	
										1.09		
										higher)		
										mgner/		
Switch t	to venlafaxin	e vs switch	to another ant	idepressant (a	acceptability	/tolerability) - N	lumber reportii	ng side ef	fects			
	1	T	Ī	Ī	T	Ī		Ī			T	
	randomised	no serious	no serious	no serious	no serious	none				3 fewer		
	trials	limitations	inconsistency	indirectness	imprecision			169/266		per 100		
								(63.5%)		(from 11		
								(03.370)	RR 0.95	fewer to 6		
							157/260		(0.83 to	more)	$\oplus \oplus \oplus \oplus$	
							(60.4%)		1.09)		HIGH	
									1.00,	3 fewer		
										per 100		
								63.7%		(from 11		
										fewer to 6		
						(0.1.1.1111				more)		
Switch	to venlafaxin	e vs switch	to another ant	idepressant (a	acceptability	/tolerability) - L	eaving treatme	nt early f	or any rea	ason		

2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	58/261 (22.2%)	50/268 (18.7%)		4 more per 100 (from 3 fewer to 13 more) 3 more per 100 (from 2 fewer to	⊕⊕OO LOW	
Switch	to venlafaxin	e vs switch	to another ant	 idepressant (a	acceptabilit	y/tolerability)	- Leaving treatme	nt early o	lue to side	11 more) e effects		
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	16/261 (6.1%)	14/268 (5.2%)	(0.58 to	1 more per 100 (from 2 fewer to 7 more)	⊕⊕OO LOW	
								5.1%		1 more per 100 (from 2 fewer to 7 more)		
Switch	to augmenta	tion strateg	y vs switch to s	single drug: et	ficacy outco	omes - Fluoxeti	ne + olanzapine v	s fluoxet	ine - non-	response		
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	183/389 (47%)	82/202 (40.6%)	RR 0.88 (0.74 to	5 fewer per 100 (from 11 fewer to 2 more)	⊕⊕⊕O MODERATE	
								48.6%	1.05)	6 fewer per 100 (from 13		

	randomised trials	no serious limitations	serious ¹	no serious indirectness	very serious ²	none	209/389 (53.7%)	69/202 (34.2%)	RR 1 (0.69 to 1.47)	0 fewer per 100 (from 11 fewer to 16 more)	⊕OOO VERY LOW	
Switch t	to augmenta	tion strategy	vs switch to s	ingle drug: ef	ficacy outco	mes - Fluoxetine	e + olanzapine v	48.4%	ine (Bette	0 fewer per 100 (from 15 fewer to 23 more)	by lower va	lues)
	io auginienta	51. 4106	, 15 51111011 10 5		neacy cutes	mes Huonetine	. · Oldillapilla i	J 1140XCC	(20110		2 , 1011C1 14	
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	389	202	-	MD 1.13 lower (3.22 lower to 0.97 higher)	⊕⊕OO LOW	
Switch t	to augmenta	tion strategy	y vs switch to s	ingle drug: ac	ceptability/	tolerability - Flu	oxetine + olanza	apine vs f	luoxetine	- leaving tr	eatment ea	rly for any
reason												
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	90/389 (23.1%)	40/202 (19.8%)	RR 1.12 (0.79 to	2 more per 100 (from 4 fewer to 12 more)	⊕⊕OO LOW	
S						tolerability - Flu		19.9%		2 more per 100 (from 4 fewer to 12 more)		de des A

	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	39/389 (10%)	7/202 (3.5%)	RR 2.41 (1.07 to 5.43)	5 more per 100 (from 0 more to 15 more)	⊕⊕⊕⊕ HIGH
	to augmenta	tion strateg	y ve switch to s	ingle drug: 20	contability/	rolorability - Elu	oxetine + olanz	3.9%	·	5 more per 100 (from 0 more to 17 more)	aporting sid
MAITCH		tion strateg	y vs switch to s	illigie ulug. at	ceptability,	cole ability - i lu	OXECUTE I CIAITZ	apilie vs i	IUOXELIIIE	- mannber i	epoi tilig sid
witch	_	no comiques	no sorious	no corious	corious ³	lnana			T	4 more real	
l	randomised		no serious inconsistency		serious ³	none	129/146 (88.4%)	119/142 (83.8%)		4 more per 100 (from 3 fewer to 13 more)	⊕⊕⊕O MODERATE

Should SSRIs or TCAs be used as first- or second-line treatment?

