Appendix 18c: Pharmacological interventions GRADE evidence profiles

Pharmacological interventions versus placebo and head-to head comparisons

Escitalopram versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Placebo	Relative (95% CI)	Absolute		
HAM-A (change from baseline) - Escitalopram (Better indicated by lower values)												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	816	696	-	MD 2.36 lower (3.28 to 1.43 lower)	⊕⊕⊕⊕ HIGH	
Non-response - Escitalopram												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	233/613 (38%)	279/494 (56.5%)	RR 0.68 (0.44 to 1.05)	181 fewer per 1000 (from 316 fewer to 28 more)	⊕⊕⊕O MODERATE	
Non-remission												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	240/344 (69.8%)	265/355 (74.6%)	RR 0.93 (0.85 to 1.02)	52 fewer per 1000 (from 112 fewer to 15 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
5	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	73/856 (8.5%)	38/745 (5.1%)	RR 1.72 (1.16 to 2.53)	37 more per 1000 (from 8 more to 78 more)	⊕⊕⊕⊕ HIGH	

Nausea												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	112/554 (20.2%)	42/432 (9.7%)	RR 2.02 (1.45 to 2.81)	99 more per 1000 (from 44 more to 176 more)	⊕⊕⊕⊕ HIGH	
Anorgasmia												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[3]	None	17/427 (4%)	0/296 (0%)	RR 13.17 (1.83 to 94.89)	0 more per 1000 (from 0 more to 0 more)	⊕⊕⊕O MODERATE	
Insomnia												
2	Randomised trials	No serious limitations	serious[4]	No serious indirectness	No serious imprecision	None	48/396 (12.1%)	21/275 (7.6%)	RR 1.81 (1.07 to 3.08)	62 more per 1000 (from 5 more to 159 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval compatible with benefit and no benefit

[2] Relatively wide confidence intervals

[3] Very wide confidence interval

[4] I-squared > 50%

Health economic profile

Escitalopram versus placebo							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£74.13	0.0396	Escitalopram dominant	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Sertraline versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sertraline**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A (change from baseline) - Sertraline (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	347	351	-	MD 2.46 lower (4.53 to 0.39 lower)	⊕⊕⊕⊕ HIGH	
Non-response - Sertraline												
2	Randomised trials	No serious limitations	serious[2]	No serious indirectness	No serious imprecision	None	150/347 (43.2%)	213/351 (60.7%)	RR 0.71 (0.6 to 0.85)	176 fewer per 1000 (from 91 fewer to 243	⊕⊕⊕O MODERATE	

										fewer)		
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	126/182 (69.2%)	154/188 (81.9%)	RR 0.85 (0.75 to 0.95)	123 fewer per 1000 (from 41 fewer to 205 fewer)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
2	Randomised trials	No serious limitations	Serious[2]	No serious indirectness	Serious[3]	None	22/347 (6.3%)	21/351 (6%)	RR 1.07 (0.6 to 1.91)	4 more per 1000 (from 24 fewer to 54 more)	⊕⊕OO LOW	
Nausea												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	88/349 (25.2%)	48/352 (13.6%)	RR 1.85 (1.35 to 2.55)	116 more per 1000 (from 48 more to 211 more)	⊕⊕⊕⊕ HIGH	
Ejaculation disorder												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[4]	None	7/184 (3.8%)	0/189 (0%)	RR 15.41 (0.89 to 267.81)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	
Insomnia												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[3]	None	65/349 (18.6%)	52/352 (14.8%)	RR 1.26 (0.9 to 1.76)	38 more per 1000 (from 15 fewer to 112 more)	⊕⊕⊕O MODERATE	

[1] Only data on 1 study

[2] I-squared >50%

[3] Wide confidence intervals compatible with benefit and harm

[4] Very small number of events

Health economic profile

Sertraline versus placebo							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£153.30	0.0423	Sertraline dominant	Probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Paroxetine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paroxetine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A Change from baseline (Better indicated by lower values)												
6	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1203	1007	-	MD 1.46 lower (2.23 to 0.69 lower)	⊕⊕⊕⊕ HIGH	
Non-response												
4	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	Serious[2]	None	309/697 (44.3%)	386/701 (55.1%)	RR 0.79 (0.65 to 0.97)	116 fewer per 1000 (from 17 fewer to 193 fewer)	⊕⊕OO LOW	

Non-remission												
5	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	711/1119 (63.5%)	655/913 (71.7%)	RR 0.87 (0.82 to 0.92)	93 fewer per 1000 (from 57 fewer to 129 fewer)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
8	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	141/1493 (9.4%)	46/1291 (3.6%)	RR 2.5 (1.81 to 3.45)	53 more per 1000 (from 29 more to 87 more)	⊕⊕⊕⊕ HIGH	
Nausea												
7	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	264/1272 (20.8%)	73/1032 (7.1%)	RR 2.98 (2.33 to 3.8)	140 more per 1000 (from 94 more to 198 more)	⊕⊕⊕O MODERATE	
Sexual problems												
7	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	96/1272 (7.5%)	9/1068 (0.8%)	RR 7.22 (3.77 to 13.83)	52 more per 1000 (from 23 more to 108 more)	⊕⊕⊕O MODERATE	
Insomnia												
4	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	42/547 (7.7%)	18/544 (3.3%)	RR 2.33 (1.35 to 4)	44 more per 1000 (from 12 more to 99 more)	⊕⊕⊕O MODERATE	

[1] I-squared >50%

[2] Confidence intervals compatible with benefit and no benefit

[3] Small number of events

Health economic profile

Paroxetine versus placebo							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£106.92	0.0364	Paroxetine dominant	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Citalopram versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Citalopram**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	6/17 (35.3%)	0%	RR 0.46 (0.23 to 0.93)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕O MODERATE	

Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	9/17 (52.9%)	14/17 (82.4%) 0%	RR 0.64 (0.39 to 1.06)	296 fewer per 1000 (from 502 fewer to 49 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	1/17 (5.9%)	0%	RR 3.00 (0.13 to 68.8)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	

[1] Only one study

Duloxetine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Duloxetine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A Mean change from baseline (Better indicated by lower values)												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	799	654	-	MD 3.15 lower (4.1 to 2.21 lower)	⊕⊕⊕⊕ HIGH	
Non-Response												
4	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	399/826 (48.3%)	433/665 (65.1%)	RR 0.75 (0.62 to 0.92)	163 fewer per 1000 (from 52 fewer to 247 fewer)	⊕⊕⊕O MODERATE	

Non-remission												
4	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	serious[1]	None	561/826 (67.9%)	532/665 (80%)	RR 0.86 (0.75 to 0.98)	112 fewer per 1000 (from 16 fewer to 200 fewer)	⊕⊕OO LOW	
Discontinuation due to adverse events												
4	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	122/826 (14.8%)	35/665 (5.3%)	RR 3.12 (1.55 to 6.31)	112 more per 1000 (from 29 more to 279 more)	⊕⊕⊕O MODERATE	
Nausea												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	206/506 (40.7%)	29/334 (8.7%)	RR 4.54 (2.91 to 7.1)	307 more per 1000 (from 166 more to 530 more)	⊕⊕⊕⊕ HIGH	
Sexual problems												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	28/506 (5.5%)	6/334 (1.8%)	RR 2.95 (1.2 to 7.29)	35 more per 1000 (from 4 more to 113 more)	⊕⊕⊕⊕ HIGH	
Insomnia												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	43/506 (8.5%)	11/334 (3.3%)	RR 2.46 (1.28 to 4.76)	48 more per 1000 (from 9 more to 124 more)	⊕⊕⊕⊕ HIGH	

