National Institute for Health and Care Excellence

Consultation draft

Depression in adults: treatment and management

Appendix U2.5: Text from CG90 Appendix 16c that has been deleted

NICE Guideline

Appendices

May 2018

Disclaimer

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

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 assessment							Summary of findings				Quality	Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Placebo	Relative (95% CI)	Absolute		
Mean endpoint depression scores (Better indicated by lower values)												
22	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	1225	1220	-	SMD 0.48 lower (0.59 to 0.37 lower)	[redacted] MODERATE	
Mean endpoint depression scores - Amitriptyline (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	176	172	-	SMD 0.61 lower (0.83 to 0.4 lower)	[redacted] HIGH	
Mean endpoint depression scores - Dosulepin (Better indicated by lower values)												
1	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	194	192	-	SMD 0.49 lower (0.7 to 0.29 lower)	[redacted] MODERATE	

Mean endpoint depression scores - Imipramine (Better indicated by lower values)												
13	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	803	800	-	SMD 0.41 lower (0.54 to 0.27 lower)	[redacted] MODERATE	
Mean endpoint depression scores - Nortriptyline (Better indicated by lower values)												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	52	56	-	SMD 0.8 lower (1.37 to 0.24 lower)	[redacted] MODERATE	
Mean depression change scores (Better indicated by lower values)												
8	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 lower)	[redacted] MODERATE	
Mean depression change scores - Amitriptyline (Better indicated by lower values)												
4	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	387	404	-	SMD 0.69 lower (1.07 to 0.3 lower)	[redacted] MODERATE	
Mean depression change scores - Imipramine (Better indicated by lower values)												
4	randomised	no serious	no serious	no serious	no serious	none	289	239	-	SMD 0.21 lower (0.41	[redacted]	

	trials	limitations	inconsistency	indirectness	imprecision					to 0.01 lower)	HIGH	
Sensitivity analysis: Mean depression change scores (Better indicated by lower values)												
7	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	604	569	-	SMD 0.35 lower (0.53 to 0.18 lower)	[redacted] MODERATE	
Sensitivity analysis: Mean depression change scores - Amitriptyline (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	315	330	-	SMD 0.5 lower (0.67 to 0.34 lower)	[redacted] HIGH	
Sensitivity analysis: Mean depression change scores - Imipramine (Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	289	239	-	SMD 0.21 lower (0.41 to 0.01 lower)	[redacted] HIGH	
Number not achieving remission												
9	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	301/478 (63%)	393/476 (82.6%) 79%	RR 0.74 (0.65 to 0.84)	215 fewer per 1000 (from 132 fewer to 289 fewer) 205 fewer per 1000	[redacted] MODERATE	

										(from 126 fewer to 277 fewer)		
Number not achieving remission - Amitriptyline												
3	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	42/81 (51.9%)	59/71 (83.1%) 76.7%	RR 0.66 (0.44 to 1)	283 fewer per 1000 (from 465 fewer to 0 more) 261 fewer per 1000 (from 430 fewer to 0 more)	[redacted] MODERATE	
Number not achieving remission - Clomipramine												
1	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	9/20 (45%)	14/18 (77.8%) 77.8%	RR 0.58 (0.34 to 1)	327 fewer per 1000 (from 513 fewer to 0 more) 327 fewer per 1000 (from 513 fewer to 0 more)	[redacted] MODERATE	
Number not achieving remission - Dosulepin												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	2/17 (11.8%)	2/20 (10%)	RR 1.18 (0.18 to 7.48)	18 more per 1000 (from 82 fewer to	[redacted] MODERATE	

										648 more)		
								10%		18 more per 1000 (from 82 fewer to 648 more)		
Number not achieving remission - Imipramine												
2	randomised trials	no serious limitations	no serious inconsistency	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)	[redacted] MODERATE	
								83.1%		141 fewer per 1000 (from 75 fewer to 208 fewer)		
Number not achieving remission - Nortriptyline												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	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)	[redacted] MODERATE	
								92.4%		296 fewer per 1000 (from 111 fewer to 444 fewer)		

Number not achieving response (50% reduction in depression scores)											
35	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1041/2444 (42.6%)	1529/2419 (63.2%) 65.9%	RR 0.69 (0.64 to 0.74)	196 fewer per 1000 (from 164 fewer to 228 fewer) 204 fewer per 1000 (from 171 fewer to 237 fewer)	[redacted] HIGH
Number not achieving response (50% reduction in depression scores) - Amitriptyline											
14	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	485/1144 (42.4%)	718/1147 (62.6%) 67.3%	RR 0.69 (0.61 to 0.78)	194 fewer per 1000 (from 138 fewer to 244 fewer) 209 fewer per 1000 (from 148 fewer to 262 fewer)	[redacted] MODERATE
Number not achieving response (50% reduction in depression scores) - Dosulepin											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	94/194 (48.5%)	126/192 (65.6%) 65.6%	RR 0.74 (0.62 to 0.88)	171 fewer per 1000 (from 79 fewer to 249 fewer) 171 fewer	[redacted] HIGH

										per 1000 (from 79 fewer to 249 fewer)		
Number not achieving response (50% reduction in depression scores) - Imipramine												
20	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	462/1106 (41.8%)	685/1080 (63.4%) 65.2%	RR 0.69 (0.62 to 0.76)	197 fewer per 1000 (from 152 fewer to 241 fewer) 202 fewer per 1000 (from 156 fewer to 248 fewer)	[redacted] MODERATE	
Sensitivity analysis: Number not achieving response (50% reduction in depression scores)												
34	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1022/2372 (43.1%)	1471/2345 (62.7%) 65.8%	RR 0.7 (0.66 to 0.75)	188 fewer per 1000 (from 157 fewer to 213 fewer) 197 fewer per 1000 (from 165 fewer to 224 fewer)	[redacted] HIGH	
Sensitivity analysis: Number not achieving response (50% reduction in depression scores) - Amitriptyline												
13	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	466/1072 (43.5%)	660/1073 (61.5%)	RR 0.71 (0.65 to	178 fewer per 1000 (from 135	[redacted] HIGH	

									0.78)	fewer to 215 fewer)		
								67.3%		195 fewer per 1000 (from 148 fewer to 236 fewer)		
Sensitivity analysis: Number not achieving response (50% reduction in depression scores) - Dosulepin												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
								65.6%		171 fewer per 1000 (from 79 fewer to 249 fewer)		
Sensitivity analysis: Number not achieving response (50% reduction in depression scores) - Imipramine												
20	randomised trials	no serious limitations	serious[1]	no serious indirectness	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)	[redacted] MODERATE	
								65.2%		202 fewer per 1000 (from 156 fewer to 248 fewer)		

[1] Moderate heterogeneity

[2] Single study

[3] Large heterogeneity
[4] Inconclusive effect size
[5] Uncertain clinical importance

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

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Placebo	Relative (95% CI)	Absolute		
Number leaving treatment early for any reason												
85	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	1864/5039 (37%)	1830/4862 (37.6%)	RR 0.99 (0.92 to 1.06)	4 fewer per 1000 (from 30 fewer to 23 more)	[redacted] MODERATE	
								39%		4 fewer per 1000 (from 31 fewer to 23 more)		
Number leaving treatment early for any reason - Amitriptyline												
23	randomised trials	no serious limitations	serious[2,3]	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)	[redacted] MODERATE	
								35.7%		25 fewer per 1000		

										(from 75 fewer to 36 more)		
Number leaving treatment early for any reason - Clomipramine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	6/30 (20%)	7/28 (25%) 23.9%	RR 0.82 (0.3 to 2.19)	45 fewer per 1000 (from 175 fewer to 298 more) 43 fewer per 1000 (from 167 fewer to 284 more)	[redacted] MODERATE	
Number leaving treatment early for any reason - Dosulepin												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	96/236 (40.7%)	94/239 (39.3%) 33.3%	RR 1.09 (0.79 to 1.5)	35 more per 1000 (from 83 fewer to 197 more) 30 more per 1000 (from 70 fewer to 167 more)	[redacted] MODERATE	
Number leaving treatment early for any reason - Imipramine												
54	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	1253/3222 (38.9%)	1198/3090 (38.8%)	RR 1.01 (0.93 to	4 more per 1000 (from 27 fewer to	[redacted] MODERATE	

									1.09)	35 more)		
								41%		4 more per 1000 (from 29 fewer to 37 more)		
Number leaving treatment early for any reason - Nortriptyline												
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)	[redacted] LOW	
								42.9%		116 fewer per 1000 (from 313 fewer to 442 more)		
Number leaving treatment early due to side effects												
65	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
								4.6%		139 more per 1000 (from 113 more to 169 more)		
Number leaving treatment early due to side effects - Amitriptyline												
16	randomised	no serious	no serious	no serious	no serious	none	199/1193	40/1157	RR 4.66	127 more	[redacted]	

	trials	limitations	inconsistency	indirectness	imprecision		(16.7%)	(3.5%)	(3.38 to 6.44)	per 1000 (from 82 more to 188 more)	HIGH	
								3.2%		117 more per 1000 (from 76 more to 174 more)		
Number leaving treatment early due to side effects - Clomipramine												
1	randomised trials	no serious limitations	serious[4]	no serious indirectness	serious[1]	none	2/20 (10%)	2/18 (11.1%)	RR 0.9 (0.14 to 5.74)	11 fewer per 1000 (from 96 fewer to 527 more)	[redacted] LOW	
								11.1%		11 fewer per 1000 (from 95 fewer to 526 more)		
Number leaving treatment early due to side effects - Dosulepin												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/207 (14.5%)	10/202 (5%)	RR 2.92 (1.47 to 5.8)	95 more per 1000 (from 23 more to 238 more)	[redacted] HIGH	
								7.3%		140 more per 1000 (from 34 more to		

										350 more)		
Number leaving treatment early due to side effects - Imipramine												
44	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	534/2665 (20%)	131/2580 (5.1%) 4.7%	RR 3.91 (3.27 to 4.67)	148 more per 1000 (from 115 more to 186 more) 137 more per 1000 (from 107 more to 172 more)	[redacted] HIGH	
Number leaving treatment early due to side effects - Nortriptyline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/66 (18.2%)	1/65 (1.5%) 1.4%	RR 7.98 (1.51 to 42.09)	107 more per 1000 (from 8 more to 632 more) 98 more per 1000 (from 7 more to 575 more)	[redacted] HIGH	
Number reporting side effects												
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	[redacted] MODERATE	

										317 more)		
								60%		240 more per 1000 (from 150 more to 336 more)		
Number reporting side effects - Amitriptyline												
7	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)	[redacted] MODERATE	
								48.4%		213 more per 1000 (from 73 more to 382 more)		
Number reporting side effects - Clomipramine												
1	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)	[redacted] LOW	
								50%		300 more per 1000 (from 100 fewer to 1100 more)		
Number reporting side effects - Dosulepin												

1	randomised trials	no serious limitations	serious[4]	no serious indirectness	no serious imprecision	none	14/25 (56%)	5/27 (18.5%)	RR 3.02 (1.27 to 7.18)	374 more per 1000 (from 50 more to 1144 more)	[redacted] MODERATE	
								18.5%		374 more per 1000 (from 50 more to 1143 more)		
Number reporting side effects - Imipramine												
20	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	1304/1757 (74.2%)	959/1657 (57.9%)	RR 1.39 (1.21 to 1.59)	226 more per 1000 (from 122 more to 341 more)	[redacted] MODERATE	
								63.3%		247 more per 1000 (from 133 more to 373 more)		
Number reporting side effects - Nortriptyline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
								80.7%		145 more per 1000 (from 24		

										more to 274 more)		

[1] Inconclusive effect size
[2] Large heterogeneity
[3] Moderate heterogeneity
[4] Single study

Escitalopram

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

Quality assessment							Summary of findings				Quality	Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Placebo	Relative (95% CI)	Absolute		
Non-response - ordered by baseline severity												
11	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	936/1881 (49.8%)	971/1614 (60.2%)	RR 0.81 (0.75 to 0.88)	114 fewer per 1000 (from 72 fewer to 150 fewer)	MODERATE	CRITICAL
								58.5%		111 fewer per 1000 (from 70 fewer to 146 fewer)		
Non-response - Escitalopram 10mg												
4	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)	99 fewer per 1000 (from 12 fewer to 173 fewer)	MODERATE	CRITICAL
								63.4%		101 fewer per 1000		