			Quality asses	ssment				Summ	ary of fin	dings		
			4,				No. of patie	ents	Ef	fect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Switching: switching to single drug (randomised first-step drug)	Control	Relative (95% CI)	Absolute	Quality	Importance
Switchi	ng strategies	: Number of	people not acl	nieving at leas	st 50% reduc	ction in depressi	ion score - Sertra	line to i	mipramin	e vs imiprar	mine to sert	raline
	randomised trials		no serious inconsistency		very serious ¹	none	65/117 (55.6%)	21/51 (41.2%)	RR 1.35 (0.94 to 1.95)	14 more per 100 (from 2 fewer to 39 more)	⊕⊕OO LOW	
								41.2%	1.55)	14 more per 100 (from 2 fewer to 39 more)		
Switchi	ng strategies	: Mean endp	ooint scores - S	ertraline to ir	nipramine v	s imipramine to	sertraline (Bette	er indica	ted by lov	ver values)		
	randomised trials		no serious inconsistency		very serious ¹	none	117	50	-	MD 2.5 higher (0.38 lower to 5.38 higher)	⊕⊕OO LOW	

<u> </u>	1	1	2	T					
randomised I trials	no serious inconsistency	no serious indirectness	serious [*]	none		5/51 (9.8%)	IXIX 2.33	15 more per 100 (from 0 more to 51	⊕⊕⊕О
					29/117 (24.8%)	9.8%	(1.04 to 6.16)	15 more per 100 (from 0	MODERATE

Single study; inconclusive effect size Single study

Is augmenting existing antidepressant treatment with another antidepressant effective for depression that has not adequately responded to treatment?

			Quality assess	sment				Summary o	of findings			
							No. of p	atients	Ef	fect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Antidepressant +Antidepressant	Antidepressant + (placebo or nothing)	Relative (95% CI)	Absolute	Quality	
Numbe	r not achievin	g response -	SSRIs + Mianser	in	!							
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	49/141 (34.8%)	65/149 (43.6%)	RR 0.71 (0.44 to 1.17)	13 fewer per 100 (from 24 fewer to 7 more)	⊕⊕OO LOW	
								63.2%	1.17)	18 fewer per 100 (from 35 fewer to 11 more)		
Numbe	er not achiev	ing respons	e - Sertraline -	+ mianserin v	s high dose	sertraline + p	lacebo					
	randomised trials		no serious inconsistency		serious ³	none	32/98 (32.7%)	45/98 (45.9%)	RR 0.71 (0.5 to 1.02)	13 fewer per 100 (from 23 fewer to 1 more)	⊕⊕⊕O MODERATE	
								45.9%		13 fewer per 100 (from 23		

										fewer to		
										1 more)		
Numb	er not achiev	ing respons	se - Antidepres	ssants + Mirta	azapine							
L	randomised trials		no serious inconsistency		serious ³	none				44 fewer per 100		
							4/11 (36.4%)	12/15 (80%)	RR 0.45 (0.2 to 1.03)	2 11101 ()	⊕⊕⊕O MODERATE	
								80%	1.03)			
lumb	er not achiev	ing remission	on - SSRIs + Mi	anserin								
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	73/130 (56.2%)	93/137 (67.9%)	RR 0.81 (0.62 to	13 fewer per 100 (from 26 fewer to 3 more)	⊕⊕OO LOW	
			serious ¹		serious ²	none	73/130 (56.2%)	-		per 100 (from 26 fewer to		
:	trials	limitations	serious ¹	indirectness		none	73/130 (56.2%)	(67.9%)	(0.62 to	per 100 (from 26 fewer to 3 more) 14 fewer per 100 (from 27 fewer to		

