1 Pharmacological interventions versus placebo and head-to head pharmacological interventions

1.1 Escitalopram vs Placebo for GAD

1,1		<u> </u>	Quality asses					S	ummary of	findings		
			~*** • 3 *****				No of pat	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Placebo	Relative (95% CI)	Absolute	Quality	
HAM-A	(change from	baseline) - Es	citalopram (Bette	er 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-resp	oonse - Escita	lopram	<u>'</u>			<u>'</u>						
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Non-rem	ission											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious²	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)	□□□□ MODERATE	
Disconti	nuation due t	o adverse ever	nts									
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												

	randomised trials mia - Escitalo	no serious limitations pram			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)		
2		no serious limitations		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)	□□□□ MODERATE	
Insomni	a											
2	randomised trials	no serious limitations	serious ⁴		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)		

¹ wide confidence interval compatible wih benefit and no benefit

Escitalopi	am versus plac	ebo]	
Study &	Limitations	Applicabili	Other comments	Increme	Incremental	ICER	Uncertainty	1	
country		ty		ntal cost	effect	(£/effect)	·		
				(£) ¹					
Guideli	Minor	Directly	• Time horizon: 42	-£ 7 4. <u>13</u> ,	0.0396	Escitalopra	Not relevant; both interventions dominated by sertraline;		Deleted: 8
ne	limitations ²	applicable ³	weeks	·		m dominant	probability of sertraline being cost-effective at £20,000/QALY:	77	
analysis			 Model included 6 				0.70		Deleted: 7
UK			drugs plus no						Deleted: 5
			treatment (placebo)						Doiotou:
1.0			O 1						`

1. Costs expressed in 2009 UK pounds

3. Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

Deleted: 1

² relatively wide confidence intervals

 $^{^{3}}$ very wide confidence interval

⁴ I-squared > 50%

^{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

1.2 Sertraline vs Placebo for GAD

			ssment					Summary of			
						No of pa	atients		Effect		Importance
Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Placebo	Relative (95% CI)	Absolute	Quality	
hange from	baseline) - Ser	traline (Better in	dicated by low	er values)							
		no serious inconsistency	no serious indirectness	no serious imprecision	none	347	351	-	MD 2.46 lower (4.53 to 0.39 lower)	HIGH	
nse - Sertral	ine										
andomised ials	no serious limitations	serious²	no serious indirectness	no serious imprecision	none	150/347 (43.2%)	213/351 (60.7%)	RR 0.71 (0.6 to 0.85)	(from 91 fower to		
sion				l	l						
		no serious inconsistency	no serious indirectness	serious¹	none	126/182 (69.2%)	154/188 (81.9%)	RR 0.85 (0.75 to 0.95)	(from 41 fewer to	DDDERATE	
ation due to	adverse even	its									
andomised ials	no serious limitations	serious²	no serious indirectness	serious³	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)	LOW	
		·		'	'	'		,		·	•
		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	
nu iii	ange from Indomised als	ange from baseline) - Sen andomised no serious limitations ase - Sertraline andomised no serious limitations ion addomised no serious limitations ation due to adverse even andomised no serious limitations ation due to adverse even andomised no serious limitations	ange from baseline) - Sertraline (Better in adomised limitations inconsistency inconsi	ange from baseline) - Sertraline (Better indicated by low indomised limitations inconsistency indirectness in	ange from baseline) - Sertraline (Better indicated by lower values) ndomised als limitations no serious inconsistency indirectness imprecision see - Sertraline ndomised als limitations serious serious² no serious indirectness imprecision ion ndomised als limitations no serious inconsistency indirectness serious¹ ation due to adverse events ndomised no serious limitations serious² no serious indirectness ation due to adverse events ndomised no serious limitations inconsistency indirectness ndomised als limitations no serious indirectness serious³ ation due to adverse events ndomised no serious limitations no serious indirectness ndomised no serious no serious indirectness	Design Limitations Inconsistency Indirectness Imprecision considerations	Design Limitations Inconsistency Indirectness Imprecision considerations Sertraline ange from baseline) - Sertraline (Better indicated by lower values) andomised als limitations no serious inconsistency indirectness imprecision none indomised als limitations limitations no serious indirectness imprecision none indirectness imprecision none indomised als limitations no serious indirectness imprecision none indomised als limitations no serious indirectness indirectness serious indirectness indirectness indirectness indirectness indirectness indirectness indirectness none indirectness imprecision none indirectness indirectness imprecision none indirectness imprecision none indirectness imprecision none imprecision non	Design Limitations Inconsistency Indirectness Imprecision considerations Sertraline Placebo considerations Cons	Design Limitations Inconsistency Indirectness Imprecision considerations Sertraline Placebo (95% CI) ange from baseline) - Sertraline (Better indicated by lower values) andomised no serious limitations inconsistency indirectness indirectness imprecision in one imprecision in o	Design Limitations Inconsistency Indirectness Imprecision Considerations Sertraline Placebo (95% CI) Absolute	Design Limitations Inconsistency Indirectness Imprecision Other considerations Sertraline Placebo (95% CI) Absolute

Ejaculati	on disorder										
			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)	□□□□ MODERATE	
Insomnia	ı										
			no serious indirectness	serious³	none	65/349 (18.6%)	52/352 (14.8%)	RR 1.26 (0.9 to 1.76)	itrom in tewer to		

¹ only data on 1 study

Sertraline	versus placebo)							
Study & country	Limitations	Applicabili ty	Other comments	Increme ntal cost (£)1	Incremental effect	ICER (£/effect)	Uncertainty		
Guideli	Minor	Directly	• Time horizon: 42	-£1 <u>53</u> ,3 <u>0</u> ,	0.0423	Sertraline	Probability of sertraline being cost-effective at £20,000/QALY:		Deleted: 68
ne analysis	limitations ²	applicable ³	weeksModel included 6			dominant	0.7 <mark>0,</mark>	();;;	Deleted: 83
UK			drugs plus no treatment (placebo)						Deleted: 2
1. Costs e	expressed in 20	09 UK pounds	пеаппені (ріасево)	<u>!</u>			<u> </u>	`,	Deleted: 1