[1] I-squared >50%

Health economic profile

Duloxetine versus placebo							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£19.46	0.0405	Duloxetine dominant	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Venlafaxine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
5	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	595	582	-	MD 3.16 lower (4.81 to 1.51 lower)	⊕⊕⊕O MODERATE	
Non-response												
8	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	607/1301 (46.7%)	550/923 (59.6%)	RR 0.79 (0.69 to 0.91)	125 fewer per 1000 (from 54 fewer to 185 fewer)	⊕⊕⊕O MODERATE	
Non-remission												
6	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	496/725 (68.4%)	586/716 (81.8%)	RR 0.83 (0.74 to 0.94)	139 fewer per 1000 (from 49 fewer to 213 fewer)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
10	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	302/1945 (15.5%)	95/1255 (7.6%)	RR 2.04 (1.58 to 2.65)	79 more per 1000 (from 44 more to 125 more)	⊕⊕⊕⊕ HIGH	

Nausea												
8	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	437/1253 (34.9%)	117/976 (12%)	RR 2.76 (2.28 to 3.34)	211 more per 1000 (from 153 more to 281 more)	⊕⊕⊕⊕ HIGH	
Ejaculation disorder												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Sserious[2]	None	68/526 (12.9%)	0/360 (0%)	RR 36.32 (7.76 to 170.02)	0 more per 1000 (from 0 more to 0 more)	⊕⊕⊕O MODERATE	
Insomnia												
6	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	140/933 (15%)	60/738 (8.1%)	RR 1.56 (1.16 to 2.09)	46 more per 1000 (from 13 more to 89 more)	⊕⊕⊕O MODERATE	

[1] I-squared >50%

[2] small number of events

Health economic profile

Venlafaxine XL versus placebo							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£95.66	0.0400	Venlafaxine XL dominant	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Imipramine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	14	14	-	SMD 0.49 lower (1.24 lower to 0.27 higher)	⊕⊕OO LOW	

[1] 1 small study and very wide confidence intervals

Pregabalin versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
5	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	821	475	-	MD 2.97 lower (3.7 to 2.24 lower)	⊕⊕⊕⊕ HIGH	
Non-response												
8	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	674/1440 (46.8%)	425/705 (60.3%)	RR 0.77 (0.71 to 0.83)	139 fewer per 1000 (from 102 fewer to 175 fewer)	⊕⊕⊕⊕ HIGH	
Non-remission												
7	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	983/1319 (74.5%)	471/577 (81.6%)	RR 0.91 (0.87 to 0.96)	73 fewer per 1000 (from 33 fewer to 106 fewer)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
8	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	164/1440 (11.4%)	60/705 (8.5%)	RR 1.31 (0.99 to 1.74)	26 more per 1000 (from 1 fewer to 63 more)	⊕⊕⊕⊕ HIGH	
Nausea												
6	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	102/980 (10.4%)	47/552 (8.5%)	RR 1.19 (0.85 to 1.66)	16 more per 1000 (from 13 fewer to 56 more)	⊕⊕⊕O MODERATE	

Insomnia												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	12/467 (2.6%)	12/298 (4%)	RR 0.7 (0.32 to 1.54)	12 fewer per 1000 (from 27 fewer to 22 more)	⊕⊕⊕O MODERATE	
Dizziness												
6	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	270/980 (27.6%)	43/552 (7.8%)	RR 3.36 (2.46 to 4.58)	184 more per 1000 (from 114 more to 279 more)	⊕⊕⊕⊕ HIGH	
Fatigue												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	12/121 (9.9%)	5/128 (3.9%)	RR 2.54 (0.92 to 6.99)	60 more per 1000 (from 3 fewer to 234 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit or harm

[2] Small number of events [3] Data only for 1 study

Health economic profile

Pregabalin versus placebo							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	£151.79	0.0403	£3,768/QALY	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Diazepam versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	12	12	-	SMD 0.21 lower (1.01 lower to 0.59 higher)	⊕⊕⊕O MODERATE	
Non-response												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	96/247 (38.9%)	149/258 (57.8%)	RR 0.67 (0.54 to 0.84)	191 fewer per 1000 (from 92 fewer to 266 fewer)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	20/259 (7.7%)	12/270 (4.4%)	RR 1.67 (0.82 to 3.39)	30 more per 1000 (from 8 fewer to 106 more)	⊕⊕⊕O MODERATE	
Libido												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	5/104 (4.8%)	0/104 (0%)	RR 11 (0.62 to 196.43)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	

Fatigue												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	17/104 (16.3%)	6/104 (5.8%)	RR 2.83 (1.16 to 6.9)	106 more per 1000 (from 9 more to 340 more)	⊕⊕⊕O MODERATE	
Dizziness												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/158 (10.1%)	5/161 (3.1%)	RR 3.26 (1.22 to 8.7)	70 more per 1000 (from 7 more to 239 more)	⊕⊕⊕⊕ HIGH	

[1] Confidence intervals compatible with benefit and no benefit

[2] Data only on 1 study

Alprazolam versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Alprazolam**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A (Better indicated by lower values)												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	209	210	-	MD 2.53 lower (3.9 to 1.17 lower)	⊕⊕⊕⊕ HIGH	
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	55/93 (59.1%)	62/91 (68.1%)	RR 0.87 (0.7 to 1.08)	89 fewer per 1000 (from 204 fewer to 55 more)	⊕⊕⊕O MODERATE	
Non-remission												
1	Randomised	No serious	No serious	No serious	serious[2]	None	69/93	76/91	RR 0.89	92 fewer per 1000	⊕⊕⊕O	

	trials	limitations	inconsistency	indirectness			(74.2%)	(83.5%)	(0.76 to 1.03)	(from 200 fewer to 25 more)	MODERATE	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	12/93 (12.9%)	9/91 (9.9%)	RR 1.3 (0.58 to 2.95)	30 more per 1000 (from 42 fewer to 193 more)	⊕⊕⊕O MODERATE	
Nausea												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	12/258 (4.7%)	16/258 (6.2%)	RR 0.74 (0.36 to 1.52)	16 fewer per 1000 (from 40 fewer to 32 more)	⊕⊕⊕O MODERATE	
Insomnia												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	3/63 (4.8%)	5/62 (8.1%)	RR 0.59 (0.15 to 2.37)	33 fewer per 1000 (from 69 fewer to 110 more)	⊕⊕⊕O MODERATE	
Fatigue												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	3/63 (4.8%)	4/62 (6.5%)	RR 0.74 (0.17 to 3.16)	17 fewer per 1000 (from 54 fewer to 139 more)	⊕⊕⊕O MODERATE	
Dizziness												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	30/258 (11.6%)	18/258 (7%)	RR 1.65 (0.95 to 2.85)	45 more per 1000 (from 3 fewer to 129 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit and no benefit

[2] No explanation was provided

Lorazepam versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Lorazepam	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	98	87	-	MD 2.49 lower (3.78 to 1.2 lower)	⊕⊕⊕⊕ HIGH	
Non-response												
4	Randomised trials	No serious limitations	serious[1]	No serious indirectness	serious[2]	None	133/230 (57.8%)	152/223 (68.2%)	RR 0.84 (0.66 to 1.07)	109 fewer per 1000 (from 232 fewer to 48 more)	⊕⊕OO LOW	
Non-remission												
3	Randomised trials	No serious limitations	serious[1]	No serious indirectness	serious[2]	None	151/200 (75.5%)	171/203 (84.2%)	RR 0.9 (0.77 to 1.05)	84 fewer per 1000 (from 194 fewer to 42 more)	⊕⊕OO LOW	
Discontinuation due to adverse events												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	83/255 (32.5%)	20/260 (7.7%)	RR 4.04 (2.55 to 6.38)	234 more per 1000 (from 119 more to 414 more)	⊕⊕⊕⊕ HIGH	