										10 more)		
								86.7%		32 fewer per 100 (from 56 fewer to 10 more)		
Numb	er not achiev	ing remission	on - Sertraline	+ mianserin \	vs high dos	e sertraline + p	olacebo					
1	randomised trials		no serious inconsistency		serious ³	none	55/98 (56.1%)	70/98 (71.4%)	RR 0.79 (0.63 to 0.97)	15 fewer per 100 (from 2 fewer to 26 fewer)	⊕⊕⊕O MODERATE	
Numb	ar not achiou	ing rominal	on Eluovetine	. docinyomi	no ve high	dose fluoxetin		71.4%	·	15 fewer per 100 (from 2 fewer to 26 fewer)		
Numbe	er not acmev	ing remissio	on - Fluoxetine			uose nuoxenn	e -	<u>, </u>			<u>, </u>	
2	randomised trials		no serious inconsistency		serious ²	none	33/46 (71.7%)	26/48 (54.2%)	RR 1.32 (0.96 to 1.81)	17 more per 100 (from 2 fewer to 44 more)	⊕⊕⊕O MODERATE	
								52.1%		17 more per 100 (from 2 fewer to 42 more)		

Mean	endpoint or	change scor	es - SSRIs + Mi	ianserin (Bett	ter indicat	ed by lower va	lues)		
		and and a		(200					
3	randomised trials	no serious limitations		no serious indirectness	serious ²	none	141	147	SMD 0.46 lower (1.07 ⊕⊕OO lower to LOW 0.15 higher)
Mean	endpoint or	change scor	es - Fluoxetine	e + desiprami	ne vs high	dose fluoxetin	e (Better indicate	ed by lower val	ues)
2	randomised trials	no serious limitations		no serious indirectness	serious ²	none	46	48	SMD 0.67 higher - (0.05 to 1.28 higher) ⊕⊕OO LOW
Mean	endpoint or	change scor	es - Antidepre	ssants + Mirt	azapine (E	Better indicated	d by lower values)	
1	randomised trials		no serious inconsistency		serious ³	none	11	15	SMD 0.83 lower - (1.64 to 0.01 lower) ⊕⊕⊕O MODERATE
Mean	endpoint or	change scor	es - Amitripty	line + Moclob	emide (Be	etter indicated	by lower values)		
1	randomised trials		no serious inconsistency		serious ³	none	20	19	SMD 0.63 lower (1.28 ⊕⊕⊕O lower to MODERATE 0.01 higher)

					. 3					CA 4D 0 22	
	randomised trials		no serious inconsistency		serious ³	none	70	71	-	SMD 0.23 lower (0.56 lower to 0.1 higher)	⊕⊕⊕O MODERATE
ing	the study e	arly - SSRIs	+ Mianserin								
l	randomised crials		no serious inconsistency		very serious ²	none	23/130 (17.7%)	17/137 (12.4%)	RR 1.44 (0.81 to	5 more per 100 (from 2 fewer to 20 more)	⊕⊕OO LOW
								14.3%	2.36)	6 more per 100 (from 3 fewer to 23 more)	
ving	the study e	arly - Fluox	etine + desipra	amine vs high	dose fluo	exetine					
	randomised trials		no serious inconsistency		very serious ²	none	8/46 (17.4%)	5/48 (10.4%)	RR 1.71 (0.61 to 4.83)	7 more per 100 (from 4 fewer to 40 more)	⊕⊕OO LOW
								11.2%	4.63)	8 more per 100 (from 4 fewer to 43 more)	

.eavin	g the study e	arly - Antid	epressants + N	/lirtazapine								
		limitations	inconsistency		very serious ⁴	none	1/11 (9.1%)	2/15 (13.3%)	RR 0.68 (0.07 to 6.61)	4 fewer per 100 (from 12 fewer to 75 more)	⊕⊕OO LOW	
								13.3%		4 fewer per 100 (from 12 fewer to 75 more)		
eavin	g the study e	ariy - Antio	epressant + bu	ispirone								
-	randomised trials		no serious inconsistency		very serious ⁴	none	7/54 (13%)	9/54 (16.7%)	RR 0.78 (0.31 to – 1.94)		LOW	
								16.7%		4 fewer per 100 (from 12 fewer to 16 more)		
eavin	g the study e	early - Sertra	aline + mianse	rin vs high do	ose sertralii	ne + placebo						
	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	none	17/98 (17.3%)	15/98 (15.3%)	RR 1.13 (0.6 to 2.14)	2 more per 100 (from 6 fewer to 17 more)	⊕⊕OO LOW	
								15.3%		2 more		