^{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

1.3 Paroxetine vs Placebo for GAD

ĺ			Summary of findings		Importance
	Quality assessment				
		No of patients	Effect	Quality	

² I-squared >50%

³ wide confidence intervals compatible with benefit and harm

⁴ very small number of events

^{3.} Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetine	Placebo	Relative (95% CI)	Absolute		
HAM-A	(change from	baseline) - Par	roxetine (Better i	ndicated by low	ver values)		<u>'</u>					
	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-resp	onse - Paroxe	etine										
	randomised trials	no serious limitations	serious¹	no serious indirectness	serious²	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)	LOW	
Non-rem	ission											
	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	
Disconti	nuation due to	o adverse ever	its									
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)	□□□□ MODERATE	
Sexual p	roblem					L						
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious³	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)	□□□□ MODERATE	

Insomni	a									
4		no serious limitations		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)	

¹ I-squared >50%

Paroxetine	versus placeb	O							
Study & country	Limitations	Applicabili ty	Other comments	Increme ntal cost (£)1	Incremental effect	ICER (£/effect)	Uncertainty		
Guideli	Minor	Directly	• Time horizon: 42	-£1 <u>0</u> 6. <u>92</u>	0.0364	Paroxetine	Not relevant; both interventions dominated by sertraline;		Deleted: 2
ne	limitations ²	applicable ³	weeks			dominant	probability of sertraline being cost-effective at £20,000/QALY:	17.	Deleted 177
analysis			 Model included 6 				0.70	\	Deleted: 176
UK			drugs plus no						Deleted: 3
1. Costs of	expressed in 200)9 UK pounds	treatment (placebo)	<u> </u>					Deleted: 1

^{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

1.4 Citalopram vs Placebo for GAD

			Quality assess	ment					Summary o	of findings		
			~** · · · · · · · · · · · · · · · · · ·				No of pa	ntients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Citalopram	Placebo	Relative (95% CI)	Absolute	Quality	
Non-resp	onse											
1	randomised	no serious	no serious	no serious	serious ¹	none	6/17	0%	RR 0.46 (0.23 to	0 fewer per 1000 (from 0 fewer to 0		

² Confidence intervals compatible with benefit and no benefit

³ small number of events

^{3.} Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

	trials	limitations	inconsistency	indirectness			(35.3%)		0.93)	fewer)	MODERATE	
Non-rem	ission											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	none	9/17 (52.9%)	14/17 (82.4%)	RR 0.64 (0.39 to 1.06)	296 fewer per 1000 (from 502 fewer to 49 more)		
Discorti								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
Disconti	nuation due to	o adverse even	ts									
1	randomised trials	no serious limitations		no serious indirectness	serious¹	none	1/17 (5.9%)	0%	RR 3.00 (0.13 to 68.8)	0 more per 1000 (from 0 fewer to 0 more)	MODERATE	

¹ Only one study

1.5 Duloxetine vs Placebo for GAD

			Quality asses	ssment				5	Summary of	f findings		
							No of pa	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Placebo	Relative (95% CI)	Absolute	Quality	
HAM-A	Mean change	from baseline	(Better indicated	l by lower valu	es)	ı						
4					no serious imprecision	none	799	654	-	MD 3.15 lower (4.1 to 2.21 lower)	HIGH	
Non-Res	sponse											
4		no serious limitations			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)	□□□□ MODERATE	

Non-rei	mission											
1	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)	LOW	
Discont	tinuation due t	to adverse eve	nts									
ŧ	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)	□□□□ 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)		
Sexual 1	problems	1		<u>'</u>								
	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	
nsomn	iia	1				1						
!	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		1		1	L			1		

¹ I-squared >50%

Duloxetin	e versus placeb	0					
Study &	Limitations	Applicabili	Other comments	Increme	Incremental	ICER	Uncertainty
country		ty		ntal cost	effect	(£/effect)	·

				(£)¹				
Guideli	Minor	Directly	• Time horizon: 42	-£ <u>19,46,</u>	0.040 <u>5</u>	Duloxetine	Not relevant; both interventions dominated by sertraline;	 Deleted: 35
ne analysis	limitations ²	applicable ³	weeksModel included 6			dominant	probability of sertraline being cost-effective at £20,000/QALY: 0.70	Deleted: 096
UK			drugs plus no treatment (placebo)					Deleted: 4
1. Costs	expressed in 20	09 UK pounds	<i>u</i> /	<u> </u>	<u> </u>			Deleted: 1

^{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

1.6 Venlafaxine vs Placebo for GAD

			Quality asses	ssment				9	Summary of	findings		
							No of pa	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Placebo	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ited by lower	values)									
5	randomised trials	no serious limitations	serious¹	no serious indirectness	no serious imprecision	none	595	582	-	MD 3.16 lower (4.81 to 1.51 lower)	□□□□ MODERATE	
Non-res	oonse											
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)	 MODERATE	
Non-rem	ission											
6	randomised trials	no serious limitations	serious¹	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	□□□□ MODERATE	