Nausea												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	29/222 (13.1%)	19/213 (8.9%)	RR 1.42 (0.82 to 2.46)	37 more per 1000 (from 16 fewer to 130 more)	⊕⊕⊕O MODERATE	
Insomnia												
3	Randomised trials	No serious limitations	Serious[1]	No serious indirectness	Very serious[2]	None	15/154 (9.7%)	7/146 (4.8%)	RR 2.21 (0.3 to 16.32)	58 more per 1000 (from 34 fewer to 735 more)	⊕OOO VERY LOW	
Dizziness												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	40/222 (18%)	14/213 (6.6%)	RR 2.76 (1.54 to 4.93)	116 more per 1000 (from 35 more to 258 more)	⊕⊕⊕⊕ HIGH	

[1] I-squared > 50%

[2] Confidence intervals compatible with benefit and no benefit

Buspirone versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Buspirone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A (Better indicated by lower values)												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	260	259	-	MD 1.93 lower (3.04 to 0.82 lower)	⊕⊕⊕⊕ HIGH	

Non-response												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	107/180 (59.4%)	127/185 (68.6%)	RR 0.87 (0.74 to 1.01)	89 fewer per 1000 (from 178 fewer to 7 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	46/293 (15.7%)	22/298 (7.4%)	RR 2.02 (1.12 to 3.67)	75 more per 1000 (from 9 more to 197 more)	⊕⊕⊕⊕ HIGH	
Nausea												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	56/178 (31.5%)	25/186 (13.4%)	RR 2.34 (1.53 to 3.58)	180 more per 1000 (from 71 more to 347 more)	⊕⊕⊕⊕ HIGH	
Insomnia												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	10/80 (12.5%)	7/82 (8.5%)	RR 1.46 (0.59 to 3.66)	39 more per 1000 (from 35 fewer to 227 more)	⊕⊕⊕O MODERATE	
Dizziness												
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	137/375 (36.5%)	38/379 (10%)	RR 3.68 (2.66 to 5.08)	269 more per 1000 (from 166 more to 409 more)	⊕⊕⊕⊕ HIGH	

[1] Confidence intervals compatible with benefit or no benefit

[2] Data only for 1 study

Hydroxyzine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxyzine	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	237	245	-	MD 3.51 lower (4.91 to 2.11 lower)	⊕⊕⊕⊕ HIGH	
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	47/81 (58%)	58/81 (71.6%)	RR 0.81 (0.64 to 1.02)	136 fewer per 1000 (from 258 fewer to 14 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	7/159 (4.4%)	5/169 (3%)	RR 1.48 (0.48 to 4.6)	14 more per 1000 (from 15 fewer to 107 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit or no benefit

Escitalopram versus paroxetine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Paroxetine	Relative (95% CI)	Absolute		
HAM-A												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/326 (0%)	0/197 (0%) 0%	SMD -0.32 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	65/269 (24.2%)	56/140 (40%) 0%	RR 0.60 (0.45 to 0.81)	160 fewer per 1000 (from 76 fewer to 220 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	22/269 (8.2%)	13/140 (9.3%) 0%	RR 0.88 (0.46 to 1.69)	11 fewer per 1000 (from 50 fewer to 64 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	

Diarrhoea												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	26/269 (9.7%)	12/140 (8.6%) 0%	RR 1.13 (0.59 to 2.17)	11 more per 1000 (from 35 fewer to 100 more) 0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	
Sexual problems												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	11/269 (4.1%)	10/140 (7.1%) 0%	RR 0.57 (0.25 to 1.32)	31 fewer per 1000 (from 54 fewer to 23 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	
Anxiety												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	7/269 (2.6%)	7/140 (5%) 0%	RR 0.52 (0.19 to 1.45)	24 fewer per 1000 (from 41 fewer to 23 more) 0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval

Health economic profile

Escitalopram versus paroxetine							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)[1]**	**Uncertainty[1]**
Iskedjian *et al.*, 2008 Canada	Potentially serious limitations[2]	Partially applicable[3]	• Measure of outcome: number of symptom-free days (SFDs) • Time horizon: 24 weeks	£32	9.4 symptom-free days	£3.4/ symptom-free day	£2.9-£4.49/ symptom-free day
Jørgensen *et al.*, 2006 UK	Potentially serious limitations[4]	Directly applicable[5]	• Measure of outcome: % of people with maintained response • Time horizon: 36 weeks	-£45	7.7% more people with maintained response	Escitalopram dominant	Escitalopram dominant
Guideline analysis UK	Minor limitations[6]	Directly applicable[7]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	£32.78	0.0032	£10,179/ QALY	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs converted and uplifted to 2009 UK pounds, using purchasing power parities (PPP) exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Efficacy data derived selectively from one RCT; many clinical and all resource use estimates based on expert opinion; limited sensitivity analysis; funded by industry
3. Conducted in Canada –Ministry of Health perspective (direct healthcare costs considered); no QALYs estimated but outcome measure considered relevant; utility scores for GAD are still scarce and of low quality
4. Efficacy data derived selectively from one RCT; some clinical and resource use estimates based on expert opinion; limited sensitivity analysis; funded by industry
5. NHS perspective; no QALYs estimated but outcome measure considered relevant; utility scores for GAD are still scarce and of low quality
6. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
7. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Sertraline versus paroxetine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Paroxetine	Relative (95% CI)	Absolute		
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	15/25 (60%)	15/28 (53.6%)	RR 1.12 (0.7 to 1.79)	64 more per 1000 (from 161 fewer to 423 more)	⊕⊕⊕O MODERATE	
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	8/25 (32%)	11/28 (39.3%)	RR 0.81 (0.39 to 1.7)	75 fewer per 1000 (from 240 fewer to 275 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

Health economic profile

Sertraline versus paroxetine							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£46.38	0.0059	Sertraline dominant	Probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Escitalopram versus venlafaxine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Escitalopram**	**Venlafaxine**	**Relative (95% CI)**	**Absolute**		
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	64/131 (48.9%)	66/133 (49.6%)	RR 0.98 (0.77 to 1.26)	10 fewer per 1000 (from 114 fewer to 129 more)	⊕⊕⊕O MODERATE	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	91/131 (69.5%)	93/133 (69.9%)	RR 0.99 (0.85 to 1.16)	7 fewer per 1000 (from 105 fewer to 112 more)	⊕⊕⊕O MODERATE	

Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[2]	None	9/131 (6.9%)	17/133 (12.8%)	RR 0.54 (0.25 to 1.16)	59 fewer per 1000 (from 96 fewer to 20 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

[2] Confidence interval compatible with benefit for escitalopram or no difference between interventions

Health economic profile

Escitalopram versus venlafaxine XL							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	£21.53	-0.0004	Venlafaxine XL dominant	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on health-related quality of life not considered; costs associated with management of side effects no considered
3. Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

Duloxetine versus venlafaxine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Venlafaxine	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	320	333	-	MD 0.2 higher (0.92 lower to 1.32 higher)	⊕⊕⊕O MODERATE	
Non-response												
2	Randomised trials	No serious limitations	serious[1,2]	No serious indirectness	Serious[1]	None	152/320 (47.5%)	150/333 (45%)	RR 1.04 (0.78 to 1.39)	18 more per 1000 (from 99 fewer to 176 more)	⊕⊕OO LOW	
Non-remission												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	219/320 (68.4%)	215/333 (64.6%)	RR 1.07 (0.94 to 1.21)	45 more per 1000 (from 39 fewer to 136 more)	⊕⊕⊕O MODERATE	
Sheehan Disability Scale (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	320	333	-	MD 0.18 higher (0.83 lower to 1.2 higher)	⊕⊕⊕O MODERATE	