Leaving the study early - Antidepressant + atomoxetine 1 randomised no serious limitations inconsistency indirectness serious 13/72 (18.1%) 13/72 (18.1%) 13/72 (18.1%) 13/74 (17.6%) RR 1.03 (0.51 to 19 more) 100 (from 9 fewer to 19 more) 100	
Leaving the study early - Antidepressant + atomoxetine Transport Transpo	
Leaving the study early - Antidepressant + atomoxetine 1 randomised no serious limitations inconsistency indirectness serious trials limitations inconsistency indirectness serious and the study early due to side effects - SSRIs + Mianserin 2 randomised no serious limitations inconsistency indirectness serious and serious are serious are serious and serious are serious are serious and serious are serious and serious are serious and serious are serio	
Leaving the study early - Antidepressant + atomoxetine 1 randomised trials limitations inconsistency indirectness limitations limit	
1 randomised no serious limitations inconsistency indirectness limitations inconsistency indirectness limitations inconsistency limitations inconsistency limitations inconsistency limitations inconsistency limitations	
trials limitations inconsistency indirectness serious ⁴ 13/72 (18.1%) 13/74 (17.6%) RR 1.03 (0.51 to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 2 more per 100 (from 2 fewer to 13 more) 3.96) 1 more per 100 (from 2 fewer to 13 more) 1 more per 100 (from 2 fewer to 13 more) 1 more per 100 (from 2 fewer to 13 more) 1 more per 100 (from 2 fewer to 13 more) 1 more per 100 (from 2 fewer to 13 more)	
13/72 (18.1%) 13/74 (17.6%) (from 9 fewer to 19 more) 13/72 (18.1%) 13/74 (17.6%) (from 9 fewer to 19 more) 17.6% 17.6% 17.6% 1 more per 100 (from 9 fewer to 19 more) 19 more) 19 more) 19 more 19 mo	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious trials no serious limitations inconsistency indirectness rejous 4 none fewer to 19 more) serious 4 no serious 13/74 (17.6%) RR 1.03 (19 more) 19 more) 13/74 (17.6%) RR 1.03 (19 more) 19 more) 10/10 (19 more) 10/10	
13/72 (18.1%) 13/72 (18.1%) RR 1.03 fewer to 19 more) 17.6% 1 more per 100 (from 9 fewer to 19 more)	
13/72 (18.1%) 13/72 (18.1%) 13/72 (18.1%) 19 more) 10 more per 100 (from 9) fewer to 19 more) 1 more per 100 (from 9) fewer to 19 more) 1 more per 100 (from 9) fewer to 19 more) 1 more per 100 (from 9) fewer to 19 more) 1 more per 100 (from 2) fewer to 13/72 (18.1%) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) 1 more per 100 (from 2) fewer to 13 more) LOW	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious trials limitations inconsistency indirectness serious 13/72 (18.1%) 1 more per 100 (from 9 fewer to 19 more) 1 more per 100 (from 9 fewer to 19 more) 2 more per 100 (from 2 fewer to 13 more) 1 more per 100 (from 2 fewer to 13 m	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious trials limitations inconsistency indirectness serious 9/130 (6.9%) 17.6% 17.6% 17.6% 17.6% 2 more per 100 (from 9 fewer to 19 more) 18. Compared the study early due to side effects - SSRIs + Mianserin 2 more per 100 (from 2 fewer to 13 more) 19/130 (6.9%) 17.6% 18. Compared to 13 more per 100 (from 2 fewer to 13 more) 18. Compared to 19. Compar	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious trials limitations inconsistency indirectness serious and serious inconsistency indirectness serious and serious indirectness serious and serious indirectness serious and serious an	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious trials limitations inconsistency indirectness serious 9/130 (6.9%) 8 pylanore fewer to 19 more) 2 more per 100 (from 2 fewer to 13 more) 9/130 (6.9%) 9/130 (6.9%)	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious limitations inconsistency indirectness serious of trials limitations inconsistency indirectness serious of the study early due to side effects - SSRIs + Mianserin 2 more per 100 (from 2 fewer to 13 more) of the study early due to side effects - SSRIs + Mianserin 2 more per 100 (from 2 fewer to 13 more) of the study early due to side effects - SSRIs + Mianserin	
Leaving the study early due to side effects - SSRIs + Mianserin 2 randomised no serious limitations inconsistency indirectness rerious indirectness 9/130 (6.9%) 9/130	
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trials limitations inconsistency indirectness serious ⁴ 9/130 (6.9%) 6/137 (4.4%) per 100 (from 2 fewer to 13 more) 13.96) 15.00	
9/130 (6.9%) 6/137 (4.4%) (from 2 fewer to 13 more) (0.58 to 3.96) (O.58 to 10 home)	
9/130 (6.9%) RR 1.52 fewer to 13 more)	
9/130 (6.9%)	
9/130 (6.9%)	
3,150 (0.576) (0.56 to 3.96) LOW	
3.50) 2 more	
per 100	
3% (from 1	
fewer to	
9 more)	
Leaving the study early due to side effects - Fluoxetine + desipramine vs high dose fluoxetine	
1 randomised no serious no serious no serious very none 0 more 0 more 0 more	
trials limitations inconsistency indirectness serious ⁴ 2/12 (16.7%) 0/15 (0%) ^{KR 6.15} per 100 LOW	•
(0.32 to from 0	