^{3.} Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

									fewer)		
tinuation due t	o adverse eve	ents									
	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	
	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	437/1253 (34.9%)	117/976 (12%)		-		
tion disorder	L					L					
randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious 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)	OODERATE	
iia			1		•	ı					
	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)	□□□□ MODERATE	
	randomised trials randomised trials tion disorder randomised trials	randomised trials limitations randomised no serious limitations tion disorder randomised no serious limitations tion disorder randomised no serious limitations	randomised no serious limitations inconsistency randomised limitations no serious inconsistency tion disorder randomised no serious inconsistency limitations inconsistency randomised no serious inconsistency	randomised trials no serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency indirectness indirectness indirectness indirectness inconsistency indirectness indirectness inconsistency indirectness ind	randomised no serious inconsistency indirectness imprecision randomised trials no serious inconsistency indirectness imprecision randomised trials no serious inconsistency indirectness imprecision tion disorder randomised no serious inconsistency indirectness imprecision randomised no serious inconsistency indirectness serious² trials limitations no serious inconsistency indirectness indirectness randomised no serious serious inconsistency indirectness no serious²	randomised trials no serious inconsistency indirectness imprecision none i	randomised trials no serious inconsistency no serious indirectness no serious imprecision none imprecision n	randomised trials no serious limitations no serious inconsistency no serious indirectness no serious inconsistency no serious indirectness indi	randomised trials no serious limitations no serious inconsistency indirectness no serious indirectness imprecision none limitations no serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency indirectness no serious inconsistency limitations no serious inconsistency indirectness no serious indirectness indirectness none limitations no serious inconsistency indirectness inconsistency indirectness inconsistency indirectness inconsistency indirectness inconsistency inconsistency indirectness inconsistency inconsistency inconsistency indirectness inconsistency	randomised trials no serious limitations n	randomised trials no serious inconsistency indirectness imprecision none indirectness imprecision indirectness imprecision none indirectness imprecision none indirectness imprecision indirectnes imprecision indirectness imprecision indirectness imprecision indi

¹ I-squared >50%

Venlafa	xine XL versus p	lacebo							
Study &	Limitations	Applicabili ty	Other comments	Increme ntal cost	Incremental effect	ICER (£/effect)	Uncertainty	/	Deleted: 109
Guideli	Minor	Directly	• Time horizon: 42	(£)1	0.0400	Venlafaxine	Not relevant; both interventions dominated by sertraline;	1/	Deleted: 156
ne	limitations ²	applicable ³	weeks	-£ <u>95,66,</u>	0.0400	XL	probability of sertraline being cost-effective at £20,000/QALY:		Deleted: 399
analysis			 Model included 6 			dominant	0.70,		Deleted: 1

² small number of events

UK	drugs plus no
	treatment (placebo)

- 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

1.7 Imipramine vs Placebo for GAD

			Quality assessn	nent				S	Summary	of findings		
							No of pat	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine		Relative (95% CI)	Absolute	Quality	
HAM-A (Better indicate	d by lower value	es)									
			no serious inconsistency	no serious indirectness	very serious¹	none	14	14	-	SMD 0.49 lower (1.24 lower to 0.27 higher)	LOW	

¹ 1 small study and very wide CIs

1.8 Pregabalin vs Placebo for GAD

			Quality asses	ssment				9	Summary of	f findings		
							No of pa	tients		Effect	Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute	Quanty	
HAM-A	(Better indica	ted by lower v	alues)									
					no serious imprecision	none	821	475	-	MD 2.97 lower (3.7 to 2.24 lower)	HIGH	

Non-res	ponse											
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)		
Non-ren	nission											
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	
Disconti	nuation due t	o adverse ever	nts									
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	serious¹	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)	□□□□ MODERATE	
Insomni	a									L		
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious²	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)	MODERATE	
Dizzine	ss					1						
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	no serious	no serious	no serious	serious ³	none	12/121	5/128	RR 2.54	60 more per 1000		

trials	limitations	inconsistency	indirectness		(9.9%)	(3.9%)	(0.92 to	(from 3 fewer to	MODERATE	
							6.99)	234 more)		

¹ Confidence intervals compatible with benefit or harm

Pregabali	n versus placeb	0					
Study & country	Limitations	Applicabili ty	Other comments	Increme ntal cost (£)1	Incremental effect	ICER (£/effect)	Uncertainty
Guideli ne analysis	Minor limitations ²	Directly applicable ³	 Time horizon: 42 weeks Model included 6	£151.79.	0.04 <u>03</u>	£3,768/QAL <u>Y</u>	Not relevant; both interventions dominated by sertraline; probability of sertraline being cost-effective at £20,000/QALY: 0.70
UK			drugs plus no treatment (placebo)				

^{1.} Costs expressed in 2009 UK pounds

Deleted: -

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 $\textbf{Deleted:} \ \operatorname{Pregabalin}$

dominant

Deleted: 1

1.9 Diazepam vs Placebo for GAD

			Quality asses	ssment					Summary o	f findings		
							No of pa	atients		Effect	Quality	Importance
No of studies	No of Design Limitations Inconsistency Indirectness Imprecision Other Diazenam Placeho Relative Absolute									Quanty		
HAM-A	(Better indica	ted by lower v	alues)									
				no serious indirectness	serious ¹	none	12	12	-	SMD 0.21 lower (1.01 lower to 0.59 higher)	□□□□ MODERATE	
Non-resp	oonse	I	1	l	ı	L	1		1	1		

² small number of events

³ data only for 1 study

^{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

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)		
Disconti	nuation due to	o adverse ever	its									
4		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)	MODERATE	
Libido												
1		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)	i i from ti fewer to ti	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)	□□□□ MODERATE	
Dizzines	is											
2		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

1.10 Alprazolam vs Placebo for GAD

			Quality asses	sment			!	Summary of	findings			
							No of pa	tients		Effect	Quality	Importance
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Alprazolam	Placebo	Relative	Absolute		