										(from 13 fewer to 178 fewer)		
Non-response - Escitalopram 20mg												
1	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	62/125 (49.6%)	89/122 (73%) 73%	RR 0.68 (0.55 to 0.84)	233 fewer per 1000 (from 117 fewer to 328 fewer) 234 fewer per 1000 (from 117 fewer to 329 fewer)	[redacted] MODERATE	CRITICAL
Non-remission - vs Placebo												
9	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	921/1508 (61.1%)	935/1363 (68.6%) 71.1%	RR 0.88 (0.82 to 0.94)	82 fewer per 1000 (from 41 fewer to 123 fewer) 85 fewer per 1000 (from 43 fewer to 128 fewer)	[redacted] MODERATE	CRITICAL
Non-remission - Escitalopram 10mg vs Placebo												
3	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	397/639 (62.1%)	331/506 (65.4%)	RR 0.92 (0.81 to	52 fewer per 1000 (from 124	[redacted] MODERATE	CRITICAL

									1.06)	fewer to 39 more)		
								66.1%		53 fewer per 1000 (from 126 fewer to 40 more)		
Mean endpoint depression scores (clinician-rated) - vs Placebo (better indicated by lower scores) (Better indicated by lower values)												
6	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	903	918	-	SMD 0.24 lower (0.35 to 0.13 lower)	[redacted] MODERATE	CRITICAL
Mean endpoint depression scores (clinician-rated) - Escitalopram 10mg vs Placebo (Better indicated by lower values)												
3	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	strong association[4]	476	488	-	SMD 0.23 lower (0.46 to 0.01 lower)	[redacted] HIGH	CRITICAL
Mean endpoint depression scores (clinician-rated) - Escitalopram 20mg vs Placebo (Better indicated by lower values)												
1	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	123	119	-	SMD 0.46 lower (0.71 to 0.2 lower)	[redacted] MODERATE	CRITICAL
Mean endpoint depression scores (clinician-rated) - vs Placebo (Better indicated by lower values)												
10	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1533	1397	-	SMD 0.26 lower (0.34 to 0.19	[redacted] HIGH	CRITICAL

										lower)		
Mean change depression scores (clinician-rated) - Escitalopram 10mg vs Placebo (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[5]	none	580	445	-	SMD 0.28 lower (0.41 to 0.15 lower)	[redacted] MODERATE	CRITICAL
Mean change depression scores (clinician-rated) - Escitalopram 20mg vs Placebo (Better indicated by lower values)												
1	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	123	119	-	SMD 0.48 lower (0.74 to 0.22 lower)	[redacted] MODERATE	CRITICAL
Leaving treatment early for any reason - vs Placebo												
11	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	413/1881 (22%)	309/1614 (19.1%) 19.3%	RR 1.11 (0.95 to 1.29)	21 more per 1000 (from 10 fewer to 56 more) 21 more per 1000 (from 10 fewer to 56 more)	[redacted] HIGH	CRITICAL
Leaving treatment early for any reason - Escitalopram 10mg vs Placebo												
4	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	[redacted] LOW	CRITICAL

									1.3)	fewer to 57 more)		
								20%		2 fewer per 1000 (from 50 fewer to 60 more)		
Leaving treatment early for any reason - Escitalopram 20mg vs Placebo												
1	randomised trials	no serious limitations	serious[3]	no serious indirectness	serious[6]	none	36/125 (28.8%)	30/122 (24.6%)	RR 1.17 (0.77 to 1.77)	42 more per 1000 (from 57 fewer to 189 more)	LOW	CRITICAL
								24.6%		42 more per 1000 (from 57 fewer to 189 more)		
Leaving treatment early due to side effects - vs Placebo												
11	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	117/1855 (6.3%)	51/1601 (3.2%)	RR 1.8 (1.18 to 2.73)	25 more per 1000 (from 6 more to 55 more)	MODERATE	CRITICAL
								3%		24 more per 1000 (from 5 more to 52 more)		

Leaving treatment early due to side effects - Escitalopram 10mg vs Placebo												
4	randomised trials	no serious limitations	serious[2]	no serious indirectness	serious[6]	none	45/758 (5.9%)	18/628 (2.9%) 2.6%	RR 2.02 (0.9 to 4.54)	29 more per 1000 (from 3 fewer to 101 more) 27 more per 1000 (from 3 fewer to 92 more)	LOW	CRITICAL
Leaving treatment early due to side effects - Escitalopram 20mg vs Placebo												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[7]	none	13/125 (10.4%)	3/122 (2.5%) 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 more to 337 more)	MODERATE	CRITICAL
Patients reporting side 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%) 66.5%	RR 1.09 (1.04 to 1.15)	58 more per 1000 (from 26 more to 97 more) 60 more	HIGH	CRITICAL

										per 1000 (from 27 more to 100 more)		
Patients reporting side effects - Escitalopram 10mg vs Placebo												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	295/483 (61.1%)	288/491 (58.7%) 56.1%	RR 1.04 (0.94 to 1.15)	23 more per 1000 (from 35 fewer to 88 more) 22 more per 1000 (from 34 fewer to 84 more)	[redacted] HIGH	CRITICAL
Patients reporting side effects - Escitalopram 20mg vs Placebo												
1	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	none	107/125 (85.6%)	86/122 (70.5%) 70.5%	RR 1.21 (1.06 to 1.39)	148 more per 1000 (from 42 more to 275 more) 148 more per 1000 (from 42 more to 275 more)	[redacted] MODERATE	CRITICAL

[1] Moderate heterogeneity
[2] Large heterogeneity
[3] Single study
[4] Large studies
[5] Unclear clinical importance

[6] Inconclusive effect size
[7] Large confidence interval

Is escitalopram more effective than other antidepressants in depression?

Quality assessment							Summary of findings				Quality	Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	All other ADs	Relative (95% CI)	Absolute		
Non-response - vs other AD												
20	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	CRITICAL
								40.2%		44 fewer per 1000 (from 20 fewer to 64 fewer)		
Non-response - vs other AD (sensitivity analysis)												
19	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	CRITICAL
								41.3%		41 fewer		

										per 1000 (from 17 fewer to 62 fewer)		
Non-remission - vs other AD												
18	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	1220/2717 (44.9%)	1346/2708 (49.7%) 52.5%	RR 0.9 (0.85 to 0.95)	50 fewer per 1000 (from 25 fewer to 75 fewer) 53 fewer per 1000 (from 26 fewer to 79 fewer)	[redacted] MODERATE	CRITICAL
Non-remission - vs other AD (sensitivity analysis)												
17	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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 fewer to 66 fewer)	[redacted] HIGH	CRITICAL
Mean endpoint depression scores (clinician-rated) - vs other AD (Better indicated by lower values)												
11	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1506	1503	-	SMD 0.1 lower (0.17 to	[redacted] HIGH	CRITICAL

										0.02 lower)		
Mean change depression scores (clinician-rated) - vs other AD (Better indicated by lower values)												
19	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2586	2572	-	SMD 0.07 lower (0.12 to 0.02 lower)	[redacted] HIGH	CRITICAL
Leaving treatment early for any reason - vs other AD												
21	randomised trials	no serious limitations	serious[2]	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)	[redacted] MODERATE	CRITICAL
								23.2%		35 fewer per 1000 (from 5 fewer to 60 fewer)		
Leaving treatment early due to side effects - vs other AD												
20	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	CRITICAL
								7.7%		28 fewer per 1000		

										(from 17 fewer to 36 fewer)		
Number reporting side effects - vs other AD												
17	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1550/2425 (63.9%)	1555/2414 (64.4%) 71.4%	RR 0.94 (0.91 to 0.98)	39 fewer per 1000 (from 13 fewer to 58 fewer) 43 fewer per 1000 (from 14 fewer to 64 fewer)	[redacted] HIGH	CRITICAL

[1] Large heterogeneity

[2] Moderate heterogeneity

Is escitalopram more effective than SSRIs in depression?

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	SSRIs	Relative (95% CI)	Absolute		
Non-response (vs SSRIs) - SSRI Citalopram												

6	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	346/955 (36.2%)	361/858 (42.1%) 46.9%	RR 0.82 (0.73 to 0.92)	76 fewer per 1000 (from 34 fewer to 114 fewer) 84 fewer per 1000 (from 38 fewer to 127 fewer)	[redacted] MODERATE	CRITICAL
Non-response (vs SSRIs) - SSRI Fluoxetine												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	159/399 (39.8%)	166/384 (43.2%) 35.9%	RR 0.92 (0.78 to 1.08)	35 fewer per 1000 (from 95 fewer to 35 more) 29 fewer per 1000 (from 79 fewer to 29 more)	[redacted] MODERATE	CRITICAL
Non-response (vs SSRIs) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	87/243 (35.8%)	87/246 (35.4%) 34.8%	RR 1.01 (0.8 to 1.28)	4 more per 1000 (from 71 fewer to 99 more) 3 more per 1000 (from 70	[redacted] MODERATE	CRITICAL

										fewer to 97 more)		
Non-response (vs SSRIs) - SSRI Paroxetine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	99/398 (24.9%)	104/386 (26.9%) 27.4%	RR 0.92 (0.73 to 1.17)	22 fewer per 1000 (from 73 fewer to 46 more) 22 fewer per 1000 (from 74 fewer to 47 more)	[redacted] MODERATE	CRITICAL
Non-response (sensitivity analysis)												
12	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	685/1886 (36.3%)	698/1764 (39.6%) 37.5%	RR 0.89 (0.82 to 0.97)	44 fewer per 1000 (from 12 fewer to 71 fewer) 41 fewer per 1000 (from 11 fewer to 68 fewer)	[redacted] HIGH	CRITICAL
Non-response (sensitivity analysis) - SSRI Citalopram												
5	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	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 fewer to	[redacted] HIGH	CRITICAL

										109 fewer)		
								50.9%		76 fewer per 1000 (from 25 fewer to 122 fewer)		
Non-response (sensitivity analysis) - SSRI Fluoxetine												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	[redacted] HIGH	CRITICAL
								35.9%		29 fewer per 1000 (from 79 fewer to 29 more)		
Non-response (sensitivity analysis) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	[redacted] HIGH	CRITICAL
								34.8%		3 more per 1000 (from 70 fewer to 97 more)		
Non-response (sensitivity analysis) - SSRI Paroxetine												

2	randomised trials	no serious limitations	serious[4]	no serious indirectness	serious[2]	none	99/398 (24.9%)	104/386 (26.9%) 27.4%	RR 0.92 (0.73 to 1.17)	22 fewer per 1000 (from 73 fewer to 46 more) 22 fewer per 1000 (from 74 fewer to 47 more)	[redacted] LOW	CRITICAL
Number not achieving remission at endpoint (vs SSRIs)												
11	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	642/1622 (39.6%)	753/1621 (46.5%) 42.6%	RR 0.85 (0.79 to 0.92)	70 fewer per 1000 (from 37 fewer to 98 fewer) 64 fewer per 1000 (from 34 fewer to 89 fewer)	[redacted] MODERATE	CRITICAL
Number not achieving remission at endpoint (vs SSRIs) - SSRI Citalopram												
4	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	206/582 (35.4%)	303/605 (50.1%) 54.9%	RR 0.71 (0.62 to 0.81)	145 fewer per 1000 (from 95 fewer to 190 fewer) 159 fewer per 1000 (from 104	[redacted] MODERATE	CRITICAL

										fewer to 209 fewer)		
Number not achieving remission at endpoint (vs SSRIs) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	123/243 (50.6%)	122/246 (49.6%) 48.8%	RR 1.02 (0.86 to 1.22)	10 more per 1000 (from 69 fewer to 109 more) 10 more per 1000 (from 68 fewer to 107 more)	[redacted] MODERATE	CRITICAL
Number not achieving remission at endpoint (vs SSRIs) - SSRI Fluoxetine												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	179/399 (44.9%)	187/384 (48.7%) 40.8%	RR 0.92 (0.8 to 1.06)	39 fewer per 1000 (from 97 fewer to 29 more) 33 fewer per 1000 (from 82 fewer to 24 more)	[redacted] MODERATE	CRITICAL
Number not achieving remission at endpoint (vs SSRIs) - SSRI 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)	29 fewer per 1000 (from 88 fewer to	[redacted] LOW	CRITICAL

										40 more)		
								37%		30 fewer per 1000 (from 89 fewer to 41 more)		
Number not achieving remission at endpoint (vs SSRIs) (sensitivity analysis)												
10	randomised trials	no serious limitations	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)	[redacted] HIGH	CRITICAL
								41.7%		42 fewer per 1000 (from 8 fewer to 71 fewer)		
Number not achieving remission at endpoint (vs SSRIs) (sensitivity analysis) - SSRI Citalopram												
3	randomised trials	no serious limitations	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)	[redacted] HIGH	CRITICAL
								59.9%		108 fewer per 1000 (from 36 fewer to 168 fewer)		
Number not achieving remission at endpoint (vs SSRIs) (sensitivity analysis) - SSRI Sertraline												