Leavinį	g the study e	arly due to	side effects - A	Antidepressa	nt + atomo	xetine		0%	117.21)	fewer to 0 more) 0 more per 100 (from 0 fewer to 0 more)		
	randomised trials		no serious inconsistency		very serious ⁴	none	7/72 (9.7%)	4/74 (5.4%)	RR 1.8 (0.55 to 5.88)	4 more per 100 (from 2 fewer to 26 more)	⊕⊕OO LOW	
Patient	ts reporting	side offects	- SSRIs + Mian	sarin				5.4%		4 more per 100 (from 2 fewer to 26 more)		
					2	I						
	randomised trials		no serious inconsistency		serious ³	none	75/98 (76.5%)	45/99 (45.5%)	RR 1.68 (1.32 to 2.14)	31 more per 100 (from 15 more to 52 more)	⊕⊕⊕O MODERATE	
								45.5%	2.14)	31 more per 100 (from 15 more to 52 more)		

75/98 (76.5%) (1.13 to 35 more) MODER 21 more per 100	randonnsed	nised no serious	no serious	no serious	serious ²	none				21 more		
21 more per 100	trials	limitation	inconsistency	indirectness			75/98 (76.5%)		(1.13 to	(from 7 more to 39 more)	⊕⊕⊕O MODERATE	
more to								55.1%	1.71)	per 100 (from 7		

¹ Significant heterogeneity - random effects model used
² Inconclusive effect size
³ Single study
⁴ Single study; inconclusive effect size

Is augmenting existing antidepressant treatment with an antipsychotic effective for depression that has not adequately responded to treatment?

			Quality asses	ssment				Summary	of finding	S		
							No. of p	patients	E	ffect		Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Antidepressant + Antipsychotic	Antidepressant + (placebo or nothing)	Relative (95% CI)	Absolute	Quality	
Numbe	r not achievin	g response										
	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	557/866 (64.3%)	72.4%	RR 0.88 (0.82 to 0.95)	87 fewer per 1000 (from 36 fewer to 130 fewer)	⊕⊕⊕ HIGH	
Numbe	er not achiev	ing respons	e - Aripiprazol	e								
	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	251/372 (67.5%)	71.8%		43 fewer per 1000 (from 136 fewer to 72 more)	⊕⊕⊕O MODERATE	
Numbe	er not achiev	ing respons	e - Olanzapine									
	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious ²	none	124/210 (59%)	71.2%		135 fewer per 1000 (from 235 fewer to 0	LOW	