² data only on 1 study

tudies						considerations			(95% CI)			
ituares						Considerations			(95% CI)			
AM-A	(Better indica	ted by lower v	alues)			·						
			-	1	_							
		no serious	no serious	no serious	no serious	none	209	210	_	MD 2.53 lower		
	trials	limitations	inconsistency	indirectness	imprecision					(3.9 to 1.17 lower)	HIGH	
lon-resp	oonse		1	J							<u> </u>	
	randomised	no serious	no serious	no serious	serious ¹	none	EE /02	(2/01	RR 0.87	89 fewer per 1000		
	trials	limitations	inconsistency	indirectness			55/93 (59.1%)	62/91 (68.1%)	(0.7 to 1.08)	(from 204 fewer to	□□□□ MODERATE	
							(39.170)	(00.170)	(0.7 to 1.00)	55 more)	MODERATE	
lon-rem	ission											
	randomised	no serious	no serious	no serious	serious ²	none			RR 0.89	92 fewer per 1000		
	trials	limitations	inconsistency	indirectness			69/93	76/91	(0.76 to	(from 200 fewer to		
			,				(74.2%)	(83.5%)	1.03)	25 more)	MODERATE	
Disconti	l nuation due t	o adverse ever	nts									
	1	1		1	1	+	1		1		1	
		no serious	no serious	no serious	serious ¹	none	12/93	9/91	RR 1.3	30 more per 1000		
	trials	limitations	inconsistency	indirectness			(12.9%)	(9.9%)	(0.58 to	(from 42 fewer to	MODERATE	
							, ,	, ,	2.95)	193 more)		
lausea		l	<u>'</u>	,							<u> </u>	
	randomised	no serious	no serious	no serious	serious ¹	none	12/258	16/258	RR 0.74	16 fewer per 1000	0000	
	trials	limitations	inconsistency	indirectness			(4.7%)	(6.2%)	(0.36 to	(from 40 fewer to	MODERATE	
							(4.7 /0)	(0.270)	1.52)	32 more)	WODEKATE	
nsomnia	a		1									
	randomised	no serious	no serious	no serious	serious ¹	none		E /62	RR 0.59	33 fewer per 1000	0000	
	trials	limitations	inconsistency	indirectness			3/63 (4.8%)	5/62 (8.1%)	(0.15 to	(from 69 fewer to	□□□□ MODERATE	
								(8.1%)	2.37)	110 more)	MODEKATE	
atigue												
_												

1			no serious indirectness	serious¹	none	3/63 (4.8%)	4/62 (6.5%)		17 fewer per 1000 (from 54 fewer to 139 more)	
Dizzines	s									
3			no serious indirectness	serious¹	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)	

¹ Confidence intervals compatible with benefit and no benefit

1.11 Lorazepam vs Placebo for GAD

			Quality asses	ssment				9	Summary o	f findings		
							No of pa	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Lorazepam	Placebo	Relative (95% CI) Absolute	Absolute	Quality	
HAM-A	(Better indica	ted by lower v	alues)									
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-res	ponse									'		
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)		
Non-ren	nission											
3	randomised trials	no serious limitations	serious ¹	no serious indirectness	serious²	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)	LOW	

² No explanation was provided

Discont	inuation due t	o adverse ever	nts									
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)		
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)	OOO OOO	
Insomn	ia											
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)	VERY LOW	
Dizzine	ss									<u>'</u>		
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%

1.12 Buspirone vs Placebo for GAD

	2 Work II								Summary o	f findings			
			Quality asses	sment				. .	. 0				
							No of pa	atients		Effect		Importance	
											Quality		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone	Placebo	Relative (95% CI)	Absolute	2		
HAM-A (Better indicated by lower values)													

² Confidence intervals compatible with benefit and no benefit

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-res	ponse											
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)	MODERATE	
Disconti	nuation due t	o adverse eve	nts									
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		1	<u> </u>			.	1	1			<u> </u>	
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	
Insomni	a	L					L	L				
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)	MODERATE	
Dizzines	SS	,	•	•			,	•		,		
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

1.13 Hydroxyzine vs Placebo for GAD

		•	Quality asses	ssment				9	Summary of	findings		
							No of pat	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxyzine	Placebo	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ted by lower v	values)									
		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-resp	onse											
		no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Disconti	nuation due t	o adverse ever	its									
		no serious limitations		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)		

¹ confidence intervals compatible with benefit or no benefit

1.14 Escitalopram vs Paroxetine for GAD

		-	Quality asses	ssment				Su	mmary of f	indings		
							No of pa	atients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Paroxetine	Relative (95% CI)	Absolute	Quality	
HAM-A								•				

2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/326 (0%)	0/197 (0%)	SMD -0.32 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	OOOO	
								0%		(from 0 fewer to 0 fewer)		
Non-res	ponse											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/269 (24.2%)	56/140 (40%)	RR 0.60 (0.45 to 0.81)	160 fewer per 1000 (from 76 fewer to 220 fewer)	HIGH	
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Disconti	nuation due t	o adverse eve	ents									
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	22/269 (8.2%)	13/140 (9.3%)	RR 0.88 (0.46 to 1.69)	11 fewer per 1000 (from 50 fewer to 64 more)		
								0%	1.09)	0 fewer per 1000 (from 0 fewer to 0 more)		
Diarrhea	1											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	26/269 (9.7%)	12/140 (8.6%)	RR 1.13 (0.59 to 2.17)			
								0%		0 more per 1000 (from 0 fewer to 0 more)		
Sexual p	roblems		•		•			•				
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	11/269 (4.1%)	10/140 (7.1%)	RR 0.57 (0.25 to 1.32)	31 fewer per 1000 (from 54 fewer to 23 more)	DDDD MODERATE	

						0%	0 fewer per 1000 (from 0 fewer to 0 more)	
Anxiety								
1		no serious indirectness	serious ¹	none	7/269 (2.6%)	7/140 (5%)	24 fewer per 1000 (from 41 fewer to 23 more)	
						0%	0 fewer per 1000 (from 0 fewer to 0 more)	

¹ Wide confidence interval

Escitatopra	m versus par	oxetine						
Study & country	Limitatio ns	Applicabilit y	Other comments	Incremen tal cost (£)1	Incremental effect	ICER (£/effect) ¹	Uncertainty ¹	
Iskedjian et al., 2008 Canada	Potentiall y serious limitation s ²	Partially applicable ³	 Measure of outcome: number of symptom- free days (SFDs) Time horizon: 24 weeks 	£32	9.4SFDs	£3.4/SFD	£2.9-£4.49/SFD	
Jørgensen et al., 2006 UK	Potentiall y serious limitation s ⁴	Directly applicable⁵	 Measure of outcome: % of people with maintained response Time horizon: 36 weeks 	-£45	7.7% more people with maintained response	Escitalopra m dominant	Escitalopram dominant	
Guideline	Minor	Directly	• Time horizon: 42	£32.78	0.0032	£1 <mark>0,179</mark> /	Not relevant; both interventions dominated by	 Deleted: 41.5
analysis UK	limitation s ⁶	applicable ⁷	weeks • Model included 6			QALY	sertraline; probability of sertraline being cost- effective at £20,000/QALY: 0.70	Deleted: 2
			drugs plus no treatment (placebo)					Deleted: 893