2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	123/243 (50.6%)	122/246 (49.6%) 48.8%	RR 1.02 (0.86 to 1.22)	10 more per 1000 (from 69 fewer to 109 more) 10 more per 1000 (from 68 fewer to 107 more)	[redacted] HIGH	CRITICAL
Number not achieving remission at endpoint (vs SSRIs) (sensitivity analysis) - SSRI Fluoxetine												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	179/399 (44.9%)	187/384 (48.7%) 40.8%	RR 0.92 (0.8 to 1.06)	39 fewer per 1000 (from 97 fewer to 29 more) 33 fewer per 1000 (from 82 fewer to 24 more)	[redacted] HIGH	CRITICAL
Number not achieving remission at endpoint (vs SSRIs) (sensitivity analysis) - SSRI Paroxetine												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	134/398 (33.7%)	141/386 (36.5%) 37%	RR 0.92 (0.76 to 1.11)	29 fewer per 1000 (from 88 fewer to 40 more) 30 fewer per 1000 (from 89	[redacted] LOW	CRITICAL

										fewer to 41 more)		
Mean endpoint scores (clinician rated) (vs SSRIs) (Better indicated by lower values)												
9	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1219	1215	-	SMD 0.11 lower (0.19 to 0.03 lower)	[redacted] HIGH	CRITICAL
Mean endpoint scores (clinician rated) (vs SSRIs) - SSRI Citalopram (Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	566	577	-	SMD 0.12 lower (0.24 lower to 0 higher)	[redacted] HIGH	CRITICAL
Mean endpoint scores (clinician rated) (vs SSRIs) - SSRI Fluoxetine (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	384	375	-	SMD 0.2 lower (0.34 to 0.06 lower)	[redacted] HIGH	CRITICAL
Mean endpoint scores (clinician rated) (vs SSRIs) - SSRI Sertraline (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	104	107	-	SMD 0.02 lower (0.29 lower to 0.25	[redacted] MODERATE	CRITICAL

										higher)		
Mean endpoint scores (clinician rated) (vs SSRIs) - SSRI Paroxetine (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	165	156	-	SMD 0.11 higher (0.11 lower to 0.33 higher)	[redacted] MODERATE	CRITICAL
Mean change (clinician rated) (vs SSRIs) (Better indicated by lower values)												
13	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1667	1670	-	SMD 0.1 lower (0.18 to 0.02 lower)	[redacted] HIGH	CRITICAL
Mean change (clinician rated) (vs SSRIs) - SSRI Citalopram (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	812	827	-	SMD 0.17 lower (0.28 to 0.05 lower)	[redacted] HIGH	CRITICAL
Mean change (clinician rated) (vs SSRIs) - SSRI Fluoxetine (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	227	222	-	SMD 0.06 lower (0.24 lower to 0.13	[redacted] HIGH	CRITICAL

										higher)		
Mean change (clinician rated) (vs SSRIs) - SSRI Sertraline (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	235	242	-	SMD 0.01 higher (0.17 lower to 0.19 higher)	[redacted] HIGH	CRITICAL
Mean change (clinician rated) (vs SSRIs) - SSRI Paroxetine (Better indicated by lower values)												
2	randomised trials	no serious limitations	very serious[1]	no serious indirectness	serious[2]	none	393	379	-	SMD 0.06 lower (0.38 lower to 0.27 higher)	[redacted] VERY LOW	CRITICAL
Leaving the study early for any reason (vs SSRIs)												
14	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	338/2011 (16.8%)	372/1999 (18.6%) 17.3%	RR 0.86 (0.71 to 1.03)	26 fewer per 1000 (from 54 fewer to 6 more) 24 fewer per 1000 (from 50 fewer to 5 more)	[redacted] MODERATE	CRITICAL

Leaving the study early for any reason (vs SSRIs) - SSRI Citalopram												
6	randomised trials	no serious limitations	serious[4]	no serious indirectness	serious[2]	none	145/955 (15.2%)	149/969 (15.4%) 19.6%	RR 0.82 (0.6 to 1.11)	28 fewer per 1000 (from 62 fewer to 17 more) 35 fewer per 1000 (from 78 fewer to 22 more)	[redacted] LOW	CRITICAL
Leaving the study early for any reason (vs SSRIs) - SSRI Fluoxetine												
4	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	82/415 (19.8%)	87/398 (21.9%) 19.9%	RR 0.91 (0.58 to 1.42)	20 fewer per 1000 (from 92 fewer to 92 more) 18 fewer per 1000 (from 84 fewer to 84 more)	[redacted] LOW	CRITICAL
Leaving the study early for any reason (vs SSRIs) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	47/243 (19.3%)	40/246 (16.3%) 16%	RR 1.19 (0.81 to 1.74)	31 more per 1000 (from 31 fewer to 120 more) 30 more	[redacted] LOW	CRITICAL

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

									1.29)	fewer to 19 more)		
								6.3%		13 fewer per 1000 (from 32 fewer to 18 more)		
Leaving the study early due to side effects (vs SSRIs) - SSRI Fluoxetine												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	[redacted] HIGH	CRITICAL
								7.6%		17 fewer per 1000 (from 40 fewer to 20 more)		
Leaving the study early due to side effects (vs SSRIs) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	[redacted] HIGH	CRITICAL
								3.7%		4 more per 1000 (from 23 fewer to 82 more)		

Leaving the study early due to side effects (vs SSRIs) - SSRI Paroxetine												
2	randomised trials	no serious limitations	serious[4]	no serious indirectness	serious[2]	none	25/397 (6.3%)	41/385 (10.6%) 9.6%	RR 0.65 (0.31 to 1.36)	37 fewer per 1000 (from 73 fewer to 38 more) 34 fewer per 1000 (from 66 fewer to 35 more)	[redacted] LOW	CRITICAL
Patients reporting side effects (vs SSRIs)												
14	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1229/1994 (61.6%)	1230/1980 (62.1%) 71.4%	RR 0.94 (0.91 to 0.98)	37 fewer per 1000 (from 12 fewer to 56 fewer) 43 fewer per 1000 (from 14 fewer to 64 fewer)	[redacted] HIGH	CRITICAL
Patients reporting side effects (vs SSRIs) - SSRI Citalopram												
6	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	551/949 (58.1%)	511/956 (53.5%) 70.9%	RR 0.95 (0.86 to 1.04)	27 fewer per 1000 (from 75 fewer to 21 more) 35 fewer	[redacted] LOW	CRITICAL

										per 1000 (from 99 fewer to 28 more)		
Patients reporting side effects (vs SSRIs) - SSRI Fluoxetine												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	231/410 (56.3%)	243/394 (61.7%) 64.1%	RR 0.92 (0.83 to 1.01)	49 fewer per 1000 (from 105 fewer to 6 more) 51 fewer per 1000 (from 109 fewer to 6 more)	[redacted] MODERATE	CRITICAL
Patients reporting side effects (vs SSRIs) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	198/238 (83.2%)	218/245 (89%) 88.8%	RR 0.94 (0.86 to 1.02)	53 fewer per 1000 (from 125 fewer to 18 more) 53 fewer per 1000 (from 124 fewer to 18 more)	[redacted] MODERATE	CRITICAL
Patients reporting side effects (vs SSRIs) - SSRI Paroxetine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	249/397 (62.7%)	258/385 (67%)	RR 0.93 (0.84 to	47 fewer per 1000 (from 107	[redacted] MODERATE	CRITICAL

									1.04)	fewer to 27 more)		
								66.1%		46 fewer per 1000 (from 106 fewer to 26 more)		
Patients reporting side effects (vs SSRIs) (sensitivity analysis)												
13	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	[redacted] HIGH	CRITICAL
								71.4%		43 fewer per 1000 (from 14 fewer to 71 fewer)		
Patients reporting side effects (vs SSRIs) (sensitivity analysis) - SSRI Citalopram												
5	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	544/841 (64.7%)	476/742 (64.2%)	RR 0.95 (0.89 to 1.02)	32 fewer per 1000 (from 71 fewer to 13 more)	[redacted] HIGH	CRITICAL
								73.1%		37 fewer per 1000 (from 80 fewer to 15 more)		

Patients reporting side effects (vs SSRIs) (sensitivity analysis) - SSRI Fluoxetine												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	231/410 (56.3%)	243/394 (61.7%) 64.1%	RR 0.92 (0.82 to 1.03)	49 fewer per 1000 (from 111 fewer to 19 more) 51 fewer per 1000 (from 115 fewer to 19 more)	[redacted] HIGH	CRITICAL
Patients reporting side effects (vs SSRIs) (sensitivity analysis) - SSRI Sertraline												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	198/238 (83.2%)	218/245 (89%) 88.8%	RR 0.93 (0.87 to 1)	62 fewer per 1000 (from 116 fewer to 0 more) 62 fewer per 1000 (from 115 fewer to 0 more)	[redacted] HIGH	CRITICAL
Patients reporting side effects (vs SSRIs) (sensitivity analysis) - SSRI Paroxetine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	249/397 (62.7%)	258/385 (67%) 66.1%	RR 0.94 (0.85 to 1.04)	40 fewer per 1000 (from 101 fewer to 27 more) 40 fewer	[redacted] HIGH	CRITICAL

										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 assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Other ADs (non SSRIs)	Relative (95% CI)	Absolute		
Non-response - SNRI Duloxetine												
3	randomised trials	no serious limitations	serious[1]	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)	[redacted] LOW	CRITICAL
								54.4%		103 fewer per 1000 (from 234 fewer to 82 more)		
Non-response - SNRI Venlafaxine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] MODERATE	CRITICAL
								39.3%		55 fewer per 1000 (from 126		

										fewer to 35 more)		
Non-response - Bupropion XL												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	119/291 (40.9%)	117/280 (41.8%) 41.8%	RR 0.98 (0.78 to 1.22)	8 fewer per 1000 (from 92 fewer to 92 more) 8 fewer per 1000 (from 92 fewer to 92 more)	[redacted] MODERATE	CRITICAL
Number not achieving remission at endpoint - SNRI Duloxetine												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	310/558 (55.6%)	315/562 (56%) 64.5%	RR 0.97 (0.83 to 1.13)	17 fewer per 1000 (from 95 fewer to 73 more) 19 fewer per 1000 (from 110 fewer to 84 more)	[redacted] MODERATE	CRITICAL
Number not achieving remission at endpoint - SNRI Venlafaxine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	CRITICAL

								47.4%		57 fewer per 1000 (from 133 fewer to 33 more)		
Number not achieving remission at endpoint - Bupropion xl												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	170/291 (58.4%)	167/280 (59.6%) 59.6%	RR 0.98 (0.79 to 1.21)	12 fewer per 1000 (from 125 fewer to 125 more) 12 fewer per 1000 (from 125 fewer to 125 more)	[redacted] LOW	CRITICAL
Mean endpoint scores (clinician rated) - SNRI Duloxetine (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	141	146	-	SMD 0.19 lower (0.42 lower to 0.04 higher)	[redacted] MODERATE	CRITICAL
Mean endpoint scores (clinician rated) - SNRI Venlafaxine (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	146	142	-	SMD 0.08 higher (0.15 lower to 0.32 higher)	[redacted] MODERATE	CRITICAL

Mean change (clinician rated) - SNRI Duloxetine (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	410	399	-	SMD 0.03 higher (0.11 lower to 0.17 higher)	[redacted] HIGH	CRITICAL
Mean change (clinician rated) - SNRI Venlafaxine (Better indicated by lower values)												
2	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)	[redacted] LOW	CRITICAL
Mean change (clinician rated) - Bupropion XL (Better indicated by lower values)												
2	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)	[redacted] HIGH	CRITICAL
Leaving the study early for any reason - SNRI Duloxetine												
3	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	119/558 (21.3%)	168/562 (29.9%) 31.1%	RR 0.7 (0.49 to 1)	90 fewer per 1000 (from 152 fewer to 0 more) 93 fewer per 1000	[redacted] MODERATE	CRITICAL