										more)		
Numbe	er not achiev	ing respons	e - Risperidon	e								
	randomised trials		no serious inconsistency		no serious imprecision	none	167/255 (65.5%)	75.2%	RR 0.86 (0.77 to 0.97)	105 fewer per 1000 (from 23 fewer to 173 fewer)	⊕⊕⊕⊕ HIGH	
Numbe	er not achiev	ing respons	e - Quetiapine									
	randomised trials		no serious inconsistency		very serious ³	none	15/29 (51.7%)	72.4%	RR 0.71	210 fewer per 1000 (from 384 fewer to 58 more)	⊕⊕OO LOW	
Numbe	er not achiev	ing remission	on				'	1				
	randomised trials		no serious inconsistency		no serious imprecision	none	640/857 (74.7%)	84.2%	RR 0.88 (0.84 to 0.92)	101 fewer per 1000 (from 67 fewer to 135 fewer)	⊕⊕⊕⊕ HIGH	
Numbe	er not achiev	ing remission	on - Aripiprazo	le								
	randomised trials		no serious inconsistency		no serious imprecision	none	278/372 (74.7%)	84.8%		102 fewer per 1000 (from 42 fewer to	⊕⊕⊕⊕ HIGH	

										153		
										fewer)		
Numbe	er not achiev	ing remission	on - Olanzapin	<u> </u>								
	randomised trials		no serious inconsistency		no serious imprecision	none	146/200 (73%)	83.5%	RR 0.87 (0.79 to 0.97)	109 fewer per 1000 (from 25 fewer to 175 fewer)	⊕⊕⊕⊕ HIGH	
Numbe	er not achiev	ing remission	on - Risperidor	ie								
	randomised trials		no serious inconsistency		no serious imprecision	none	196/256 (76.6%)	84%	RR 0.88 (0.81 to 0.96)	101 fewer per 1000 (from 34 fewer to 160 fewer)	⊕⊕⊕ HIGH	
Numbe	er not achiev	ing remission	on - Quetiapin	e								
	randomised trials		no serious inconsistency		serious ²	none	20/29 (69%)	82.8%	RR 0.83	141 fewer per 1000 (from 315 fewer to 99 more)	AAAO	
Mean (endpoint (Be	tter indicat	ed by lower va	ilues)								

6	randomised trials	no serious limitations	serious ²	no serious indirectness		none	568	578	-	SMD 0.45 lower (0.62 to 0.28 lower)	⊕⊕⊕O MODERATE	
Mean	endpoint - A	ripiprazole (Better indicat	ed by lower v	ralues)							
1	randomised trials		no serious inconsistency		serious ²	none	185	184	-	SMD 0.32 lower (0.53 to 0.12 lower)	⊕⊕⊕O MODERATE	
Mean e	endpoint - O	lanzapine (I	Better indicate	d by lower va	alues)							
2	randomised trials	no serious limitations	serious ³	no serious indirectness	serious ²	none	198	203	-	SMD 0.35 lower (0.77 lower to 0.07 higher)	⊕⊕OO LOW	
Mean	endpoint - Ri	speridone (Better indicate	ed by lower v	alues)							
2	randomised trials		no serious inconsistency			none	156	162	-	SMD 0.56 lower (0.78 to 0.33 lower)	⊕⊕⊕⊕ HIGH	
Mean (endpoint - Q	uetiapine (E	Better indicate	d by lower va	alues)							

		limitations	no serious inconsistency ly for any reas	indirectness	serious ²	none	29	29	-	SMD 0.77 lower (1.3 to 0.23 lower)	⊕⊕⊕O MODERATE
	randomised trials		no serious inconsistency		serious ²	none	121/626 (19.3%)	18.6%		35 more per 1000 (from 13 fewer to 95 more)	⊕⊕⊕O MODERATE
Numbe	r leaving tre	atment ear	ly for any reas	on - Aripipra	zole						
	randomised trials		no serious inconsistency		very serious ²	none	22/182 (12.1%)	9.3%	2.39)	28 more per 1000 (from 27 fewer to 129 more)	⊕⊕OO LOW
Numbe	r leaving tre	atment ear	ly for any reas	on - Olanzapi	ine						
	randomised trials		no serious inconsistency		serious ²	none	53/210 (25.2%)	20.2%	(0.9 to 1.84)	59 more per 1000 (from 20 fewer to 170 more)	⊕⊕⊕O MODERATE