- 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 health-related quality of life not considered; costs associated with management of side effects no considered
- 7. Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

1.15 Sertraline vs Paroxetine for GAD

									Summary o	f findings		
			Quality assess	ment					•	Ü		
							No of	patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Paroxetine	Relative (95% CI)	Absolute	Quality	
Non-rem	ission											
1			no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Non-resp	oonse											
1			no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	

¹ Confidence intervals compatible with benefit for either intervention

	Sertraline	versus paroxet	ine						1	
	Study & country	Limitations	Applicabili ty	Other comments	Increme ntal cost (£)1	Incremental effect	ICER (£/effect)	Uncertainty		
	Guideli ne	Minor	Directly	• Time horizon: 42	-£4 <u>6,38,</u>	0.0059	Sertraline	Probability of sertraline being cost-effective at £20,000/QALY:		Deleted: 2
I	ne analysis	limitations ²	applicable ³	weeks • Model included 6			dominant	0.70	(````	Deleted: 207
	UK			drugs plus no						Deleted: 1
				treatment (placebo)						

^{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

1.16 Escitalopram vs Venlafaxine for GAD

		_	Quality assess	sment				Sui	mmary of fi	indings		
							No of p	atients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram	Venlafaxine	Relative (95% CI)	Absolute	Quality	
Non-resp	onse						-	-				
1	randomised trials		no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Non-rem	ission											
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)	□□□□ MODERATE	
Disconti	nuation due t	o adverse ever	nts									
1	randomised trials		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)	□□□□ MODERATE	

¹ Confidence intervals compatible with benefit for either intervention

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

Escitalop	ram versus venl	afaxine XL						1
Study & country	Limitations	Applicabili ty	Other comments	Increme ntal cost (£)1	Incremental effect	ICER (£/effect)	Uncertainty	
Guideli	Minor	Directly	 Time horizon: 42 	£21. <u>53</u>	-0.0004	Venlafaxine	Not relevant; both interventions dominated by sertraline;	
ne	limitations ²	applicable ³	weeks	=		XL	probability of sertraline being cost-effective at £20,000/QALY:	1
analysis			 Model included 6 			dominant	0.70	
UK			drugs plus no					1
			treatment (placebo)					

Deleted: 4

Deleted: 458

Deleted: 1

1.17 Duloxetine vs Venlafaxine for GAD

			Quality assess	sment				Su	mmary of f	indings		
							No of 1	patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Venlafaxine	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ted by lower v	alues)		L			<u> </u>				
2				no serious indirectness	serious¹	none	320	333	-	MD 0.2 higher (0.92 lower to 1.32 higher)	□□□□ MODERATE	
Non-res	ponse											
2		no serious limitations		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)		
Non-rem	nission											
2	randomised trials			no serious indirectness	serious³	none	219/320 (68.4%)	215/333 (64.6%)	RR 1.07 (0.94 to	45 more per 1000 (from 39 fewer to	□□□□ MODERATE	

^{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

									1.21)	136 more)		
heeha	n Disability So	ale (Better inc	licated by lower	values)								
	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)	MODERATE	
Discont	inuation due t	o adverse eve	nts									
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	MODERATE	
Diarrhe	a											
	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)	MODERATE	

¹ Confidence intervals compatible with benefit for either intervention

Duloxeti	ne versus venla	faxine XL]	
Study & country	Limitations	Applicabili ty	Other comments	Increme ntal cost (£)1	Incremental effect	ICER (£/effect)	Uncertainty		
Guideli	Minor	Directly	 Time horizon: 42 	£7 <u>6,2</u> 0	0.0005	£15 <u>4</u> ,7 <u>42</u>	Not relevant; both interventions dominated by sertraline;		Deleted: 4
ne	limitations ²	applicable ³	weeks			/QALY	probability of sertraline being cost-effective at £20,000/QALY:	11	2 1 1 1 60
analysis			 Model included 6 				0.7 <u>Q</u>	```.	Deleted: 60
UK			drugs plus no treatment (placebo)						Deleted: 0
1. Costs	expressed in 20	09 UK pounds	4 /					, , , , , , , , , , , , , , , , , , ,	Deleted: 61

^{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

25

Deleted: 1

² I-squared >50%

³ Confidence intervals compatible with benefit for venlafaxine or no difference

^{3.} Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

1.18 Venlafaxine vs Pregabalin for GAD

			Quality asse	ssment				Su	mmary of f	findings		
							No of p	atients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Pregabalin	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ated 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)	MODERATE	
Non-res	ponse											
2	randomised trials	no serious limitations	serious²	no serious indirectness	serious³	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)		
Non-ren	nission		L	I.		L						
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)	MODERATE	
Q-LES-Q	(Better indic	cated 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)	□□□□ MODERATE	
Disconti	nuation due	to adverse eve	nts	-		<u> </u>				<u> </u>		1
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	45/238 (18.9%)	36/328 (11%)	RR 1.72 (1.15 to 2.58)	79 more per 1000 (from 16 more to 173 more)		
				•								

Dizzines	SS											
2		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	
Insomni	a											
2		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	
Somnole	ence											
2		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		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

Venlafaxin	e XL versus p	regabalin					
Study &	Limitatio	Applicabili	Other comments	Increme	Incrementa	ICER	Uncertainty ¹
country	ns	ty		ntal cost	1 effect	(£/effect)1	
				(£)¹			

² I-squared > 50%

 $^{^{\}scriptscriptstyle 3}$ Confidence intervals compatible with benefit for either intervention