										(from 159 fewer to 0 more)		
Leaving the study early for any reason - SNRI Venlafaxine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	49/246 (19.9%)	55/245 (22.4%) 24.2%	RR 0.88 (0.63 to 1.23)	27 fewer per 1000 (from 83 fewer to 52 more) 29 fewer per 1000 (from 90 fewer to 56 more)	[redacted] MODERATE	CRITICAL
Leaving the study early for any reason - Bupropion XL												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	81/291 (27.8%)	72/280 (25.7%) 25.8%	RR 1.08 (0.82 to 1.41)	21 more per 1000 (from 46 fewer to 105 more) 21 more per 1000 (from 46 fewer to 106 more)	[redacted] MODERATE	CRITICAL
Leaving the study early due to side effects - SNRI Duloxetine												
3	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	30/558 (5.4%)	63/562 (11.2%)	RR 0.47 (0.25 to	59 fewer per 1000 (from 12	[redacted] MODERATE	CRITICAL

									0.89)	fewer to 84 fewer)		
								12.3%		65 fewer per 1000 (from 14 fewer to 92 fewer)		
Leaving the study early due to side effects - SNRI Venlafaxine												
2	randomised trials	no serious limitations	serious[1]	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)	LOW	CRITICAL
								13.5%		72 fewer per 1000 (from 112 fewer to 42 more)		
Leaving the study early due to side effects - Bupropion XL												
2	randomised trials	no serious limitations	very serious[1]	no serious indirectness	serious[2]	none	12/281 (4.3%)	17/276 (6.2%)	RR 0.78 (0.16 to 3.7)	14 fewer per 1000 (from 52 fewer to 166 more)	VERY LOW	CRITICAL
								6.2%		14 fewer per 1000 (from 52 fewer to 167 more)		

Patients reporting side effects - SNRI Duloxetine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/283 (78.8%)	223/289 (77.2%) 77.3%	RR 1.02 (0.94 to 1.11)	15 more per 1000 (from 46 fewer to 85 more) 15 more per 1000 (from 46 fewer to 85 more)	[redacted] HIGH	CRITICAL
Patients reporting side effects - SNRI Venlafaxine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	98/148 (66.2%)	102/145 (70.3%) 70.3%	RR 0.94 (0.81 to 1.1)	42 fewer per 1000 (from 134 fewer to 70 more) 42 fewer per 1000 (from 134 fewer to 70 more)	[redacted] HIGH	CRITICAL

[1] Large heterogeneity

[2] Inconclusive effect size

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

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	All other ADs (citalopram separated)	Relative (95% CI)	Absolute		
Non-response												
10	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	635/1713 (37.1%)	730/1724 (42.3%)	RR 0.87 (0.81 to 0.94)	55 fewer per 1000 (from 25 fewer to 80 fewer)	[redacted] HIGH	CRITICAL
								42.8%		56 fewer per 1000 (from 26 fewer to 81 fewer)		
Non-response - Escitalopram 10mg vs Other antidepressant												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] MODERATE	CRITICAL
								44.6%		18 fewer per 1000 (from 62		

										fewer to 27 more)		
Non-response - Escitalopram 10mg vs Citalopram												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	108/294 (36.7%)	127/307 (41.4%) 43.4%	RR 0.89 (0.73 to 1.08)	46 fewer per 1000 (from 112 fewer to 33 more) 48 fewer per 1000 (from 117 fewer to 35 more)	[redacted] MODERATE	CRITICAL
Non-response - Escitalopram 20mg vs Other antidepressant												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	113/474 (23.8%)	148/478 (31%) 25.8%	RR 0.77 (0.63 to 0.95)	71 fewer per 1000 (from 15 fewer to 115 fewer) 59 fewer per 1000 (from 13 fewer to 95 fewer)	[redacted] HIGH	CRITICAL
Non-response - Escitalopram 20mg vs Citalopram												
2	randomised trials	no serious limitations	serious[2]	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	[redacted] MODERATE	CRITICAL

									0.93)	fewer to 178 fewer)		
								48.6%		112 fewer per 1000 (from 34 fewer to 180 fewer)		
Non-remission												
9	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	CRITICAL
								42.6%		38 fewer per 1000 (from 77 fewer to 0 more)		
Non-remission - Escitalopram 10mg vs Other antidepressant												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	372/678 (54.9%)	367/662 (55.4%)	RR 0.98 (0.88 to 1.11)	11 fewer per 1000 (from 67 fewer to 61 more)	[redacted] MODERATE	CRITICAL
								53.5%		11 fewer per 1000 (from 64 fewer to		

										59 more)		
Non-remission - Escitalopram 10mg vs Citalopram												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	49/175 (28%)	59/182 (32.4%) 32.4%	RR 0.86 (0.63 to 1.19)	45 fewer per 1000 (from 120 fewer to 62 more) 45 fewer per 1000 (from 120 fewer to 62 more)	[redacted] MODERATE	
Non-remission - Escitalopram 20mg vs Other antidepressant												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	151/474 (31.9%)	186/478 (38.9%) 34.4%	RR 0.82 (0.7 to 0.97)	70 fewer per 1000 (from 12 fewer to 117 fewer) 62 fewer per 1000 (from 10 fewer to 103 fewer)	[redacted] HIGH	CRITICAL
Non-remission - Escitalopram 20mg vs Citalopram												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/142 (47.2%)	91/152 (59.9%)	RR 0.79 (0.63 to	126 fewer per 1000 (from 12	[redacted] HIGH	CRITICAL

									0.98)	fewer to 222 fewer)		
								59.9%		126 fewer per 1000 (from 12 fewer to 222 fewer)		
Mean endpoint depression scores (clinician-rated) (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	938	954	-	SMD 0.19 lower (0.28 to 0.1 lower)	[redacted] HIGH	CRITICAL
Mean endpoint depression scores (clinician-rated) - Escitalopram 10mg vs Other antidepressant (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	392	384	-	SMD 0.19 lower (0.33 to 0.05 lower)	[redacted] HIGH	CRITICAL
Mean endpoint depression scores (clinician-rated) - Escitalopram 10mg vs Citalopram (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	282	299	-	SMD 0.17 lower (0.33 to 0.01	[redacted] HIGH	CRITICAL

										lower)		
Mean endpoint depression scores (clinician-rated) - Escitalopram 20mg vs Other antidepressant (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	141	146	-	SMD 0.19 lower (0.42 lower to 0.04 higher)	[redacted] MODERATE	CRITICAL
Mean endpoint depression scores (clinician-rated) - Escitalopram 20mg vs Citalopram (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	123	125	-	SMD 0.22 lower (0.47 lower to 0.03 higher)	[redacted] MODERATE	CRITICAL
Mean change scores (clinician-rated) (Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1408	1434	-	SMD 0.13 lower (0.2 to 0.05 lower)	[redacted] HIGH	CRITICAL
Mean change scores (clinician-rated) - Escitalopram 10mg vs Other antidepressant (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	496	493	-	SMD 0 higher (0.13 lower to 0.12	[redacted] MODERATE	CRITICAL

										higher)		
Mean change scores (clinician-rated) - Escitalopram 10mg vs Citalopram (Better indicated by lower values)												
3	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	390	407	-	SMD 0.17 lower (0.31 to 0.03 lower)	[redacted] MODERATE	CRITICAL
Mean change scores (clinician-rated) - Escitalopram 20mg vs Citalopram (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	261	267	-	SMD 0.22 lower (0.39 to 0.05 lower)	[redacted] HIGH	CRITICAL
Mean change scores (clinician-rated) - Escitalopram 20mg vs Citalopram (Better indicated by lower values)												
2	no methodology chosen					none	261	267	-	SMD 0.22 lower (0.39 to 0.05 lower)		
Leaving treatment early for any reason												
12	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	338/1838 (18.4%)	444/1848 (24%)	RR 0.76 (0.68 to 0.87)	58 fewer per 1000 (from 31 fewer to 77 fewer)	[redacted] HIGH	CRITICAL

								25.6%		61 fewer per 1000 (from 33 fewer to 82 fewer)		
Leaving treatment early for any reason - Escitalopram 10mg vs Other antidepressant												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/678 (19.2%)	159/662 (24%)	RR 0.8 (0.65 to 0.98)	48 fewer per 1000 (from 5 fewer to 84 fewer)	[redacted] HIGH	CRITICAL
								20.1%		40 fewer per 1000 (from 4 fewer to 70 fewer)		
Leaving treatment early for any reason - Escitalopram 10mg vs Citalopram												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/403 (13.9%)	81/417 (19.4%)	RR 0.72 (0.53 to 0.98)	54 fewer per 1000 (from 4 fewer to 91 fewer)	[redacted] HIGH	CRITICAL
								25.6%		72 fewer per 1000 (from 5 fewer to 120 fewer)		
Leaving treatment early for any reason - Escitalopram 20mg vs Other antidepressant												
4	randomised	no serious	no serious	no serious	no serious	none	106/490	147/492	RR 0.73	81 fewer	[redacted]	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 early for any reason - Escitalopram 20mg vs Citalopram												
2	randomised trials	no serious limitations	serious[2]	no serious indirectness	serious[1]	none	46/267 (17.2%)	57/277 (20.6%)	RR 0.83 (0.58 to 1.17)	35 fewer per 1000 (from 86 fewer to 35 more)	LOW	CRITICAL
								21%		36 fewer per 1000 (from 88 fewer to 36 more)		
Leaving treatment early due to side effects												
11	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	107/1722 (6.2%)	176/1728 (10.2%)	RR 0.61 (0.48 to 0.77)	40 fewer per 1000 (from 23 fewer to 53 fewer)	HIGH	CRITICAL
								8.8%		34 fewer per 1000		

										(from 20 fewer to 46 fewer)		
Leaving treatment early due to side effects - Escitalopram 10mg vs Other antidepressant												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	39/675 (5.8%)	49/662 (7.4%)	RR 0.77 (0.52 to 1.16)	17 fewer per 1000 (from 36 fewer to 12 more)	[redacted] MODERATE	CRITICAL
								5.8%		13 fewer per 1000 (from 28 fewer to 9 more)		
Leaving treatment early due to side effects - Escitalopram 10mg vs Citalopram												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/294 (5.1%)	29/307 (9.4%)	RR 0.54 (0.3 to 0.99)	43 fewer per 1000 (from 1 fewer to 66 fewer)	[redacted] HIGH	CRITICAL
								9.4%		43 fewer per 1000 (from 1 fewer to 66 fewer)		
Leaving treatment early due to side effects - Escitalopram 20mg vs Other antidepressant												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/490 (7.3%)	78/492 (15.9%)	RR 0.46 (0.32 to	86 fewer per 1000 (from 51	[redacted] HIGH	CRITICAL

									0.68)	fewer to 108 fewer)		
								15.7%		85 fewer per 1000 (from 50 fewer to 107 fewer)		
Leaving treatment early due to side effects - Escitalopram 20mg vs Citalopram												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	17/263 (6.5%)	20/267 (7.5%)	RR 0.86 (0.46 to 1.6)	10 fewer per 1000 (from 40 fewer to 45 more)	[redacted] MODERATE	CRITICAL
								7.6%		11 fewer per 1000 (from 41 fewer to 46 more)		
Number reporting side effects												
9	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	[redacted] HIGH	CRITICAL
								72.3%		43 fewer per 1000 (from 7 fewer to		

										80 fewer)		
Number reporting side effects - Escitalopram 10mg vs Other antidepressant												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	232/400 (58%)	242/389 (62.2%) 56.7%	RR 0.94 (0.85 to 1.05)	37 fewer per 1000 (from 93 fewer to 31 more) 34 fewer per 1000 (from 85 fewer to 28 more)	[redacted] MODERATE	CRITICAL
Number reporting side effects - Escitalopram 10mg vs Citalopram												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	204/294 (69.4%)	241/307 (78.5%) 79.7%	RR 0.88 (0.8 to 0.97)	94 fewer per 1000 (from 24 fewer to 157 fewer) 96 fewer per 1000 (from 24 fewer to 159 fewer)	[redacted] HIGH	CRITICAL
Number reporting side effects - Escitalopram 20mg vs Other antidepressant												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	275/391 (70.3%)	285/392 (72.7%)	RR 0.97 (0.89 to	22 fewer per 1000 (from 80	[redacted] MODERATE	CRITICAL

									1.06)	fewer to 44 more)		
								71.4%		21 fewer per 1000 (from 79 fewer to 43 more)		
Number reporting side effects - Escitalopram 20mg vs Citalopram												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	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)	MODERATE	CRITICAL
								51.4%		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 assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo	Relative (95% CI)	Absolute		
Mean change scores at endpoint - data for doses above licensed dose (60 mg) - Sensitivity analysis: 60 mg (measured with: HAMD-17; range of scores: 0-52; Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	729	511	-	MD 1.85 lower (2.71 to 0.98 lower)	[redacted] MODERATE	
Mean change scores at endpoint - data for doses above licensed dose (60 mg) - 80 mg (Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	353	369	-	MD 1.97 lower (2.83 to 1.11 lower)	[redacted] MODERATE	
Mean change scores at endpoint - data for doses above licensed dose (60 mg) - 120 mg (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	261	260	-	MD 2.57 lower (3.77 to 1.37 lower)	[redacted] MODERATE	