Discontinuation due to adverse events												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	43/320 (13.4%)	38/333 (11.4%)	RR 1.18 (0.78 to 1.77)	21 more per 1000 (from 25 fewer to 88 more)	⊕⊕⊕O MODERATE	
Diarrhoea												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	22/162 (13.6%)	12/164 (7.3%)	RR 1.86 (0.95 to 3.62)	63 more per 1000 (from 4 fewer to 192 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

[2] I-squared >50%

[3] Confidence intervals compatible with benefit for venlafaxine or no difference

Health economic profile

Duloxetine versus venlafaxine XL							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)**	**Uncertainty**
Guideline analysis UK	Minor limitations[2]	Directly applicable[3]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	£76.20	0.0005	£154,742 /QALY	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs expressed in 2009 UK pounds
2. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
3. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Venlafaxine versus pregabalin for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Pregabalin	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	231	319	-	MD 1.35 higher (0.82 lower to 3.53 higher)	⊕⊕⊕O MODERATE	
Non-response												
2	Randomised trials	No serious limitations	Serious[2]	No serious indirectness	Serious[3]	None	113/238 (47.5%)	134/328 (40.9%)	RR 1.13 (0.79 to 1.63)	53 more per 1000 (from 86 fewer to 257 more)	⊕⊕OO LOW	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	73/113 (64.6%)	135/207 (65.2%)	RR 0.99 (0.84 to 1.17)	7 fewer per 1000 (from 104 fewer to 111 more)	⊕⊕⊕O MODERATE	
Q-LES-Q (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	125	121	-	SMD 0.09 lower (0.34 lower to 0.16 higher)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
2	Randomised	No serious	No serious	No serious	No serious	None	45/238	36/328	RR 1.72 (1.15 to	79 more per 1000 (from 16 more to	⊕⊕⊕⊕	

	trials	limitations	inconsistency	indirectness	imprecision		(18.9%)	(11%)	2.58)	173 more)	HIGH	
Dizziness												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	26/238 (10.9%)	76/328 (23.2%)	RR 0.49 (0.32 to 0.74)	118 fewer per 1000 (from 60 fewer to 158 fewer)	⊕⊕⊕⊕ HIGH	
Insomnia												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	20/238 (8.4%)	9/328 (2.7%)	RR 2.8 (1.31 to 6.01)	49 more per 1000 (from 9 more to 137 more)	⊕⊕⊕⊕ HIGH	
Somnolence												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	10/238 (4.2%)	39/328 (11.9%)	RR 0.36 (0.18 to 0.72)	76 fewer per 1000 (from 33 fewer to 97 fewer)	⊕⊕⊕⊕ HIGH	
Nausea												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	63/238 (26.5%)	38/328 (11.6%)	RR 2.27 (1.57 to 3.29)	147 more per 1000 (from 66 more to 265 more)	⊕⊕⊕⊕ HIGH	

[1] Confidence intervals compatible with benefit for pregabalin or no difference

[2] I-squared > 50%

[3] Confidence intervals compatible with benefit for either intervention

[4] Data from only one study

Health economic profile

Venlafaxine XL versus pregabalin							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)[1]**	**Uncertainty[1]**
Vera-Llonch *et al.*, 2010 Spain	Potentially serious limitations[2]	Partially applicable[3]	• Time horizon: 12 months, but treatment effect assumed to last from 8 weeks (end of treatment) until 12 months	-£468	-0.027	£17,565/ QALY	£14,567-£26,442/QALY Probabilistic analysis: pregabalin cost effective in roughly 95% of iterations at a cost-effectiveness threshold of £20,000/QALY
Guideline analysis UK	Minor limitations[4]	Directly applicable[5]	• Time horizon: 42 weeks • Model included 6 drugs plus no treatment (placebo)	-£247.45	-0.0003	£783,543 /QALY	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost effective at £20,000/QALY: 0.70

1. Costs converted and uplifted to 2009 UK pounds, using purchasing power parities (PPP) exchange rates (http://www.oecd.org/std/ppp) and the UK HCHS inflation index.
2. Efficacy data derived selectively from one RCT; treatment effect assumed to last for 44 weeks beyond end of treatment; funded by industry
3. Spanish third party payer perspective; valuation of QALYs derived from Spanish population
4. Evidence synthesis based on network (mixed treatment comparison) meta-analytic techniques; resource use based on data reported in RCTs, a national survey and GDG expert opinion; impact of tolerable side effects on HRQOL not considered; costs associated with management of side effects not considered
5. Analysis conducted to assist guideline development; NHS and personal social services perspective; QALYs estimated based on SF-6D

Venlafaxine versus buspirone for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Buspirone	Relative (95% CI)	Absolute		
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	116/203 (57.1%)	55/98 (56.1%)	RR 1.02 (0.82 to 1.26)	11 more per 1000 (from 101 fewer to 146 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	50/203 (24.6%)	15/98 (15.3%)	RR 1.61 (0.95 to 2.72)	93 more per 1000 (from 8 fewer to 263 more)	⊕⊕⊕O MODERATE	
Dizziness												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	38/203 (18.7%)	46/98 (46.9%)	RR 0.4 (0.28 to 0.57)	282 fewer per 1000 (from 202 fewer to 338 fewer)	⊕⊕⊕⊕ HIGH	
Nausea												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	78/203 (38.4%)	29/98 (29.6%)	RR 1.3 (0.91 to 1.85)	89 more per 1000 (from 27 fewer to 252 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

[2] Confidence intervals compatible with benefit for buspirone or no difference

Venlafaxine versus diazepam for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Diazepam	Relative (95% CI)	Absolute		
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	160/370 (43.2%)	39/89 (43.8%)	RR 0.99 (0.76 to 1.28)	4 fewer per 1000 (from 105 fewer to 123 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	40/370 (10.8%)	2/89 (2.2%)	RR 4.81 (1.18 to 19.53)	86 more per 1000 (from 4 more to 416 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

[2] Confidence intervals compatible with benefit for diazepam or no difference

Health economic profile

Venlafaxine XL versus diazepam							
Study & country	**Limitations**	**Applicability**	**Other comments**	**Incremental cost (£)[1]**	**Incremental effect**	**ICER (£/effect)[1]**	**Uncertainty[1]**
Guest *et al.*, 2004 UK	Potentially serious limitations[2]	Partially applicable[3]	• Measure of outcome: percentage of people with successful treatment defined as CGI score of 1 at 6 months • Time horizon: 6 months	£56	10.8% extra successfully treated people	£516/ successfully treated person	Venlafaxine XL dominates - £2,203/successfully treated person Probabilistic analysis: venlafaxine XL dominated diazepam in at least 25% of iterations

1. Costs uplifted to 2009 UK pounds using the UK HCHS inflation index
2. Efficacy data derived selectively from one RCT; resource use estimated based on expert opinion; limited sensitivity analysis; funded by industry
3. UK / NHS perspective; no QALYs estimated but outcome measure considered relevant; utility scores for GAD are still scarce and of low quality

Hydroxyzine versus buspirone for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxyzine	Buspirone	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	81	82	-	SMD 0.26 lower (0.57 lower to 0.05 higher)	⊕⊕⊕O MODERATE	
At least one side effect												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	32/81 (39.5%)	31/82 (37.8%)	RR 1.05 (0.71 to 1.54)	19 more per 1000 (from 110 fewer to 204 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for hydroxyzine or no difference