⁴ data from only one study

Vera- Llonch et al., 2010 Spain	Potentiall y serious limitation s 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	Minor	Directly	• Time horizon: 42	-£247,45	<u>-</u> 0.00 <u>0</u> 3	£ <u>783,543</u>	Not relevant; both interventions dominated by sertraline;
analysis UK	limitation s ⁴	applicable⁵	weeks • Model included 6 drugs plus no treatment (placebo)			/QALY	probability of sertraline being cost-effective at £20,000/QALY: 0.74

1. Costs converted and uplifted to 2009 UK pounds, using 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 health-related quality of life not considered; costs associated with management of side effects no considered

5. Analysis conducted to assist guideline development; NHS & personal social services perspective; QALYs estimated based on SF-6D

1.19 Venlafaxine vs Buspirone for GAD

			Quality asses	ssment				Sı	ımmary of	findings		
							No of pa	atients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Buspirone	Relative (95% CI)	Absolute	Quality	
Non-resp	ponse											
			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)	MODERATE	
Disconti	nuation due t	o adverse ever	nts			,				·		
1			no serious inconsistency	no serious indirectness	serious²	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)	OODERATE	

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Dizzines	s										
1				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 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)	□□□□ MODERATE	

¹ Confidence intervals compatible with benefit for either intervention

1.20 Venlafaxine vs Diazepam for GAD

			and parameter of					C.	ummary of	findings		
			Quality assess	ment				3	ummary or	imumgs		
			~ ,				No of pa	ntients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	Diazepam	Relative (95% CI)	Absolute	- Quality	
Non-resp	onse											
	randomised trials	no serious limitations		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)	DDDERATE	
Disconti	nuation due t	o adverse ever	its									
	randomised trials	no serious limitations		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)	MODERATE	

¹ Confidence intervals compatible with benefit for either intervention

 $^{^{\}rm 2}$ Confidence intervals compatible with benefit for buspirone or no difference

² Confidence intervals compatible with benefit for diazepam or no difference

Venlafax	cine XL versus	diazepam					
Study & countr	Limitatio ns	Applicability	Other comments	Incremen tal cost (£)¹	Incremental effect	ICER (£/effect) ¹	Uncertainty ¹
Guest et al., 2004 UK	Potentially serious limitations	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

1.21 Hydroxyzine vs Buspirone for GAD

			Quality assess	ment				Sı	ummary of	findings		
							No of pa	atients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxyzine	Buspirone	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ted by lower v	alues)									
				no serious indirectness	serious ¹	none	81	82	-	SMD 0.26 lower (0.57 lower to 0.05 higher)	□□□□ MODERATE	
At least o	one side effec				,							
				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)	□□□□ MODERATE	

¹ Confidence intervals compatible with benefit for hydroxyzine or no difference

² Confidence intervals compatible with benefit for either intervention

1.22 Buspirone vs Lorazepam for GAD

			Quality assess	ment				5	Summary	of findings		
							No of p	oatients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone	Lorazepam	Relative (95% CI)	Absolute	Quality	
HAM-A	Better indicate	ed by lower val	ues)									
		no serious limitations		no serious indirectness	serious ¹	none	23	20	ı	SMD 0.29 lower (0.89 lower to 0.32 higher)	□□□□ MODERATE	

¹ Confidence intervals compatible with benefit for either intervention

1.23 Pregabalin vs Lorazepam for GAD

			Quality asses	ssment				Sı	ımmary of	findings		
			~,				No of p	patients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Lorazepam	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ited by lower v	values)									
1				no serious indirectness	serious ¹	none	66	68	-	MD 1.55 lower (3.22 lower to 0.12 higher)	□□□□ MODERATE	
Non-resp	ponse					,						
3		no serious limitations		no serious indirectness	serious³	none	232/410 (56.6%)	108/200 (54%)	RR 1.04 (0.76 to 1.44)	22 more per 1000 (from 130 fewer to 238 more)	LOW	

Non-ren	nission											
3		no serious limitations		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)		
Disconti	nuation due t	to adverse ever	nts									
3		no serious limitations		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	
Dizzines	SS											
2		no serious limitations		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)		
Somnole	ence											
2		no serious limitations	serious²	no serious indirectness	serious¹	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)	LOW	

¹ Confidence intervals compatible with benefit for pregabalin or no difference

1.24 Pregabalin vs Alprazolam for GAD

			Quality asses	ssment				St	ımmary of i	findings		
							No of 1	patients		Effect	Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Alprazolam	Relative (95% CI)	Absolute	Quanty	

² I-squared > 50%

³ Confidence intervals compatible with benefit or no benefit

⁴ Confidence intervals compatible with benefit for lorazepam or no difference

	randomised	no serious	no serious	no serious	serious1	none				SMD 0.09 lower	
	trials	limitations	inconsistency	indirectness			261	88	-	(0.33 lower to 0.15 higher)	MODERATE
on-res	ponse										
	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)	□□□□ MODERATE
on-rer	nission										
	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
Discont	inuation due	to adverse eve	ents								
	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)	MODERATE
Dizzine	ss	I.							ı		
	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 3.93)	205 more per 1000 (from 63 more to 441 more)	HIGH
											L L
omnol	ence										

¹ Confidence intervals compatible with benefit for either intervention

 $^{^{\}rm 2}$ Confidence intervals compatible with benefit for pregabalin or no difference