Mean change scores at endpoint - data for doses above licensed dose (60 mg) - 40 mg - 120 mg (Better indicated by lower values)											
1	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)	[redacted] VERY LOW
Mean change scores at endpoint - overall (Better indicated by lower values)											
10	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)	[redacted] MODERATE
Non-response - data for doses above licensed dose (60 mg) - 60 mg (HAMD < 50% reduction)											
6	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)	[redacted] MODERATE
Non-response - data for doses above licensed dose (60 mg) - 80 mg (HAMD < 50% reduction)											
4	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)	[redacted] LOW
Non-response - data for doses above licensed dose (60 mg) - 120 mg (HAMD < 50% reduction)											
1	randomised	no serious	no serious	serious[1]	very	none	38/70	45/70	RR 0.84 (0.64 to	10 fewer per 100	[redacted]

	trials	limitations	inconsistency		serious[2]		(54.3%)	(64.3%)	1.11)	(from 23 fewer to 7 more)	VERY LOW
Non-response - data for doses above licensed dose (60 mg) - 40 mg - 120 mg (HAMD < 50% reduction)											
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	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)	[redacted] VERY LOW
Non-response - overall (HAMD < 50% reduction)											
12	randomised trials	no serious limitations	serious	serious[1]	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)	[redacted] LOW
Non-remission - data for doses above licensed dose (60 mg) - Sensitivity analysis: 60 mg											
5	randomised trials	no serious limitations	no serious inconsistency	serious[1]	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)	[redacted] MODERATE
Non-remission - data for doses above licensed dose (60 mg) - 80 mg											
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	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	[redacted] MODERATE

										fewer)		
Non-remission - data for doses above 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)	VERY LOW	
Non-remission - data for doses above 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)	MODERATE	
Non-remission - overall												
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)	MODERATE	
Depression-related pain: BPI item 5 average pain (measured with: BP item 5 average pain in last 24 hrs; range of scores: 1-11; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	288	295	-	MD 0.74 lower (1.13 to 0.34	MODERATE	

										lower)		

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

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

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo - acceptability and tolerability	Relative (95% CI)	Absolute		
Leaving treatment early - any reason (data by doses above licensed dose 60mg) - 60 mg												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	318/1034 (30.8%)	227/808 (28.1%)	RR 1.13 (0.98 to 1.3)	4 more per 100 (from 1 fewer to 8 more)	[redacted] MODERATE	
Leaving treatment early - any reason (data by doses above licensed dose 60mg) - Sensitivity analysis: 80 mg												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[2]	none	60/279 (21.5%)	68/281 (24.2%)	RR 0.88 (0.66 to 1.17)	3 fewer per 100 (from 8 fewer to 4 more)	[redacted] VERY LOW	

Leaving treatment early - any reason (data by doses above licensed dose 60mg) - 120 mg												
3	randomised trials	no serious limitations	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)	[redacted] VERY LOW	
Leaving treatment early - any reason (data by doses above licensed dose 60mg) - 40 mg - 120 mg												
1	randomised trials	no serious limitations	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)	11 fewer per 100 (from 21 fewer to 5 more)	[redacted] VERY LOW	
Leaving treatment early - any reason (overall)												
11	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[4]	none	447/1661 (26.9%)	350/1234 (28.4%)	RR 1.02 (0.91 to 1.15)	1 more per 100 (from 3 fewer to 4 more)	[redacted] LOW	
Leaving treatment early - adverse reactions (data by doses above licensed 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)	[redacted] LOW	

Leaving treatment early - adverse reactions (data by doses above licensed dose 60 mg) - 80 mg											
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	35/363 (9.6%)	16/371 (4.3%)	RR 2.11 (1.18 to 3.76)	5 more per 100 (from 1 more to 12 more)	[redacted] MODERATE
Leaving treatment early - adverse reactions (data by doses above licensed dose 60 mg) - 120 mg											
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[6]	none	14/266 (5.3%)	8/262 (3.1%)	RR 1.72 (0.72 to 4.07)	2 more per 100 (from 1 fewer to 9 more)	[redacted] LOW
Leaving treatment early - adverse reactions (overall)											
11	randomised trials	no serious limitations	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)	[redacted] MODERATE
Leaving treatment early - lack of efficacy (data by doses above licensed dose 60 mg) - 60 mg (sensitivity analysis)											
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	38/911 (4.2%)	60/686 (8.7%)	RR 0.30 (0.18 to 0.51)	6 fewer per 100 (from 4 fewer to 7 fewer)	[redacted] MODERATE

Leaving treatment early - lack of efficacy (data by doses above licensed dose 60 mg) - 80 mg											
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[2]	none	6/188 (3.2%)	11/192 (5.7%)	RR 0.55 (0.21 to 1.46)	3 fewer per 100 (from 5 fewer to 3 more)	VERY LOW
Leaving treatment early - lack of efficacy (data by doses above licensed dose 60 mg) - 120 mg											
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[2]	none	4/196 (2%)	11/192 (5.7%)	RR 0.36 (0.12 to 1.1)	4 fewer per 100 (from 5 fewer to 1 more)	VERY LOW
Leaving treatment early - lack of efficacy (overall): sensitivity analysis											
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	48/1295 (3.7%)	71/878 (8.1%)	RR 0.34 (0.22 to 0.54)	5 fewer per 100 (from 4 fewer to 6 fewer)	MODERATE
Number reporting side effects (data by doses above licensed dose 60 mg) - 60 mg											
5	randomised trials	no serious limitations	serious[5]	serious[1]	no serious imprecision	none	705/893 (78.9%)	455/667 (68.2%)	RR 1.14 (1.06 to 1.23)	10 more per 100 (from 4 more to 16 more)	LOW
Number reporting side effects (data by doses above licensed dose 60 mg) - 120 mg											

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)	[redacted] MODERATE	
Number reporting side effects (data by doses above licensed dose 60 mg) - 40 mg - 120 mg												
1	randomised trials	no serious limitations	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)	[redacted] LOW	
Number reporting side effects (data by doses above licensed dose 60 mg) - 80 mg												
4	randomised trials	no serious limitations	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)	[redacted] MODERATE	
Number reporting side effects (overall)												
10	randomised trials	no serious limitations	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)	[redacted] MODERATE	
Mean weight change (kg) at endpoint (by doses above licensed dose 60 mg) - 60 mg (measured with: kg; Better indicated by lower values)												
3	randomised	no serious	serious[5]	serious[1]	no serious	none	479	364	-	MD 0.49 lower	[redacted]	

	trials	limitations			imprecision					(1.04 lower to 0.05 higher)	LOW	
Mean weight change (kg) at endpoint (by doses above licensed dose 60 mg) - 80 mg (measured with: kg; Better indicated by lower values)												
3	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)	LOW	
Mean weight change (kg) at endpoint (by doses above licensed dose 60 mg) - 120 mg (measured with: kg; Better indicated by lower values)												
2	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)	VERY LOW	
Mean weight change (kg) at endpoint (by doses above licensed dose 60 mg) - 40 mg - 120 mg (measured with: kg; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[5]	none	81	72	-	MD 1.09 lower (1.71 to 0.47 lower)	LOW	
Mean weight change (kg) at endpoint (overall) (measured with: kg ; Better indicated by lower values)												
8	randomised	no serious	serious[5]	serious[1]	no serious	none	890	773	-	MD 0.69 lower (1		

	trials	limitations			imprecision					to 0.38 lower)	LOW	

[1] Selected outpatients from multiple sites
[2] Inconclusive effect size
[3] Inconsistent effect size; single study
[4] Wide range of control group risks in individual studies (13% to 42%)
[5] 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 assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine at different doses	Control	Relative (95% CI)	Absolute	Quality	
Mean change scores at endpoint - 30 mg vs 60 mg (measured with: HAMD; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[2]	none	202	198	-	MD 0.83 higher (0.43 lower to 2.09 higher)	[redacted] VERY LOW	
Mean change scores at endpoint - 40 mg vs 80 mg (measured with: HAMD; Better indicated by lower 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)	[redacted] VERY LOW	
Mean change scores at endpoint - 80 mg vs 120 mg (measured with: HAMD; Better indicated 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)	[redacted] VERY LOW	

Non-response - 30 mg 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)	MODERATE
Non-response - 40 mg 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)	LOW
Non-response - 80 mg vs 120 mg											
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)	LOW
Non-remission - 40 mg vs 80 mg											
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)	VERY LOW
Non-remission - 30 mg 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	MODERATE

										more)		
Non-remission - 80 mg vs 120 mg												
2	randomised trials	no serious limitations	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)	[redacted] LOW	

[1] Selective outpatients from multiple sites
[2] Inconclusive effect size; single study
[3] Inconclusive effect size
[4] Unlikely to be a difference
[5] Significant heterogeneity; random effects model used

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

Quality assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine at different doses - acceptability and tolerability	Control	Relative (95% CI)	Absolute	Quality	
Leaving treatment early - any reason - 30 mg vs 60 mg												
1	randomised trials	no serious limitations	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)	[redacted] VERY LOW	
Leaving treatment early - any reason - 40 mg vs 80 mg												
1	randomised trials	no serious limitations	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)	[redacted] VERY LOW	
Leaving treatment early - any reason - 80 mg vs 120 mg												
2	randomised trials	no serious limitations	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	[redacted] LOW	

										11 more)		
Leaving treatment early - due to adverse reaction - 30 mg vs 60 mg												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[4]	none	10/219 (4.6%)	42/428 (9.8%)	RR 0.47 (0.24 to 0.91)	5 fewer per 100 (from 1 fewer to 7 fewer)	LOW	
Leaving treatment early - due to adverse reaction - 40 mg vs 80 mg												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[3]	none	21/177 (11.9%)	27/175 (15.4%)	RR 0.77 (0.45 to 1.31)	4 fewer per 100 (from 8 fewer to 5 more)	VERY LOW	
Leaving treatment early - due to adverse reaction - 80 mg vs 120 mg												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[3]	none	8/188 (4.3%)	7/196 (3.6%)	RR 1.2 (0.44 to 3.24)	1 more per 100 (from 2 fewer to 8 more)	VERY LOW	
Leaving treatment early - lack of efficacy - 30 mg vs 60 mg												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[2]	none	3/219 (1.4%)	6/428 (1.4%)	RR 0.98 (0.25 to 3.87)	0 fewer per 100 (from 1 fewer to 4 more)	VERY LOW	

Leaving treatment early - lack of efficacy - 80 mg vs 120 mg											
2	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)	VERY LOW
No reporting side effects - 30 mg 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)	LOW
No reporting side effects - 40 mg 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)	MODERATE
No reporting side effects - 80 mg 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)	LOW

Mean weight change (kg) at endpoint - 30 mg vs 60 mg (measured with: kg; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[4]	none	168	155	-	MD 0.35 lower (1 lower to 0.3 higher)	[redacted] LOW	
Mean weight change (kg) at endpoint - 40 mg vs 80 mg (measured with: kg; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[3]	none	158	167	-	MD 0.19 lower (0.69 lower to 0.31 higher)	[redacted] LOW	
Mean weight change (kg) at endpoint - 80 mg vs 120 mg (measured with: kg; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[3]	none	93	93	-	MD 0.08 lower (0.69 lower to 0.53 higher)	[redacted] LOW	

[1] Selected outpatients from multiple sites
[2] Inconclusive effect size; single study
[3] Inconclusive effect size
[4] Single study
[5] Unlikely to be a difference

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

Quality assessment							Summary of findings				Quality	Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Other antidepressants	Relative (95% CI)	Absolute		
Mean change scores at endpoint (all data) (measured with: HAMD; Better indicated by lower values)												
12	randomised trials	no serious limitations	serious[1]	serious[2]	no serious imprecision[3]	none	1601	1544	-	MD 0.19 higher (0.44 lower to 0.81 higher)	[redacted] LOW	
Mean change scores at endpoint - paroxetine (measured with: HAMD; Better indicated by lower values)												
5	randomised trials	no serious limitations	serious[1]	serious[2]	no serious imprecision	none	591	593	-	MD 0.2 lower (1.14 lower to 0.74 higher)	[redacted] LOW	
Mean change scores at endpoint - fluoxetine (measured with: HAMD; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[2]	very serious[4]	none	147	70	-	MD 1.1 lower (3.03 lower to	[redacted] VERY LOW	