[2] Confidence intervals compatible with benefit for either intervention

Buspirone versus lorazepam for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone	Lorazepam	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	23	20	-	SMD 0.29 lower (0.89 lower to 0.32 higher)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

Pregabalin versus lorazepam for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Lorazepam	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	66	68	-	MD 1.55 lower (3.22 lower to 0.12 higher)	⊕⊕⊕O MODERATE	
Non-response												
3	Randomised trials	No serious limitations	Serious[2]	No serious indirectness	Serious[3]	None	232/410 (56.6%)	108/200 (54%)	RR 1.04 (0.76 to	22 more per 1000 (from 130 fewer	⊕⊕OO LOW	

									1.44)	to 238 more)		
Non-remission												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	325/410 (79.3%)	151/200 (75.5%)	RR 1.05 (0.95 to 1.15)	38 more per 1000 (from 38 fewer to 113 more)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	59/410 (14.4%)	69/200 (34.5%)	RR 0.42 (0.31 to 0.56)	200 fewer per 1000 (from 152 fewer to 238 fewer)	⊕⊕⊕⊕ HIGH	
Dizziness												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	62/205 (30.2%)	22/136 (16.2%)	RR 1.85 (1.18 to 2.91)	138 more per 1000 (from 29 more to 309 more)	⊕⊕⊕O MODERATE	
Somnolence												
2	Randomised trials	No serious limitations	Serious[2]	No serious indirectness	Serious[1]	None	68/205 (33.2%)	78/136 (57.4%)	RR 0.62 (0.35 to 1.11)	218 fewer per 1000 (from 373 fewer to 63 more)	⊕⊕OO LOW	

[1] Confidence intervals compatible with benefit for pregabalin or no difference

[2] I-squared > 50%

[3] Confidence intervals compatible with benefit or no benefit

[4] Confidence intervals compatible with benefit for lorazepam or no difference

Pregabalin versus alprazolam for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Alprazolam	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	261	88	-	SMD 0.09 lower (0.33 lower to 0.15 higher)	⊕⊕⊕O MODERATE	
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	130/270 (48.1%)	55/93 (59.1%)	RR 0.81 (0.66 to 1)	112 fewer per 1000 (from 201 fewer to 0 more)	⊕⊕⊕O MODERATE	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	203/270 (75.2%)	69/93 (74.2%)	RR 1.01 (0.88 to 1.16)	7 more per 1000 (from 89 fewer to 119 more)	⊕⊕⊕⊕ HIGH	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	22/270 (8.1%)	12/93 (12.9%)	RR 0.63 (0.33 to 1.23)	48 fewer per 1000 (from 86 fewer to 30 more)	⊕⊕⊕O MODERATE	
Dizziness												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	96/270 (35.6%)	14/93 (15.1%)	RR 2.36 (1.42 to	205 more per 1000 (from 63 more to 441	⊕⊕⊕⊕ HIGH	

									3.93)	more)		
Somnolence												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	97/270 (35.9%)	39/93 (41.9%)	RR 0.86 (0.64 to 1.14)	59 fewer per 1000 (from 151 fewer to 59 more)	⊕⊕⊕O MODERATE	

[1] Confidence intervals compatible with benefit for either intervention

[2] Confidence intervals compatible with benefit for pregabalin or no difference

Comparing the effectiveness of different dosages

Venlafaxine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Control	Relative (95% CI)	Absolute		
HAM-A - Venlafaxine 75mg versus 150mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	87	87	-	MD 1.5 lower (3.15 lower to 0.15 higher)	⊕⊕⊕O MODERATE	
Non-response - Venlafaxine 75mg versus 150mg												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	122/278 (43.9%)	48.2%	RR 0.93 (0.78 to 1.12)	34 fewer per 1000 (from 106 fewer to 58 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Venlafaxine 37.5mg versus 75mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	11/141 (7.8%)	12.7%	RR 0.61 (0.3 to 1.26)	50 fewer per 1000 (from 89 fewer to 33 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Venlafaxine 75mg versus 150mg												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	34/325 (10.5%)	12.3%	RR 0.85 (0.55 to 1.32)	18 fewer per 1000 (from 55 fewer to 39 more)	⊕⊕⊕O MODERATE	

Nausea - Venlafaxine 37.5mg versus 75mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	31/140 (22.1%)	34.3%	RR 0.65 (0.44 to 0.95)	120 fewer per 1000 (from 17 fewer to 192 fewer)	⊕⊕⊕⊕ HIGH	
Nausea - Venlafaxine 75mg versus 150mg												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	120/328 (36.6%)	43.6%	RR 0.82 (0.68 to 0.98)	78 fewer per 1000 (from 9 fewer to 140 fewer)	⊕⊕⊕⊕ HIGH	
Nausea - Venlafaxine 150mg versus 225mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	46/91 (50.5%)	46.7%	RR 1.08 (0.8 to 1.46)	37 more per 1000 (from 93 fewer to 215 more)	⊕⊕⊕O MODERATE	
Insomnia - Venlafaxine 75mg versus 150mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/92 (17.4%)	29.7%	RR 0.59 (0.34 to 1.01)	122 fewer per 1000 (from 196 fewer to 3 more)	⊕⊕⊕⊕ HIGH	
Insomnia - Venlafaxine 150mg versus 225mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	27/91 (29.7%)	31.1%	RR 0.95 (0.61 to 1.48)	16 fewer per 1000 (from 121 fewer to 149 more)	⊕⊕⊕O MODERATE	
Nervousness - Venlafaxine 75mg versus 150mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	10/92 (10.9%)	17.6%	RR 0.62 (0.3 to 1.29)	67 fewer per 1000 (from 123 fewer to 51 more)	⊕⊕⊕O MODERATE	
Nervousness - Venlafaxine 150mg versus 225mg												
1	Randomised	No serious	No serious	No serious	Serious[1]	None	16/91	10%	RR 1.76	76 more per 1000	⊕⊕⊕O	

	trials	limitations	inconsistency	indirectness			(17.6%)		(0.82 to 3.77)	(from 18 fewer to 277 more)	MODERATE	
Dizziness - Venlafaxine 37.5mg versus 75mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	21/140 (15%)	21.6%	RR 0.69 (0.42 to 1.15)	67 fewer per 1000 (from 125 fewer to 32 more)	⊕⊕⊕O MODERATE	
Dizziness - Venlafaxine 75mg versus 150mg												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	70/328 (21.3%)	22%	RR 0.82 (0.56 to 1.2)	40 fewer per 1000 (from 97 fewer to 44 more)	⊕⊕⊕O MODERATE	
Dizziness - Venlafaxine 150mg versus 225mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	20/91 (22%)	7.6%	RR 2.91 (1.6 to 5.29)	145 more per 1000 (from 46 more to 326 more)	⊕⊕⊕⊕ HIGH	
Asthenia - Venlafaxine 75mg versus 150mg												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	24/194 (12.4%)	17.5%	RR 0.7 (0.43 to 1.13)	53 fewer per 1000 (from 100 fewer to 23 more)	⊕⊕⊕O MODERATE	
Asthenia - Venlafaxine 150mg versus 225mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	12/91 (13.2%)	21.1%	RR 0.62 (0.32 to 1.21)	80 fewer per 1000 (from 143 fewer to 44 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval

[2] No explanation was provided

Escitalopram for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Control	Relative (95% CI)	Absolute		
HAM-A - Escitalopram 5mg versus 10mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	134	134	-	SMD 0.23 higher (0.01 lower to 0.47 higher)	⊕⊕⊕O MODERATE	
HAM-A - Escitalopram 10mg versus 20mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	134	132	-	SMD 0.07 lower (0.31 lower to 0.17 higher)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	7/134 (5.2%)	5.9%	RR 0.89 (0.33 to 2.38)	6 fewer per 1000 (from 40 fewer to 81 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	8/136 (5.9%)	10.5%	RR 0.56 (0.24 to 1.29)	46 fewer per 1000 (from 80 fewer to 30 more)	⊕⊕⊕O MODERATE	

Nausea - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	20/134 (14.9%)	20.6%	RR 0.72 (0.43 to 1.22)	58 fewer per 1000 (from 117 fewer to 45 more)	⊕⊕⊕O MODERATE	
Nausea - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	28/136 (20.6%)	21.1%	RR 0.98 (0.61 to 1.56)	4 fewer per 1000 (from 82 fewer to 118 more)	⊕⊕⊕O MODERATE	
Fatigue - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	11/134 (8.2%)	10.3%	RR 0.8 (0.38 to 1.69)	21 fewer per 1000 (from 64 fewer to 71 more)	⊕⊕⊕O MODERATE	
Fatigue - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	14/136 (10.3%)	16.5%	RR 0.62 (0.33 to 1.16)	63 fewer per 1000 (from 111 fewer to 26 more)	⊕⊕⊕O MODERATE	
Headache - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	21/134 (15.7%)	25%	RR 0.63 (0.38 to 1.02)	93 fewer per 1000 (from 155 fewer to 5 more)	⊕⊕⊕O MODERATE	
Headache - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	34/136 (25%)	15.8%	RR 1.58 (0.97 to 2.58)	92 more per 1000 (from 5 fewer to 250 more)	⊕⊕⊕O MODERATE	
Insomnia - Escitalopram 5mg versus 10mg												
1	Randomised	No serious	No serious	No serious	Serious[1]	None	12/134 (9%)	12.5%	RR 0.72	35 fewer per 1000	⊕⊕⊕O	

	trials	limitations	inconsistency	indirectness					(0.36 to 1.44)	(from 80 fewer to 55 more)	MODERATE	
Insomnia - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	17/136 (12.5%)	10.5%	RR 1.19 (0.61 to 2.31)	20 more per 1000 (from 41 fewer to 138 more)	⊕⊕⊕O MODERATE	
Somnolence - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	10/134 (7.5%)	3.7%	RR 2.03 (0.71 to 5.78)	38 more per 1000 (from 11 fewer to 177 more)	⊕⊕⊕O MODERATE	
Somnolence - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	5/136 (3.7%)	7.5%	RR 0.49 (0.17 to 1.39)	38 fewer per 1000 (from 62 fewer to 29 more)	⊕⊕⊕O MODERATE	
Anxiety - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	9/134 (6.7%)	2.2%	RR 3.04 (0.84 to 11)	45 more per 1000 (from 4 fewer to 220 more)	⊕⊕⊕O MODERATE	
Anxiety - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	3/136 (2.2%)	3%	RR 0.73 (0.17 to 3.21)	8 fewer per 1000 (from 25 fewer to 66 more)	⊕⊕⊕O MODERATE	
Dizziness - Escitalopram 5mg versus 10mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	6/134 (4.5%)	10.3%	RR 0.43 (0.17 to 1.1)	59 fewer per 1000 (from 85 fewer to 10 more)	⊕⊕⊕O MODERATE	

Dizziness - Escitalopram 10mg versus 20mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	14/136 (10.3%)	9%	RR 1.14 (0.55 to 2.37)	13 more per 1000 (from 41 fewer to 123 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval

[2] No explanation was provided

Paroxetine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paroxetine**	**Control**	**Relative (95% CI)**	**Absolute**		
HAM-A - Paroxetine 20mg versus 40mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	188	197	-	MD 0.3 lower (2.02 lower to 1.42 higher)	⊕⊕⊕O MODERATE	
HADS-A - Paroxetine 20mg versus 40mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	188	197	-	MD 0.3 lower (2.02 lower to 1.42 higher)	⊕⊕⊕O MODERATE	
Non-response - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	72/189 (38.1%)	32%	RR 1.19 (0.91 to 1.57)	61 more per 1000 (from 29 fewer to 182 more)	⊕⊕⊕O MODERATE	

Non-remission - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	132/189 (69.8%)	64%	RR 1.09 (0.95 to 1.26)	58 more per 1000 (from 32 fewer to 166 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	19/189 (10.1%)	12.2%	RR 0.83 (0.47 to 1.46)	21 fewer per 1000 (from 65 fewer to 56 more)	⊕⊕⊕O MODERATE	
Nausea - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	36/189 (19%)	16.8%	RR 1.14 (0.74 to 1.74)	24 more per 1000 (from 44 fewer to 124 more)	⊕⊕⊕O MODERATE	
Somnolence - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	38/189 (20.1%)	17.8%	RR 1.13 (0.75 to 1.71)	23 more per 1000 (from 44 fewer to 126 more)	⊕⊕⊕O MODERATE	
Decreased libido - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	24/189 (12.7%)	10.7%	RR 1.19 (0.69 to 2.07)	20 more per 1000 (from 33 fewer to 114 more)	⊕⊕⊕O MODERATE	
Decreased appetite - Paroxetine 20mg versus 40mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	13/189 (6.9%)	6.1%	RR 1.13 (0.53 to 2.41)	8 more per 1000 (from 29 fewer to 86 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval

Duloxetine for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Control	Relative (95% CI)	Absolute		
HAM-A - Duloxetine 20mg versus 60-120mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	83	151	-	MD 0.6 higher (1.09 lower to 2.29 higher)	⊕⊕⊕O MODERATE	
HAM-A - Duloxetine 60mg versus 120mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	165	169	-	MD 0.34 lower (2.47 lower to 1.79 higher)	⊕⊕⊕O MODERATE	
HADS-A - Duloxetine 20mg versus 60-120mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	83	151	-	MD 0.7 higher (0.19 lower to 1.59 higher)	⊕⊕⊕O MODERATE	
HADS-A - Duloxetine 60mg versus 120mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	160	163	-	MD 0.18 lower (1.2 lower to 0.84 higher)	⊕⊕⊕O MODERATE	
Non-response - Duloxetine 20mg versus 60-120mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	34/84 (40.5%)	38%	RR 1.07 (0.77 to	27 more per 1000 (from 87 fewer to	⊕⊕⊕O	

									1.48)	182 more)	MODERATE	
Non-response - Duloxetine 60mg versus 120mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	71/168 (42.3%)	44.1%	RR 0.96 (0.75 to 1.22)	18 fewer per 1000 (from 110 fewer to 97 more)	⊕⊕⊕O MODERATE	
Non-remission - Duloxetine 60mg versus 120mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	116/168 (69%)	61.8%	RR 1.12 (0.96 to 1.31)	74 more per 1000 (from 25 fewer to 192 more)	⊕⊕⊕O MODERATE	
Sheehan Disability Scale - Duloxetine 60mg versus 120mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	156	160	-	MD 0.99 lower (2.9 lower to 0.92 higher)	⊕⊕⊕O MODERATE	
Q-LES-Q-SF - Duloxetine 60mg versus 120mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	136	129	-	MD 0.18 higher (2.21 lower to 2.57 higher)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Duloxetine 20mg versus 60-120mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	4/84 (4.8%)	12.7%	RR 0.38 (0.13 to 1.06)	79 fewer per 1000 (from 110 fewer to 8 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Duloxetine 60mg versus 120mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	19/168 (11.3%)	15.3%	RR 0.74 (0.43 to 1.28)	40 fewer per 1000 (from 87 fewer to 43 more)	⊕⊕⊕O MODERATE	