2 Comparing the effectiveness of different dosages

2.1 Venlafaxine for GAD

2.1	Veniur	axille for G							Summary	of findings		
			Quality asses	ssment								
			~ ,		No of patients		Effect			Importance		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine	control	Relative (95% CI)	Absolute	Quality	
HAM-A	HAM-A - Venlafaxine 75mg vs 150mg (Better indicated by lower values)											
								_				
1		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)	□□□□ MODERATE	
Non Res	ponse - Venla	faxine 75mg vs	5 150mg			<u>'</u>				l		
2		no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Disconti	nuation due to	Adverse Ever	nts - Venlafaxine	37.5mg vs 75mg	5	<u> </u>						
1		no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Disconti	nuation due to	Adverse Ever	nts - Venlafaxine	75mg vs 150mg								
2		no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	□□□□ MODERATE	
Nausea -	Venlafaxine 3	37.5mg vs 75mg	g	<u>'</u>	,	<u>'</u>				 		
1	randomised	no serious	no serious	no serious	no serious	none	31/140	34.3%	RR 0.65 (0.44 to	120 fewer per 1000 (from 17 fewer to	0000	

	trials	limitations	inconsistency	indirectness	imprecision		(22.1%)		0.95)	192 fewer)	HIGH	
Nausea	- Venlafaxine	75mg vs 150m	ng									
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 vs 2251	mg	•			•	l				
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)	DDDERATE	
Insomn	ia - Venlafaxin	e 75mg vs 150	Omg									
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	
Insomn	ia - Venlafaxin	e 150mg vs 22	25mg	•								
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)	MODERATE	
Nervous	sness - Venlafa	xine 75mg vs	150mg	1							<u> </u>	
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	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)	DDD MODERATE	
Nervous	sness - Venlafa	ixine 150mg v	rs 225mg									
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	none	16/91 (17.6%)	10%	RR 1.76 (0.82 to 3.77)	76 more per 1000 (from 18 fewer to 277 more)	□□□□ MODERATE	
Dizzine	ss - Venlafaxir	ne 37.5mg vs 7	75mg									

			1	t	1	1	1						
		no serious limitations		no serious indirectness	serious¹	none	21/140 (15%)	21.6%	RR 0.69 (0.42 to 1.15)	67 fewer per 1000 (from 125 fewer to 32 more)	MODERATE		
Dizziness	vizziness - Venlafaxine 75mg vs 150mg												
		no serious limitations		no serious indirectness	serious¹	none	70/328 (21.3%)	22%	RR 0.82 (0.56 to 1.2)	40 fewer per 1000 (from 97 fewer to 44 more)	MODERATE		
Dizziness	s - Venlafaxin	e 150mg vs 22	5mg										
		no serious limitations		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	e 75mg vs 150n	ng										
		no serious limitations		no serious indirectness	serious¹	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)	MODERATE		
Asthenia - Venlafaxine 150mg vs 225mg													
	randomised trials	no serious limitations		no serious indirectness	serious¹	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)	□□□□ MODERATE		

¹ Wide confidence interval

2.2 Escitalopram for GAD

			Quality assess	ment								
								No of patients		Effect		Importance
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Escitalopram	control	Relative	Absolute		

² No explanation was provided

studies						considerations			(95% CI)			
HAM-A	 - Escitalopram	 5mg vs 10mg	(Better indicated	by lower value	s)							
					-,							
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)	□□□□ MODERATE	
HAM-A	- Escitalopram	10mg vs 20m	g (Better indicate	d by lower valu	es)							
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)	MODERATE	
Disconti	nuation due to	Adverse ever	nts - Escitalopram	5mg vs 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)	□□□□ MODERATE	
Disconti	nuation due to	Adverse ever	nts - Escitalopram	10mg vs 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)	□□□□ MODERATE	
Nausea -	Escitalopram	5mg vs 10mg			1						<u> </u>	
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)	MODERATE	
Nausea -	Escitalopram	10mg vs 20mg	5	•	•							
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)	□□□□ MODERATE	
Fatigue -	Escitalopram	5mg vs 10mg										

	1	1	1	1	1	1	-					
1	randomised	no serious	no serious	no serious	serious ¹	none			RR 0.8 (0.38	21 fewer per 1000		
	trials	limitations	inconsistency	indirectness			11/134 (8.2%)	10.3%	to 1.69)	(from 64 fewer to	MODERATE	
									10 1.05)	71 more)	,,,obbit	
Fatigue -	Escitalopram	10mg vs 20mg										
1	randomised	no serious	no serious	no serious	serious1	none	14/136		RR 0.62	63 fewer per 1000		
	trials	limitations	inconsistency	indirectness				16.5%	(0.33 to	(from 111 fewer to	MODERATE	
							(10.3%)		1.16)	26 more)	MODEKATE	
									·			
Headach	e - Escitalopra	m 5mg vs 10m	g									
	•	Ü										
1	randomised	no serious	no serious	no serious	serious1	none	04 (40)		RR 0.63	93 fewer per 1000		
	trials	limitations	inconsistency	indirectness			21/134	25%	(0.38 to	(from 155 fewer to		
							(15.7%)		1.02)	5 more)	MODERATE	
									,	,		
Headach	e - Escitalopra	m 10mg vs 201	ng									
			8									
1	randomised	no serious	no serious	no serious	serious1	none			RR 1.58	92 more per 1000		
1	trials	limitations	inconsistency	indirectness	Serio as	110110	34/136 (25%)	15.8%	(0.97 to	(from 5 fewer to		
	triais	minations	niconsistency	man ceness			34/ 130 (23%)	15.070	2.58)	250 more)	MODERATE	
									2.30)	250 111016)		
Incomni	- Essitalonra	m 5mg vs 10m						<u> </u>				
11150111111	a - Escitatopia	m onig vs rom	5									
1	randomised	no serious	no serious	no serious	serious ¹	none	1	1	RR 0.72	35 fewer per 1000	1	
1	trials	limitations		indirectness	serious	Horie	12/134 (9%)	12.5%	(0.36 to	(from 80 fewer to		
	triais	limitations	inconsistency	indirectness			12/134 (9%)	12.5 /6	`	,	MODERATE	
									1.44)	55 more)		
T	. Fastri.											
insomnia	a - Escitalopra	m 10mg vs 20n	ng									
		1 .			1			1	DD 4.4C	00 4000	1	
1	randomised	no serious	no serious	no serious	serious ¹	none	17/136	40 - 22	RR 1.19	20 more per 1000		
	trials	limitations	inconsistency	indirectness			(12.5%)	10.5%	(0.61 to	(from 41 fewer to	MODERATE	
							()		2.31)	138 more)		
		<u> </u>										
Somnole	nce - Escitalo _l	oram 5mg vs 10)mg									
1	randomised	no serious	no serious	no serious	serious1	none			RR 2.03	38 more per 1000		
Ī	trials	limitations	inconsistency	indirectness	5511045	The state of the s	10/134 (7.5%)	3.7%	(0.71 to	(from 11 fewer to		
	uiais	mintations	inconsistency	munectiess			10/134 (7.3%)	3.7 /0	`	`	MODERATE	
									5.78)	177 more)		
	L	L	ļ.				_					