										0.83 higher)		
Mean change scores at endpoint - escitalopram (measured with: HAMD; Better indicated by lower 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)	[redacted] LOW	
Mean change scores at endpoint - venlafaxine (measured with: HAMD; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	318	330	-	MD 1.06 higher (0.02 lower to 2.14 higher)	[redacted] MODERATE	
Non-response (all data)												
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)	[redacted] LOW	
Non-response - paroxetine												

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)	LOW	
Non-response - fluoxetine												
2	randomised trials	no serious limitations	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)	LOW	
Non-response - escitalopram												
3	randomised trials	no serious limitations	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)	MODERATE	
Non-response - venlafaxine												
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)	VERY LOW	
Non-remission (all data)												
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		

	trials	limitations			imprecision		(57.6%)	(56.2%)	1.11)	(from 3 fewer to 6 more)	LOW	
Non-remission - paroxetine												
5	randomised trials	no serious limitations	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)	MODERATE	
Non-remission - fluoxetine												
2	randomised trials	no serious limitations	very serious[1]	serious[2]	very serious[4]	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)	VERY LOW	
Non-remission - escitalopram												
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)	LOW	
Non-remission - venlafaxine												
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	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 assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Other antidepressants - acceptability and tolerability	Relative (95% CI)	Absolute		
Leaving treatment early - any reason												
11	randomised trials	no serious limitations	serious[1]	serious[2]	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)	[redacted] LOW	
Leaving treatment early - any reason - paroxetine												
5	randomised trials	no serious limitations	no serious inconsistency	serious[2]	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	[redacted] MODERATE	

										11 more)		
Leaving treatment early - any reason - fluoxetine												
2	randomised trials	no serious limitations	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)	5 fewer per 100 (from 15 fewer to 10 more)	VERY LOW	
Leaving treatment early - any reason - escitalopram												
2	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)	13 more per 100 (from 1 fewer to 37 more)	LOW	
Leaving treatment early - any reason - venlafaxine												
2	randomised trials	no serious limitations	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)	MODERATE	
Leaving treatment early - adverse reactions												
10	randomised trials	no serious limitations	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)	4 more per 100 (from 1 more to 7 more)	MODERATE	

Leaving treatment early - adverse reactions - paroxetine											
5	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[3]	none	55/601 (9.2%)	42/599 (7%)	RR 1.32 (0.9 to 1.93)	2 more per 100 (from 1 fewer to 7 more)	[redacted] LOW
Leaving treatment early - adverse reactions - fluoxetine											
1	randomised trials	no serious limitations	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)	[redacted] VERY LOW
Leaving treatment early - adverse reactions - escitalopram											
2	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)	[redacted] VERY LOW
Leaving treatment early - adverse reactions - venlafaxine											
2	randomised trials	no serious limitations	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)	[redacted] MODERATE
Leaving treatment early - lack of efficacy											

7	randomised trials	no serious limitations	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)	MODERATE	
Leaving treatment early - lack of efficacy - paroxetine												
3	randomised trials	no serious limitations	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)	VERY LOW	
Leaving treatment early - lack of efficacy - fluoxetine - no data												
0	no evidence available					none	0/0 (0%)	0%	not pooled	not pooled		
Leaving treatment early - lack of efficacy - escitalopram												
2	randomised trials	no serious limitations	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)	VERY LOW	
Leaving treatment early - lack of efficacy - venlafaxine												
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		

	trials	limitations	inconsistency		serious[3]		(3.3%)		2.95)	(from 1 fewer to 5 more)	VERY LOW	
No. reporting side effects												
9	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	1010/1274 (79.3%)	949/1243 (76.3%)	RR 1.02 (0.98 to 1.07)	2 more per 100 (from 2 fewer to 5 more)	MODERATE	
No. reporting side effects - paroxetine												
5	randomised trials	no serious limitations	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)	MODERATE	
No. reporting side effects - fluoxetine												
1	randomised trials	no serious limitations	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)	LOW	
No. reporting side effects - escitalopram												
1	randomised trials	no serious limitations	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	LOW	

										8 more)		
No. reporting side effects - venlafaxine												
2	randomised trials	no serious limitations	serious[1]	serious[2]	no serious 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)	[redacted] LOW	
Mean weight change (kg) at endpoint (sensitivity analysis) (measured with: kg; Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	1042	1016	-	MD 0 higher (0.03 lower to 0.03 higher)	[redacted] MODERATE	
Mean weight change (kg) at endpoint - paroxetine (measured with: kg; Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	422	412	-	MD 0 higher (0.03 lower to 0.03 higher)	[redacted] MODERATE	
Mean weight change (kg) at endpoint - fluoxetine (measured with: kg; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[5]	none	65	33	-	MD 0.01 lower (0.74 lower to	[redacted] LOW	

										0.72 higher)		
Mean weight change (kg) at endpoint - escitalopram (measured with: kg; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[5]	none	273	274	-	MD 0.06 higher (1.08 lower to 1.2 higher)	[redacted] LOW	
Mean weight change (kg) at endpoint - venlafaxine (measured with: kg; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	282	297	-	MD 0.39 higher (0.09 lower to 0.86 higher)	[redacted] 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 assessment							Summary of findings					Importance
							No. of patients		Effect			
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	
Mean change scores from end of acute phase - 80 mg (measured with: HAMD; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[1]	none	70	70	-	MD 1 lower (2.5 lower to 0.5 higher)	[redacted] LOW	
Mean change scores from end of acute phase - 120 mg (measured with: HAMD; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[1]	none	80	70	-	MD 0.2 lower (1.78 lower to 1.38 higher)	[redacted] LOW	

Leaving treatment early - for any reason - 80 mg											
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[1]	none	58/71 (81.7%)	62/71 (87.3%)	RR 0.94 (0.81 to 1.08)	5 fewer per 100 (from 17 fewer to 7 more)	[redacted] LOW
Leaving treatment early - for any reason - 120 mg											
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[1]	none	62/81 (76.5%)	62/71 (87.3%)	RR 0.88 (0.75 to 1.02)	10 fewer per 100 (from 22 fewer to 2 more)	[redacted] LOW
Leaving treatment early - adverse reactions - 80 mg											
2	randomised trials	no serious limitations	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)	0 fewer per 100 (from 3 fewer to 8 more)	[redacted] MODERATE
Leaving treatment early - adverse reactions - 120 mg											
2	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	6/151 (4%)	6/129 (4.7%)	RR 0.84 (0.28 to 2.54)	1 fewer per 100 (from 3 fewer to 7 more)	[redacted] MODERATE

Leaving treatment early - lack of efficacy - 80 mg												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	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)	[redacted] LOW	
Leaving treatment early - lack of efficacy - 120 mg												
1	randomised trials	no serious limitations	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)	[redacted] 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 assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation phase for those with 30% improvement in baseline HAMD-17 scores: duloxetine at different doses	Control	Relative (95% CI)	Absolute	Quality	
Mean change scores from end of acute phase - 80 mg vs 120 mg (measured with: HAMD; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	70	80	-	MD 0.8 lower (2.18 lower to 0.58 higher)	⨁◯◯◯ LOW	
Leaving treatment early - for any reason - 80 mg vs 120 mg												
1	randomised trials	no serious limitations	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)	⨁◯◯◯ LOW	
Leaving treatment early - adverse reactions - 80 mg vs 120 mg												
1	randomised	no serious	no serious	serious[1]	very	none	2/71 (2.8%)	3/81	RR 0.76	1 fewer		

	trials	limitations	inconsistency		serious[3]			(3.7%)	(0.13 to 4.42)	per 100 (from 3 fewer to 13 more)	VERY LOW	
Leaving treatment early - lack of efficacy - 80 mg vs 120 mg												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	very serious[3]	none	1/71 (1.4%)	4/81 (4.9%)	RR 0.29 (0.03 to 2.49)	4 fewer per 100 (from 5 fewer to 7 more)	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 assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation phase for those with 30% improvement in baseline HAMD-17 scores: duloxetine	Other drugs	Relative (95% CI)	Absolute	Quality	
Mean change scores from end of acute phase - 80 mg vs paroxetine (measured with: HAMD; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	70	70	-	MD 0.3 higher (1.06 lower to 1.66 higher)	⨁◯◯◯ LOW	
Leaving treatment early - for any reason - paroxetine												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[1]	none	58/71 (81.7%)	61/70 (87.1%)	RR 0.94 (0.81 to 1.08)	5 fewer per 100 (from 17 fewer to 7 more)	⨁◯◯◯ LOW	
Leaving treatment early - adverse reactions - paroxetine												
2	randomised trials	no serious limitations	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	⨁◯◯◯ VERY	

									11.6)	0 fewer to 15 more)	LOW	
Leaving treatment early - lack of efficacy - paroxetine												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	very serious[4]	none	1/71 (1.4%)	2/70 (2.9%)	RR 0.49 (0.05 to 5.31)	1 fewer per 100 (from 3 fewer to 12 more)	VERY LOW	

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

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

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuation phase no entry criteria: duloxetine	Other drugs	Relative (95% CI)	Absolute	Quality	
Mean scores at endpoint - escitalopram (measured with: HAMD; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	146	141	-	MD 1.34 higher (0.25 lower to 2.93 higher)	LOW	

Non-response - escitalopram											
1	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)	VERY LOW
Non-remission - escitalopram											
1	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)	LOW
Leaving treatment early - any reason - escitalopram											
1	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)	VERY LOW
Leaving treatment early - adverse reactions - escitalopram											
1	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)	LOW
Leaving treatment early - lack of efficacy - escitalopram											
1	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	VERY

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

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

Next-step treatments

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

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dose escalation	Control	Relative (95% CI)	Absolute		
Mean depression scores (overall) (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	228	215	-	SMD 0.11 lower (0.29 lower to 0.08 higher)	[redacted] HIGH	
Mean depression scores - Same or increased-dose duloxetine 60mg vs high-dose duloxetine 120mg (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	130	118	-	SMD 0.01 lower (0.26 lower to 0.24 higher)	[redacted] MODERATE	

Mean depression scores - Same-dose sertraline (100mg) vs high-dose sertraline (200mg) (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	98	97	-	SMD 0.22 lower (0.51 lower to	[redacted] MODERATE	

										0.06 higher)		
Number not achieving 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%) 71.2%	RR 0.94 (0.83 to 1.06)	4 fewer per 100 (from 12 fewer to 4 more) 4 fewer per 100 (from 12 fewer to 4 more)	[redacted] HIGH	
Number not achieving remission - Same or increased-dose duloxetine 60mg vs high-dose duloxetine 120mg												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	92/131 (70.2%)	88/124 (71%) 71%	RR 0.99 (0.84 to 1.16)	1 fewer per 100 (from 11 fewer to 11 more) 1 fewer per 100 (from 11 fewer to 11 more)	[redacted] MODERATE	
Number not achieving remission - Same-dose sertraline (100mg) vs high-dose sertraline (200mg)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	62/99 (62.6%)	70/98 (71.4%) 71.4%	RR 0.88 (0.72 to 1.07)	9 fewer per 100 (from 20 fewer to 5 more) 9 fewer per 100 (from 20 fewer to 5 more)	[redacted] MODERATE	

Number not achieving 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 1.1)	11 fewer per 100 (from 22 fewer to 5 more)	LOW
								53.6%		11 fewer per 100 (from 22 fewer to 5 more)	
Number not achieving response - Same or increased-dose duloxetine 60mg vs high-dose duloxetine 120mg											
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 1.12)	6 fewer per 100 (from 16 fewer to 7 more)	LOW
								61.3%		6 fewer per 100 (from 16 fewer to 7 more)	
Number not achieving response - Same-dose sertraline (100mg) vs high-dose sertraline (200mg)											
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)	MODERATE
								45.9%		16 fewer per 100 (from 2	

										fewer to 25 fewer)		
Leaving treatment early for any reason (overall)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	36/230 (15.7%)	49/222 (22.1%)	RR 0.7 (0.48 to 1.04)	7 fewer per 100 (from 11 fewer to 1 more)	[redacted] MODERATE	
								21.4%		6 fewer per 100 (from 11 fewer to 1 more)		
Leaving treatment early for any reason - Same or increased-dose duloxetine 60mg vs high-dose duloxetine 120mg												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	26/131 (19.8%)	34/124 (27.4%)	RR 0.72 (0.46 to 1.13)	8 fewer per 100 (from 15 fewer to 4 more)	[redacted] MODERATE	
								27.4%		8 fewer per 100 (from 15 fewer to 4 more)		
Leaving treatment early for any reason - Same-dose sertraline (100mg) vs high-dose sertraline (200mg)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[3]	none	10/99 (10.1%)	15/98 (15.3%)	RR 0.66 (0.31 to 1.4)	5 fewer per 100 (from 11 fewer to 6 more)	[redacted] LOW	
								15.3%		5 fewer per 100 (from 11 fewer to 6 more)		