Discontinuation due to any reason - Duloxetine 60mg versus 120mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	33/168 (19.6%)	27.1%	RR 0.73 (0.49 to 1.08)	73 fewer per 1000 (from 138 fewer to 22 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval

Pregabalin for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Control	Relative (95% CI)	Absolute		
HAM-A - Pregabalin 150mg versus 600mg (Better indicated by lower values)												
1	No methodology chosen	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	69	61	-	MD 2.28 higher (0.58 to 3.98 higher)	⊕⊕⊕O MODERATE	
HAM-A - Pregabalin 200mg versus 400mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	78	89	-	MD 0.5 higher (1.07 lower to 2.07 higher)	⊕⊕⊕O MODERATE	
HAM-A - Pregabalin 300mg versus 450mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	89	87	-	MD 1.2 lower (2.77 lower to 0.37 higher)	⊕⊕⊕O MODERATE	

HAM-A - Pregabalin 400mg versus 450mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	89	88	-	MD 0.5 lower (2.07 lower to 1.07 higher)	⊕⊕⊕O MODERATE	
HAM-A - Pregabalin 400mg versus 600mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	94	104	-	MD 3.1 lower (4.69 to 1.51 lower)	⊕⊕⊕⊕ HIGH	
HAM-A - Pregabalin 450mg versus 600mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	87	85	-	MD 0.8 higher (0.77 lower to 2.37 higher)	⊕⊕⊕O MODERATE	
HADS-A - Pregabalin 400mg versus 600mg (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	94	104	-	MD 0.4 lower (1.41 lower to 0.61 higher)	⊕⊕⊕O MODERATE	
Non-response - Pregabalin 300mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	35/91 (38.5%)	53.3%	RR 0.72 (0.52 to 1)	149 fewer per 1000 (from 256 fewer to 0 more)	⊕⊕⊕⊕ HIGH	
Non-response - Pregabalin 450mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	48/90 (53.3%)	47.2%	RR 1.13 (0.84 to 1.51)	61 more per 1000 (from 76 fewer to 241 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Pregabalin 150mg versus 600mg												
1	Randomised	No serious	No serious	No serious	No serious	None	7/69	28.6%	RR 0.36	183 fewer per	⊕⊕⊕⊕	

	trials	limitations	inconsistency	indirectness	imprecision		(10.1%)		(0.16 to 0.79)	1000 (from 60 fewer to 240 fewer)	HIGH	
Discontinuation due to adverse events - Pregabalin 300mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	3/91 (3.3%)	7.8%	RR 0.42 (0.11 to 1.59)	45 fewer per 1000 (from 69 fewer to 46 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Pregabalin 400mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	6/97 (6.2%)	13.6%	RR 0.45 (0.18 to 1.12)	75 fewer per 1000 (from 112 fewer to 16 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events - Pregabalin 450mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	7/90 (7.8%)	14.6%	RR 0.53 (0.22 to 1.27)	69 fewer per 1000 (from 114 fewer to 39 more)	⊕⊕⊕O MODERATE	
Discontinuation for any reason - Pregabalin 400mg versus 600mg												
1	No methodology chosen					None	16/97 (16.5%)	26.4%	RR 0.63 (0.36 to 1.08)	98 fewer per 1000 (from 169 fewer to 21 more)		
Somnolence - Pregabalin 150mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	10/69 (14.5%)	35.7%	RR 0.41 (0.21 to 0.78)	211 fewer per 1000 (from 79 fewer to 282 fewer)	⊕⊕⊕⊕ HIGH	
Somnolence - Pregabalin 200mg versus 400mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	24/78 (30.8%)	37.1%	RR 0.83 (0.54 to	63 fewer per 1000 (from 171 fewer to	⊕⊕⊕O	

									1.27)	100 more)	MODERATE	
Somnolence - Pregabalin 300mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	35/91 (38.5%)	40%	RR 0.96 (0.67 to 1.38)	16 fewer per 1000 (from 132 fewer to 152 more)	⊕⊕⊕O MODERATE	
Somnolence - Pregabalin 400mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	33/89 (37.1%)	23.9%	RR 1.55 (0.98 to 2.46)	131 more per 1000 (from 5 fewer to 349 more)	⊕⊕⊕⊕ HIGH	
Somnolence - Pregabalin 400mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	13/97 (13.4%)	13.6%	RR 0.98 (0.49 to 1.96)	3 fewer per 1000 (from 69 fewer to 131 more)	⊕⊕⊕O MODERATE	
Somnolence - Pregabalin 450mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	36/90 (40%)	41.6%	RR 0.96 (0.68 to 1.37)	17 fewer per 1000 (from 133 fewer to 154 more)	⊕⊕⊕O MODERATE	
Dizziness - Pregabalin 150mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	16/69 (23.2%)	38.6%	RR 0.6 (0.36 to 1.01)	154 fewer per 1000 (from 247 fewer to 4 more)	⊕⊕⊕O MODERATE	
Dizziness - Pregabalin 200mg versus 400mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	27/78 (34.6%)	49.4%	RR 0.7 (0.48 to 1.01)	148 fewer per 1000 (from 257 fewer to 5 more)	⊕⊕⊕O MODERATE	

Dizziness - Pregabalin 300mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	37/91 (40.7%)	37.8%	RR 1.08 (0.75 to 1.55)	30 more per 1000 (from 94 fewer to 208 more)	⊕⊕⊕O MODERATE	
Dizziness - Pregabalin 400mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	44/89 (49.4%)	42.1%	RR 1.18 (0.85 to 1.62)	76 more per 1000 (from 63 fewer to 261 more)	⊕⊕⊕O MODERATE	
Dizziness - Pregabalin 400mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	22/97 (22.7%)	26.4%	RR 0.86 (0.53 to 1.39)	37 fewer per 1000 (from 124 fewer to 103 more)	⊕⊕⊕O MODERATE	
Dizziness - Pregabalin 450mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	34/90 (37.8%)	39.3%	RR 0.96 (0.66 to 1.39)	16 fewer per 1000 (from 134 fewer to 153 more)	⊕⊕⊕O MODERATE	
Nausea - Pregabalin 150mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	5/69 (7.2%)	8.6%	RR 0.85 (0.27 to 2.64)	13 fewer per 1000 (from 63 fewer to 141 more)	⊕⊕⊕O MODERATE	
Nausea - Pregabalin 300mg versus 450mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	10/91 (11%)	14.4%	RR 0.76 (0.35 to 1.65)	35 fewer per 1000 (from 94 fewer to 94 more)	⊕⊕⊕O MODERATE	

Nausea - Pregabalin 400mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	9/97 (9.3%)	12.7%	RR 0.73 (0.33 to 1.61)	34 fewer per 1000 (from 85 fewer to 77 more)	⊕⊕⊕O MODERATE	
Nausea - Pregabalin 450mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	13/90 (14.4%)	11.2%	RR 1.29 (0.59 to 2.78)	32 more per 1000 (from 46 fewer to 199 more)	⊕⊕⊕O MODERATE	
Headache - Pregabalin 150mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	13/69 (18.8%)	21.4%	RR 0.88 (0.45 to 1.71)	26 fewer per 1000 (from 118 fewer to 152 more)	⊕⊕⊕O MODERATE	
Headache - Pregabalin 400mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	7/97 (7.2%)	8.2%	RR 0.88 (0.34 to 2.28)	10 fewer per 1000 (from 54 fewer to 105 more)	⊕⊕⊕O MODERATE	
Insomnia - Pregabalin 400mg versus 600mg												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	1/97 (1%)	2.7%	RR 0.38 (0.04 to 3.57)	17 fewer per 1000 (from 26 fewer to 69 more)	⊕⊕⊕O MODERATE	