2	randomised trials	no serious limitations	serious ²	no serious indirectness	very serious ²	none	35/205 (17.1%)	15.1%	(0.64 to 2.29)	32 more per 1000 (from 54 fewer to 195 more)	⊕OOO VERY LOW
Numb	er leaving tre	atment ear	ly for any reas	on - Quetiap	ine		'				
1	randomised trials		no serious inconsistency		very serious ²	none	11/29 (37.9%)	48.3%	RR 0.79 (0.43 to 1.43)	101 fewer per 1000 (from 275 fewer to 208 more)	⊕⊕OO LOW
Numb	er leaving tre	atment ear	ly due to side	effects							
7	randomised trials	no serious Iimitations	serious ²	no serious indirectness	no serious imprecision	none	64/807 (7.9%)	2.3%	RR 2.43 (1.18 to 5.03)	(from 4	⊕⊕⊕O MODERATE
Numb	er leaving tre	atment ear	ly due to side	effects - Arip	iprazole						
2	randomised trials		no serious inconsistency		serious ²	none	13/373 (3.5%)	1.7%	RR 2.01 (0.76 to 5.33)	17 more per 1000 (from 4 fewer to 74 more)	⊕⊕⊕O MODERATE
Numb	er leaving tre	atment ear	ly due to side	effects - Olan	zapine						
2	randomised	no serious	no serious	no serious	no serious	none	27/200 (13.5%)	2.4%		109 more per 1000	++++

	er leaving tre	atment ear	ly due to side	effects - Risp	eridone				14.08)	(from 28 more to 314 more)	HIGH	
		limitations		indirectness	serious ²	none	16/205 (7.8%)	11.7%	RR 1.13 (0.27 to 4.74)	15 more per 1000 (from 85 fewer to 438 more)	⊕⊕OO LOW	
Numbe	er leaving tre	atment ear	ly due to side	effects - Que	tiapine							
1	randomised trials		no serious inconsistency		very serious ²	none	8/29 (27.6%)	6.9%	RR 4 (0.93 to 17.25)	207 more per 1000 (from 5 fewer to 1121 more)	⊕⊕OO LOW	
Numbe	er reporting s	side effects	- Aripiprazole									
1	randomised trials		no serious inconsistency		very serious ²	none	19/30 (63.3%)	56.7%		68 more per 1000 (from 147 fewer to 391 more)	⊕⊕OO LOW	
Numbe	er reporting s	side effects	- Risperidone									
2	randomised trials		no serious inconsistency		very serious ²	none	129/199 (64.8%)	67.9%	RR 1.11 (0.94 to	75 more per 1000 (from 41	⊕⊕OO LOW	

				1.31)	fewer to	
					210 more)	

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

Is augmenting existing antidepressant treatment with another psychotropic drug effective for depression that has not adequately responded to treatment?

			Quality asses	eemont				Sum	mary of f	indings		
			Quality asses	SSIIIEIII			No. of pat	ients	E	ffect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: AD + other psychotropic drug	AD + (placebo or nothing)	Relative (95% CI)	Absolute	Quality	Importance
Number	not achievir	ng response	 Antidpressan 	ts + lithium								
	randomised trial	no serious limitations	serious ¹	no serious indirectness	no serious imprecision ²	none	56/87 (64.4%)	68/86 (79.1%)	RR 0.83 (0.66 to 1.03)	13 fewer per 100 (from 27 fewer to 2 more)	⊕⊕⊕OMODERATE	
								81.8%	1.00)	13 fewer per 100		
Number	not achievir	ng remission	- Antidepressa	nts + lithium								
3	randomised trial	no serious limitations	serious2	no serious indirectness	serious3	none	57/107 (53.3%)	53/109 (48.6%)	RR 1.26 (0.72 to	13 more per 100 (from 14 fewer to 57 more)	⊕⊕OOLOW	
								53.3%	2.17)	13 more per 100		
Number	not achievir	ng remission	- Antidepressa	ints + atomox	etine							
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious4	none	43/72 (59.7%)	36/74 (48.6%)	RR 1.23 (0.91 to 1.66)	11 more per 100 (from -4 fewer to 32 more)	⊕⊕OOLOW	
								48.7%	1.00)	11 more per 100		
Mean en	dpoint or ch	ange scores	- Antidepressa	ants + lithium	(range of sco	ores: Better indi	cated by less)					
7	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	135	138	-	SMD - 0.32 (- 0.56 to - 0.08)	⊕⊕⊕⊕HIGH	
Mean en	dpoint or ch	ange scores	- Antidepressa	ants + atomox	cetine (range	of scores: Bette	r indicated by le	ss)			19	1