Leaving treatment early due to side effects (overall)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	12/230 (5.2%)	12/223 (5.4%) 5.4%	RR 0.97 (0.45 to 2.11)	0 fewer per 100 (from 3 fewer to 6 more) 0 fewer per 100 (from 3 fewer to 6 more)	[redacted] LOW
Leaving treatment early due to side effects - Same or increased-dose duloxetine 60mg vs high-dose duloxetine 120mg											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	6/131 (4.6%)	7/124 (5.6%) 5.7%	RR 0.81 (0.28 to 2.35)	1 fewer per 100 (from 4 fewer to 8 more) 1 fewer per 100 (from 4 fewer to 8 more)	[redacted] LOW
Leaving treatment early due to side effects - Same-dose sertraline (100mg) vs high-dose sertraline (200mg)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	6/99 (6.1%)	5/99 (5.1%) 5.1%	RR 1.2 (0.38 to 3.8)	1 more per 100 (from 3 fewer to 14 more) 1 more per 100 (from 3 fewer to 14 more)	[redacted] LOW
Leaving treatment early due to lack of efficacy - Same or increased-dose duloxetine 60mg vs high-dose duloxetine 120mg											

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 1.35)	4 fewer per 100 (from 7 fewer to 3 more)	[redacted] LOW	
								8.1%		4 fewer per 100 (from 7 fewer to 3 more)		
Number reporting side effects - Same-dose sertraline (100mg) vs high-dose sertraline (200mg)												
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)	[redacted] LOW	
								55.1%		10 fewer per 100 (from 21 fewer to 5 more)		

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

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

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Switching:	Switching	Relative	Absolute		

studies						considerations	continuing AD		(95% CI)			
Number not achieving 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)	[redacted] LOW	
								28.9%		2 more per 100 (from 9 fewer to 19 more)		
Number not achieving response - Fluoxetine vs mianserin												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	24/38 (63.2%)	18/34 (52.9%)	RR 1.19 (0.8 to 1.78)	10 more per 100 (from 11 fewer to 41 more)	[redacted] LOW	
								52.9%		10 more per 100 (from 11 fewer to 41 more)		
Number not achieving response - Venlafaxine vs 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)	[redacted] MODERATE	

								83.3%		5 fewer per 100 (from 18 fewer to 10 more)		
Number not achieving remission - Nortriptyline vs fluoxetine												
1	randomised trials	no serious limitations	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)	[redacted] LOW	
								13.4%		4 more per 100 (from 4 fewer to 21 more)		
Number not achieving remission - Fluoxetine vs mianserin												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	31/38 (81.6%)	22/34 (64.7%)	RR 1.26 (0.94 to 1.69)	17 more per 100 (from 4 fewer to 45 more)	[redacted] LOW	
								64.7%		17 more per 100 (from 4 fewer to 45 more)		
Number not achieving remission - Venlafaxine vs fluoxetine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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	[redacted] MODERATE	

										more)		
								68.3%		18 fewer per 100 (from 31 fewer to 1 more)		
Other comparisons: mean endpoint scores (self-rated) - Nortriptyline vs fluoxetine (Better indicated by lower values)												
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)	MODERATE	
Other comparisons: mean endpoint scores (self-rated) - Fluoxetine vs mianserin (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	38	33	-	MD 1.8 higher (1.63 lower to 5.23 higher)	LOW	
Other comparisons: mean endpoint scores (self-rated) - Venlafaxine vs fluoxetine (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	59	60	-	MD 2.03 lower (5.22 lower to 1.16 higher)	LOW	
Other comparisons: number leaving treatment early for any reason - Nortriptyline vs fluoxetine												
1	randomised	no serious	no serious	no serious	very	none	8/68	28/142	RR 0.6	8 fewer per		

	trials	limitations	inconsistency	indirectness	serious[1]		(11.8%)	(19.7%)	(0.29 to 1.24)	100 (from 14 fewer to 5 more)	LOW	
								19.7%		8 fewer per 100 (from 14 fewer to 5 more)		
Other comparisons: number leaving treatment early for any reason - Venlafaxine versus fluoxetine												
1	randomised trials	no serious limitations	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)	LOW	
								20%		5 more per 100 (from 7 fewer to 30 more)		
Other comparisons: number leaving treatment early because of side effects - Nortriptyline vs fluoxetine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	2/68 (2.9%)	4/142 (2.8%)	RR 1.04 (0.2 to 5.56)	0 more per 100 (from 2 fewer to 13 more)	LOW	
								2.9%		0 more per 100 (from 2 fewer to 13 more)		
Other comparisons: number leaving treatment early because of side effects - Fluoxetine continuation vs mianserin												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	7/38 (18.4%)	12/34 (35.3%)	RR 0.52 (0.23 to	17 fewer per 100		

									1.17)	(from 27 fewer to 6 more)	LOW	
								35.3%		17 fewer per 100 (from 27 fewer to 6 more)		
Other comparisons: number leaving treatment early because of side effects - Venlafaxine vs fluoxetine												
1	randomised trials	no serious limitations	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)	[redacted] LOW	
								5%		3 fewer per 100 (from 5 fewer to 11 more)		
Other comparisons: number reporting side effects - Nortriptyline vs fluoxetine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	58/68 (85.3%)	119/142 (83.8%)	RR 0.98 (0.87 to 1.11)	2 fewer per 100 (from 11 fewer to 9 more)	[redacted] MODERATE	
								85.3%		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 assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Switching: switching to single or combination drugs	Control	Relative (95% CI)	Absolute	Quality	
Switch to venlafaxine vs switch to another antidepressant (efficacy) - Non-response												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	157/255 (61.6%)	173/264 (65.5%)	RR 0.91 (0.73 to 1.14)	6 fewer per 100 (from 18 fewer to 9 more)	[redacted] LOW	
								67.4%		6 fewer per 100 (from 18 fewer to 9 more)		
Switch to venlafaxine vs switch to another antidepressant (efficacy) - Non-remission												
2	randomised	no serious	serious[1]	no serious	serious[2]	none	133/255	144/264	RR 0.91	5 fewer	[redacted]	

	trials	limitations		indirectness			(52.2%)	(54.5%)	(0.67 to 1.24)	per 100 (from 18 fewer to 13 more)	LOW	
								64.2%		6 fewer per 100 (from 21 fewer to 15 more)		
Switch to venlafaxine vs switch to another antidepressant (efficacy) - versus SSRI (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	194	202	-	MD 0.5 lower (2.09 lower to 1.09 higher)	[redacted] MODERATE	
Switch to venlafaxine vs switch to another antidepressant (acceptability/tolerability) - Number reporting side effects												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/260 (60.4%)	169/266 (63.5%)	RR 0.95 (0.83 to 1.09)	3 fewer per 100 (from 11 fewer to 6 more)	[redacted] HIGH	
								63.7%		3 fewer per 100 (from 11 fewer to 6 more)		
Switch to venlafaxine vs switch to another antidepressant (acceptability/tolerability) - Leaving treatment early for any reason												

2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	58/261 (22.2%)	50/268 (18.7%) 16.1%	RR 1.19 (0.85 to 1.67)	4 more per 100 (from 3 fewer to 13 more) 3 more per 100 (from 2 fewer to 11 more)	[redacted] LOW	
Switch to venlafaxine vs switch to another antidepressant (acceptability/tolerability) - Leaving treatment early due to side 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%) 5.1%	RR 1.17 (0.58 to 2.36)	1 more per 100 (from 2 fewer to 7 more) 1 more per 100 (from 2 fewer to 7 more)	[redacted] LOW	
Switch to augmentation strategy vs switch to single drug: efficacy outcomes - Fluoxetine + olanzapine vs fluoxetine - non-response												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	183/389 (47%)	82/202 (40.6%) 48.6%	RR 0.88 (0.74 to 1.05)	5 fewer per 100 (from 11 fewer to 2 more) 6 fewer per 100 (from 13 fewer to 2 more)	[redacted] MODERATE	
Switch to augmentation strategy vs switch to single drug: efficacy outcomes - Fluoxetine + olanzapine vs fluoxetine - non-remission												

2	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)	[redacted] VERY LOW	
								48.4%		0 fewer per 100 (from 15 fewer to 23 more)		
Switch to augmentation strategy vs switch to single drug: efficacy outcomes - Fluoxetine + olanzapine vs fluoxetine (Better indicated by lower values)												
2	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)	[redacted] LOW	
Switch to augmentation strategy vs switch to single drug: acceptability/tolerability - Fluoxetine + olanzapine vs fluoxetine - leaving treatment early for any reason												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	90/389 (23.1%)	40/202 (19.8%)	RR 1.12 (0.79 to 1.59)	2 more per 100 (from 4 fewer to 12 more)	[redacted] LOW	
								19.9%		2 more per 100 (from 4 fewer to 12 more)		
Switch to augmentation strategy vs switch to single drug: acceptability/tolerability - Fluoxetine + olanzapine vs fluoxetine - leaving treatment early due to												

side effects											
2	randomised trials	no serious limitations	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
								3.9%		5 more per 100 (from 0 more to 17 more)	
Switch to augmentation strategy vs switch to single drug: acceptability/tolerability - Fluoxetine + olanzapine vs fluoxetine - number reporting side effects											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	129/146 (88.4%)	119/142 (83.8%)	RR 1.05 (0.96 to 1.16)	4 more per 100 (from 3 fewer to 13 more)	MODERATE
								83.8%		4 more per 100 (from 3 fewer to 13 more)	

[1] Significant heterogeneity - random effects model used

[2] Inconclusive effect size

[3] Single study

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

Quality assessment							Summary of findings					
							No. of patients		Effect			
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
Switching strategies: Number of people not achieving at least 50% reduction in depression score - Sertraline to imipramine vs imipramine to sertraline												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] LOW	
								41.2%		14 more per 100 (from 2 fewer to 39 more)		
Switching strategies: Mean endpoint scores - Sertraline to imipramine vs imipramine to sertraline (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	117	50	-	MD 2.5 higher (0.38 lower to 5.38 higher)	[redacted] LOW	

Switching strategies: Leaving the study early - Sertraline to imipramine vs imipramine to sertraline												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	29/117 (24.8%)	5/51 (9.8%)	RR 2.53 (1.04 to 6.16)	15 more per 100 (from 0 more to 51 more)	[redacted] MODERATE	
								9.8%		15 more per 100 (from 0 more to 51 more)		

[1] Single study; inconclusive effect size

[2] Single study

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

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Antidepressant +Antidepressant	Antidepressant + (placebo or nothing)	Relative (95% CI)	Absolute		
Number not achieving response - SSRIs + Mianserin												
3	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)	LOW	
								63.2%		18 fewer per 100 (from 35 fewer to 11 more)		
Number not achieving response - Sertraline + mianserin vs high dose sertraline + placebo												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	MODERATE	
								45.9%		13 fewer per 100 (from 23		

										fewer to 1 more)		
Number not achieving response - Antidepressants + Mirtazapine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	4/11 (36.4%)	12/15 (80%)	RR 0.45 (0.2 to 1.03)	44 fewer per 100 (from 64 fewer to 2 more)	[redacted] MODERATE	
								80%		44 fewer per 100 (from 64 fewer to 2 more)		
Number not achieving remission - SSRIs + Mianserin												
2	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 1.04)	13 fewer per 100 (from 26 fewer to 3 more)	[redacted] LOW	
								72.1%		14 fewer per 100 (from 27 fewer to 3 more)		
Number not achieving remission - Antidepressants + Mirtazapine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[4]	none	6/11 (54.5%)	13/15 (86.7%)	RR 0.63 (0.35 to 1.12)	32 fewer per 100 (from 56 fewer to	[redacted] MODERATE	

										10 more)		
								86.7%		32 fewer per 100 (from 56 fewer to 10 more)		
Number not achieving remission - Sertraline + mianserin vs high dose sertraline + placebo												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] MODERATE	
								71.4%		15 fewer per 100 (from 2 fewer to 26 fewer)		
Number not achieving remission - Fluoxetine + desipramine vs high dose fluoxetine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] MODERATE	
								52.1%		17 more per 100 (from 2 fewer to 42 more)		