[1] Wide confidence interval

Maintenance treatment

Pregabalin versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute		
Relapse												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	71/168 (42.3%)	65.3%	RR 0.65 (0.53 to 0.8)	229 fewer per 1000 (from 131 fewer to 307 fewer)	⊕⊕⊕O MODERATE	
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	168	170	-	SMD 0.52 lower (0.73 to 0.3 lower)	⊕⊕⊕O MODERATE	
Discontinuation for any reason												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	61/168 (36.3%)	22.4%	RR 1.62 (1.15 to 2.29)	139 more per 1000 (from 34 more to 289 more)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	10/168 (6%)	2.4%	RR 2.53 (0.81 to 7.91)	37 more per 1000 (from 5 fewer to 166 more)	⊕⊕⊕O MODERATE	

[1] Only one study

[2] Wide confidence interval

Duloxetine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo	Relative (95% CI)	Absolute		
Relapse												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	28/204 (13.7%)	41.8%	RR 0.33 (0.22 to 0.48)	280 fewer per 1000 (from 217 fewer to 326 fewer)	⊕⊕⊕O MODERATE	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	68/213 (31.9%)	60.7%	RR 0.53 (0.42 to 0.66)	285 fewer per 1000 (from 206 fewer to 352 fewer)	⊕⊕⊕O MODERATE	
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1,2,3]	None	213	211	-	SMD 0.7 lower (0.9 to 0.51 lower)	⊕⊕⊕O MODERATE	
Q-LES-Q-SF (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	209	198	-	SMD 0.74 lower (0.94 to 0.53 lower)	⊕⊕⊕O MODERATE	
Discontinuation for any reason												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	49/216 (22.7%)	45.5%	RR 0.5 (0.37 to 0.66)	228 fewer per 1000 (from 155 fewer to 287 fewer)	⊕⊕⊕O MODERATE	

Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	4/216 (1.9%)	0.9%	RR 1.97 (0.37 to 10.65)	9 more per 1000 (from 6 fewer to 87 more)	⊕⊕⊕O MODERATE	

[1] High drop out
[2] Only one study
[3] Wide confidence interval

Paroxetine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Paroxetine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1,2]	None	30/274 (10.9%)	40.1%	RR 0.27 (0.19 to 0.39)	293 fewer per 1000 (from 245 fewer to 325 fewer)	⊕⊕⊕O MODERATE	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1,2]	None	74/274 (27%)	65.5%	RR 0.41 (0.33 to 0.51)	386 fewer per 1000 (from 321 fewer to 439 fewer)	⊕⊕⊕O MODERATE	
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1,2]	None	274	287	-	SMD 1.03 lower (1.2 to 0.85 lower)	⊕⊕⊕O MODERATE	

Discontinuation for any reason												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1,2]	None	62/278 (22.3%)	49%	RR 0.46 (0.36 to 0.58)	265 fewer per 1000 (from 206 fewer to 314 fewer)	⊕⊕⊕O MODERATE	
Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	11/278 (4%)	3.1%	RR 1.27 (0.53 to 3.01)	8 more per 1000 (from 15 fewer to 62 more)	⊕⊕⊕O MODERATE	

[1] Large drop out

[2] Only one study

Escitalopram versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Escitalopram**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Relapse												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	38/187 (20.3%)	56.4%	RR 0.36 (0.26 to 0.49)	361 fewer per 1000 (from 288 fewer to 417 fewer)	⊕⊕⊕O MODERATE	
Discontinuation for any reason												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	71/187 (38%)	72.3%	RR 0.52 (0.43 to 0.64)	347 fewer per 1000 (from 260 fewer to 412 fewer)	⊕⊕⊕O MODERATE	

Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	13/187 (7%)	8.5%	RR 0.82 (0.4 to 1.65)	15 fewer per 1000 (from 51 fewer to 55 more)	⊕⊕⊕O MODERATE	

[1] Only one study

Augmentation

Olanzapine versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: olanzapine	Placebo	Relative (95% CI)	Absolute		
HAM-A (Better indicated by lower values)												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	9	12	-	SMD 0.3 lower (1.17 lower to 0.57 higher)	⊕⊕OO LOW	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	8/12 (66.7%)	11/12 (91.7%)	RR 0.73 (0.47 to 1.12)	247 fewer per 1000 (from 486 fewer to 110 more)	⊕⊕OO LOW	
								91.7%		248 fewer per 1000 (from 486 fewer to 110 more)		
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	7/12 (58.3%)	11/12 (91.7%)	RR 0.64 (0.38 to 1.06)	330 fewer per 1000 (from 568 fewer to 55 more)	⊕⊕OO LOW	
								91.7%		330 fewer per 1000 (from 569 fewer to 55 more)		

Discontinuation due to adverse events												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	4/12 (33.3%)	8.3%	RR 4 (0.52 to 30.76)	249 more per 1000 (from 40 fewer to 2470 more)	⊕⊕OO LOW	

[1] 1 small study

Risperidone versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmentation: risperidone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A (Better indicated by lower values)												
2	Randomised trials	No serious limitations	serious[2]	No serious indirectness	serious[1]	None	215	214	-	SMD 0.27 lower (0.9 lower to 0.36 higher)	⊕⊕OO LOW	
Non-remission												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	158/196 (80.6%)	82%	RR 0.98 (0.89 to 1.08)	16 fewer per 1000 (from 90 fewer to 66 more)	⊕⊕⊕⊕ HIGH	
Non-response												
1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	117/196 (59.7%)	117/194 (60.3%)	RR 0.99 (0.84 to 1.16)	6 fewer per 1000 (from 96 fewer to 96 more)	⊕⊕⊕O MODERATE	
								60.3%		6 fewer per 1000 (from 96		

										fewer to 96 more)		
Discontinuation due to adverse events												
2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	24/215 (11.2%)	11/214 (5.1%)	RR 2.17 (1.09 to 4.32)	60 more per 1000 (from 5 more to 171 more)	⊕⊕⊕O MODERATE	
								5.1%		60 more per 1000 (from 5 more to 169 more)		

[1] Confidence intervals compatible with benefit and no benefit
[2]I-squared >50%

Antipsychotics versus placebo for GAD

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmentation: antipsychotics**	**Placebo**	**Relative (95% CI)**	**Absolute**		
HAM-A (Better indicated by lower values)												
5	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	245	244	-	MD 1.04 lower (2.49 lower to 0.41 higher)	⊕⊕⊕O MODERATE	
Non-response												
2	Randomised trials	No serious limitations	serious[3]	No serious indirectness	serious[2]	None	124/208 (59.6%)	128/206 (62.1%)	RR 0.85 (0.56 to 1.28)	93 fewer per 1000 (from 273 fewer to 174 more)	⊕⊕OO LOW	

								76%		114 fewer per 1000 (from 334 fewer to 213 more)		
Non-remission												
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	serious[1]	None	173/219 (79%)	179/217 (82.5%)	RR 0.93 (0.78 to 1.09)	58 fewer per 1000 (from 181 fewer to 74 more)	⊕⊕⊕O MODERATE	
								82%		57 fewer per 1000 (from 180 fewer to 74 more)		
Discontinuation due to adverse events												
5	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	37/279 (13.3%)	13/258 (5%)	RR 2.53 (1.38 to 4.64)	77 more per 1000 (from 19 more to 183 more)	⊕⊕⊕⊕ HIGH	
								5.2%		80 more per 1000 (from 20 more to 189 more)		

[1] Confidence intervals compatible with benefit for treatment or placebo

[2] 1 small study and 1 large study

[3] I-squared > 50%