1	randomised trial	no serious limitations			very serious4	none	70	71	-	SMD - 0.23 (- 0.56 to 0.1)	⊕⊕OOLOW	
Leaving	the study ea	arly - Antide	oressants + lith	ium								
8	randomised trial	no serious limitations	ll l	no serious indirectness	no serious imprecision	none	55/178 (30.9%)	31/178 (17.4%)	RR 1.79 (1.23 to 2.6)	14 more per 100 (from 4 more to 28 more)	⊕⊕⊕⊕HIGH	
								9.8%	2.0)	7 more per 100		
Leaving	the study ea	arly - Antide _l	oressants + ato	moxetine								
1	randomised trial	no serious limitations	ll	no serious indirectness	very serious4	none	13/72 (18.1%)	13/74 (17.6%)	RR 1.03 (0.51 to 2.06)	1 more per 100 (from -9 fewer to 19 more)	⊕⊕OOLOW	
								17.6%	2.00)	0 more per 100		
Leaving	the study ea	arly due to s	ide effects - An	tidepressants	+ atomoxeti	ne						
1	randomised trial	no serious limitations	ll l		very serious4	none	7/72 (9.7%)	4/74 (5.4%)	RR 1.8 (0.55 to 5.88)	4 more per 100 (from -2 fewer to 26 more)	⊕⊕OOLOW	
								5.4%		4 more per 100		

¹ Significant heterogeneity - random effects model used ² Not needed 3 Inconclusive effect size 4 Single study; inconclusive effect size

Electroconvulsive therapy (ECT)

Is ECT effective in severe depression?

Quality assessment								Summary of findings					
Quality discission							No. of patients		Effect			Importance	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Comparisons involving ECT	Control	Relative (95% CI)	Absolute	Quality		
Low-dose bilateral ECT vs low-dose unilateral ECT - non-responders													
	randomised trials	no serious limitations		no serious indirectness	very serious ²	none	51/98 (52%)	83/119 (69.7%) 67.9%	(0.35 to 1.21)	24 fewer per 100 (from 45 fewer to 15 more) 24 fewer per 100 (from 44 fewer to 14 more)	⊕OOO VERY LOW		
Low-dose bilateral ECT vs low-dose unilateral ECT - non-remission													
	randomised trials				no serious imprecision	none	43/67 (64.2%)	46/67 (68.7%) 57.8%	RR 0.93 (0.77 to 1.14)	5 fewer per 100 (from 16 fewer to 10 more) 4 fewer per	⊕⊕⊕⊕ HIGH		

Low-do 2	randomised		unilateral - mea	n endpoint d no serious indirectness	very	none	cated by lower	r values)	-	100 (from 13 fewer to 8 more) SMD 0.46 lower (1.69 lower to 0.76 higher)	
Low-do	ose bilateral E	CT vs high-d	ose unilateral	ECT - non-res	ponders						
7	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	63/179 (35.2%)			1 fewer per 100 (from 9 fewer to 10 more)	⊕⊕⊕⊕ HIGH
								38.5%		1 fewer per 100 (from 10 fewer to 11 more)	
ow-do	ose bilateral E	CT vs high-d	ose unilateral	CT - non-ren	nission			•			
5	randomised trials		no serious no serious inconsistency indirectness	serious ²	none	62/118 (52.5%)	51/119 (42.9%)		10 more per 100 (from 1 fewer to 26 more)	⊕⊕⊕O MODERATE	
								31.8%		8 more per 100 (from 1 fewer to 19 more)	

Bilateral ECT (low dose) vs high-dose unilateral ECT - mean endpoint scores (Better indicated by lower values)												
4	randomised trials			no serious indirectness	serious ²	none	107	97	-	SMD 0.01 higher (0.27 lower to 0.29 higher)	⊕⊕⊕O MODERATE	

Significant heterogeneity - random effects model used Inconclusive effect size