Mean endpoint or change scores - SSRIs + Mianserin (Better indicated by lower values)											
3	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	141	147	-	SMD 0.46 lower (1.07 lower to 0.15 higher)	[redacted] LOW
Mean endpoint or change scores - Fluoxetine + desipramine vs high dose fluoxetine (Better indicated by lower values)											
2	randomised trials	no serious limitations	serious[2]	no serious indirectness	serious[2]	none	46	48	-	SMD 0.67 higher (0.05 to 1.28 higher)	[redacted] LOW
Mean endpoint or change scores - Antidepressants + Mirtazapine (Better indicated by lower values)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	11	15	-	SMD 0.83 lower (1.64 to 0.01 lower)	[redacted] MODERATE
Mean endpoint or change scores - Amitriptyline + Moclobemide (Better indicated by lower values)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	20	19	-	SMD 0.63 lower (1.28 lower to 0.01 higher)	[redacted] MODERATE

Mean endpoint or change scores - Antidepressant + atomoxetine (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	70	71	-	SMD 0.23 lower (0.56 lower to 0.1 higher)	[redacted] MODERATE	
Leaving the study early - SSRIs + Mianserin												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	23/130 (17.7%)	17/137 (12.4%)	RR 1.44 (0.81 to 2.58)	5 more per 100 (from 2 fewer to 20 more)	[redacted] LOW	
								14.3%		6 more per 100 (from 3 fewer to 23 more)		
Leaving the study early - Fluoxetine + desipramine vs high dose fluoxetine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] LOW	
								11.2%		8 more per 100 (from 4 fewer to 43 more)		

Leaving the study early - Antidepressants + Mirtazapine											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	1/11 (9.1%)	2/15 (13.3%) 13.3%	RR 0.68 (0.07 to 6.61)	4 fewer per 100 (from 12 fewer to 75 more) 4 fewer per 100 (from 12 fewer to 75 more)	[redacted] LOW
Leaving the study early - Antidepressant + buspirone											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	7/54 (13%)	9/54 (16.7%) 16.7%	RR 0.78 (0.31 to 1.94)	4 fewer per 100 (from 12 fewer to 16 more) 4 fewer per 100 (from 12 fewer to 16 more)	[redacted] LOW
Leaving the study early - Sertraline + mianserin vs high dose sertraline + placebo											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	17/98 (17.3%)	15/98 (15.3%) 15.3%	RR 1.13 (0.6 to 2.14)	2 more per 100 (from 6 fewer to 17 more) 2 more	[redacted] LOW

										per 100 (from 6 fewer to 17 more)		
Leaving the study early - Antidepressant + atomoxetine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	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)	[redacted] LOW	
								17.6%		1 more per 100 (from 9 fewer to 19 more)		
Leaving the study early due to side effects - SSRIs + Mianserin												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	9/130 (6.9%)	6/137 (4.4%)	RR 1.52 (0.58 to 3.96)	2 more per 100 (from 2 fewer to 13 more)	[redacted] LOW	
								3%		2 more per 100 (from 1 fewer to 9 more)		
Leaving the study early due to side effects - Fluoxetine + desipramine vs high dose fluoxetine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	2/12 (16.7%)	0/15 (0%)	RR 6.15 (0.32 to	0 more per 100 (from 0	[redacted] LOW	

									117.21)	fewer to 0 more)		
								0%		0 more per 100 (from 0 fewer to 0 more)		
Leaving the study early due to side effects - Antidepressant + atomoxetine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	LOW	
								5.4%		4 more per 100 (from 2 fewer to 26 more)		
Patients reporting side effects - SSRIs + Mianserin												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	MODERATE	
								45.5%		31 more per 100 (from 15 more to 52 more)		

Patients reporting side effects - Sertraline + mianserin vs high dose sertraline + placebo												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	75/98 (76.5%)	54/98 (55.1%)	RR 1.39 (1.13 to 1.71)	21 more per 100 (from 7 more to 39 more)	[redacted] MODERATE	
								55.1%		21 more per 100 (from 7 more to 39 more)		

[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 assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Antidepressant + Antipsychotic	Antidepressant + (placebo or nothing)	Relative (95% CI)	Absolute	Quality	
Number not achieving response												
9	randomised trials	no serious limitations	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)	[redacted] HIGH	
Number not achieving response - Aripiprazole												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	251/372 (67.5%)	71.8%	RR 0.94 (0.81 to 1.1)	43 fewer per 1000 (from 136 fewer to 72 more)	[redacted] MODERATE	
Number not achieving response - Olanzapine												
3	randomised trials	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	124/210 (59%)	71.2%	RR 0.81 (0.67 to 1)	135 fewer per 1000 (from 235 fewer to 0	[redacted] LOW	

										more)		
Number not achieving response - Risperidone												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
Number not achieving response - Quetiapine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[3]	none	15/29 (51.7%)	72.4%	RR 0.71 (0.47 to 1.08)	210 fewer per 1000 (from 384 fewer to 58 more)	[redacted] LOW	
Number not achieving remission												
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
Number not achieving remission - Aripiprazole												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	278/372 (74.7%)	84.8%	RR 0.88 (0.82 to 0.95)	102 fewer per 1000 (from 42 fewer to	[redacted] HIGH	

										153 fewer)		
Number not achieving remission - Olanzapine												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
Number not achieving remission - Risperidone												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] HIGH	
Number not achieving remission - Quetiapine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	20/29 (69%)	82.8%	RR 0.83 (0.62 to 1.12)	141 fewer per 1000 (from 315 fewer to 99 more)	[redacted] MODERATE	
Mean endpoint (Better indicated by lower values)												

6	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	568	578	-	SMD 0.45 lower (0.62 to 0.28 lower)	MODERATE	
Mean endpoint - Aripiprazole (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	185	184	-	SMD 0.32 lower (0.53 to 0.12 lower)	MODERATE	
Mean endpoint - Olanzapine (Better indicated by lower values)												
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)	LOW	
Mean endpoint - Risperidone (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	156	162	-	SMD 0.56 lower (0.78 to 0.33 lower)	HIGH	
Mean endpoint - Quetiapine (Better indicated by lower values)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	29	29	-	SMD 0.77 lower (1.3 to 0.23 lower)	MODERATE	
Number leaving treatment early for any reason												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	121/626 (19.3%)	18.6%	RR 1.19 (0.93 to 1.51)	35 more per 1000 (from 13 fewer to 95 more)	MODERATE	
Number leaving treatment early for any reason - Aripiprazole												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	22/182 (12.1%)	9.3%	RR 1.3 (0.71 to 2.39)	28 more per 1000 (from 27 fewer to 129 more)	LOW	
Number leaving treatment early for any reason - Olanzapine												
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	53/210 (25.2%)	20.2%	RR 1.29 (0.9 to 1.84)	59 more per 1000 (from 20 fewer to 170 more)	MODERATE	
Number leaving treatment early for any reason - Risperidone												

2	randomised trials	no serious limitations	serious[2]	no serious indirectness	very serious[2]	none	35/205 (17.1%)	15.1%	RR 1.21 (0.64 to 2.29)	32 more per 1000 (from 54 fewer to 195 more)	VERY LOW	
Number leaving treatment early for any reason - Quetiapine												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	LOW	
Number leaving treatment early due to side effects												
7	randomised trials	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	64/807 (7.9%)	2.3%	RR 2.43 (1.18 to 5.03)	33 more per 1000 (from 4 more to 93 more)	MODERATE	
Number leaving treatment early due to side effects - Aripiprazole												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	MODERATE	
Number leaving treatment early due to side effects - Olanzapine												
2	randomised	no serious	no serious	no serious	no serious	none	27/200 (13.5%)	2.4%	RR 5.53 (2.17 to	109 more per 1000		

	trials	limitations	inconsistency	indirectness	imprecision				14.08)	(from 28 more to 314 more)	HIGH
Number leaving treatment early due to side effects - Risperidone											
2	randomised trials	no serious limitations	serious[1]	no serious 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)	[redacted] LOW
Number leaving treatment early due to side effects - Quetiapine											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	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)	[redacted] LOW
Number reporting side effects - Aripiprazole											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	19/30 (63.3%)	56.7%	RR 1.12 (0.74 to 1.69)	68 more per 1000 (from 147 fewer to 391 more)	[redacted] LOW
Number reporting side effects - Risperidone											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	129/199 (64.8%)	67.9%	RR 1.11 (0.94 to	75 more per 1000 (from 41	[redacted] 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 assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: AD + other psychotropic drug	AD + (placebo or nothing)	Relative (95% CI)	Absolute	Quality	
Number not achieving response - Antidpressants + lithium												
6	randomised trial	no serious limitations	serious[1]	no serious indirectness	no serious imprecision[2]	none	56/87 (64.4%)	68/86 (79.1%) 81.8%	RR 0.83 (0.66 to 1.03)	13 fewer per 100 (from 27 fewer to 2 more) 13 fewer per 100	⊕⊕⊕OMODERATE	
Number not achieving remission - Antidepressants + lithium												
3	randomised trial	no serious limitations	serious2	no serious indirectness	serious3	none	57/107 (53.3%)	53/109 (48.6%) 53.3%	RR 1.26 (0.72 to 2.17)	13 more per 100 (from 14 fewer to 57 more) 13 more per 100	⊕⊕OOLOW	
Number not achieving remission - Antidepressants + atomoxetine												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious4	none	43/72 (59.7%)	36/74 (48.6%) 48.7%	RR 1.23 (0.91 to 1.66)	11 more per 100 (from -4 fewer to 32 more) 11 more per 100	⊕⊕OOLOW	
Mean endpoint or change scores - Antidepressants + lithium (range of scores: Better indicated 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 endpoint or change scores - Antidepressants + atomoxetine (range of scores: Better indicated by less)												

1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious4	none	70	71	-	SMD -0.23 (-0.56 to 0.1)	⊕⊕OOLOW	
Leaving the study early - Antidepressants + lithium												
8	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/178 (30.9%)	31/178 (17.4%) 9.8%	RR 1.79 (1.23 to 2.6)	14 more per 100 (from 4 more to 28 more) 7 more per 100	⊕⊕⊕⊕HIGH	
Leaving the study early - Antidepressants + atomoxetine												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious4	none	13/72 (18.1%)	13/74 (17.6%) 17.6%	RR 1.03 (0.51 to 2.06)	1 more per 100 (from -9 fewer to 19 more) 0 more per 100	⊕⊕OOLOW	
Leaving the study early due to side effects - Antidepressants + atomoxetine												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious4	none	7/72 (9.7%)	4/74 (5.4%) 5.4%	RR 1.8 (0.55 to 5.88)	4 more per 100 (from -2 fewer to 26 more) 4 more per 100	⊕⊕OOLOW	

[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	Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Comparisons involving ECT	Control	Relative (95% CI)	Absolute		
Low-dose bilateral ECT vs low-dose unilateral ECT - non-responders												
4	randomised trials	no serious limitations	serious[1]	no serious indirectness	very serious[2]	none	51/98 (52%)	83/119 (69.7%)	RR 0.65 (0.35 to 1.21)	24 fewer per 100 (from 45 fewer to 15 more)	[redacted] VERY LOW	
								67.9%		24 fewer per 100 (from 44 fewer to 14 more)		
Low-dose bilateral ECT vs low-dose unilateral ECT - non-remission												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/67 (64.2%)	46/67 (68.7%)	RR 0.93 (0.77 to 1.14)	5 fewer per 100 (from 16 fewer to 10 more)	[redacted] HIGH	
								57.8%		4 fewer per		

										100 (from 13 fewer to 8 more)		
Low-dose bilateral vs low-dose unilateral - mean endpoint depression scores (Better indicated by lower values)												
2	randomised trials	no serious limitations	serious[1]	no serious indirectness	very serious[2]	none	49	42	-	SMD 0.46 lower (1.69 lower to 0.76 higher)	[redacted] VERY LOW	
Low-dose bilateral ECT vs high-dose unilateral ECT - non-responders												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/179 (35.2%)	66/183 (36.1%)	RR 0.98 (0.74 to 1.29)	1 fewer per 100 (from 9 fewer to 10 more)	[redacted] HIGH	
								38.5%		1 fewer per 100 (from 10 fewer to 11 more)		
Low-dose bilateral ECT vs high-dose unilateral ECT - non-remission												
5	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	62/118 (52.5%)	51/119 (42.9%)	RR 1.24 (0.97 to 1.6)	10 more per 100 (from 1 fewer to 26 more)	[redacted] 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 limitations	no serious inconsistency	no serious indirectness	serious[2]	none	107	97	-	SMD 0.01 higher (0.27 lower to 0.29 higher)	[redacted] MODERATE	

[1] Significant heterogeneity - random effects model used

[2] Inconclusive effect size