mnole	ence - Escitalo	pram 10mg vs	20mg									
	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)	MODERATE	
nxiety	- Escitalopram	15mg vs 10mg										
	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)	MODERATE	
nxiety	- Escitalopram	10mg vs 20m	g									
<u>l</u>	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)	MODERATE	
Dizzines	ss - Escitalopra	nm 5mg vs 10n	ng		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)	MODERATE	
Dizzines	ss - Escitalopra	nm 10mg vs 20	mg	•	1	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)	MODERATE	
	1	1	1	1		1	1	<u> </u>	1		1	

¹ Wide confidence interval

2.3 Paroxetine for GAD

Quality assessment		Summary of findings		Importance
	No of patients	Effect	Quality	

² No explanation was provided

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetine	control	Relative (95% CI)	Absolute		
HAM-A	Paroxetine 20	omg vs 40mg (B	etter 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)	□□□□ MODERATE	
HADS-A	- Paroxetine 2	20mg vs 40mg (Better indicated b	y 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)	DDDD MODERATE	
Non-resp	onse - Paroxe	tine 20mg vs 40	mg									
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)	MODERATE	
Non-rem	ission - Parox	etine 20mg vs 4	0mg		1							
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)	DDDD MODERATE	
Disconti	nuation due to	Adverse Even	ts - Paroxetine 201	mg vs 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)	□□□□ MODERATE	
Nausea -	Paroxetine 20	mg vs 40mg									<u> </u>	
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)	DDD MODERATE	

Somnole	nce - Paroxeti	ne 20mg vs 40n	ng									
	randomised trials	no serious limitations		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)	□□□□ MODERATE	
)ecrease	d libido - Paro	oxetine 20mg v	s 40mg									
	randomised trials			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)	□□□□ MODERATE	
Decrease	d appetite - Pa	aroxetine 20mg	vs 40mg				_					
		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)	□□□□ MODERATE	

¹ Wide confidence interval

2.4 Duloxetine for GAD

			Quality assess	ment					Summary	of findings		
							No of pat	ients		Effect	Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	control	Relative (95% CI)	Absolute	Quanty	
HAM-A	- Duloxetine 2	0mg vs 60-120n	ng (Better indicat	ed by lower valu	ies)							
1	randomised trials	no serious limitations		no serious indirectness	serious ¹	none	83	151	-	MD 0.6 higher (1.09 lower to 2.29 higher)	□□□□ MODERATE	
HAM-A	- Duloxetine 6	0mg vs 120mg	(Better indicated	by lower values)							
1	randomised	no serious	no serious	no serious	serious¹	none	165	169	-	MD 0.34 lower (2.47 lower to 1.79		

trial	ls 1	imitations	inconsistency	indirectness						higher)	MODERATE	
DS-A - Du	uloxetine 2	0mg vs 60-120	mg (Better indica	ited by lower va	lues)			l				
ranc trial		no serious imitations	no serious inconsistency	no serious indirectness	serious ¹	none	83	151	-	MD 0.7 higher (0.19 lower to 1.59 higher)	□□□□ MODERATE	
DS-A - Du	uloxetine 6	0mg vs 120mg	(Better indicated	by lower value	es)	1		ı				
rand trial		no serious imitations	no serious inconsistency	no serious indirectness	serious ¹	none	160	163	-	MD 0.18 lower (1.2 lower to 0.84 higher)	□□□□ MODERATE	
n-response	e - Duloxet	ine 20mg vs 6	0-120mg									
ranc trial		no serious imitations	no serious inconsistency	no serious indirectness	serious¹	none	34/84 (40.5%)	38%	RR 1.07 (0.77 to 1.48)	27 more per 1000 (from 87 fewer to 182 more)	□□□□ MODERATE	
n-response	e - Duloxet	ine 60mg vs 1	20mg		l			l				
ranc trial		no serious imitations	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)	□□□□ MODERATE	
n-remissio	on - Duloxe	etine 60mg vs	l 120mg									
rand trial		no serious imitations	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)	□□□□ MODERATE	
eehan Disa	ability Scal	e - Duloxetino	e 60mg vs 120mg	(Better indicate	d by lower va	alues)		L				
ranc trial		no serious imitations	no serious inconsistency	no serious indirectness	serious ¹	none	156	160	-	MD 0.99 lower (2.9 lower to 0.92 higher)	□□□□ MODERATE	
LES-Q-SF -	- Duloxetir	ne 60mg vs 120	 Omg (Better indicate)	l ated by lower va	lues)	<u> </u>						

				no serious indirectness	serious ¹	none	136	129	-	MD 0.18 higher (2.21 lower to 2.57 higher)	OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO	
Discontir	nuation due to	Adverse Even	ts - Duloxetine 20	mg vs 60-120mg	5							
				no serious indirectness	serious¹	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)	MODERATE	
Discontir	nuation due to	Adverse Even	ts - Duloxetine 60	mg vs 120mg								
				no serious indirectness	serious¹	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)	□□□□ MODERATE	
Discontir	nuation due to	Any Reason -	Duloxetine 60mg	vs 120mg								
				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)	MODERATE	

¹ Wide confidence interval

2.5 Pregablin for [health problem]

			Quality assess	ment					Summary	of findings		
							No of pa	tients		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregablin	control	Relative (95% CI)	Absolute	Quality	
HAM-A	- Pregablin 150m	ng vs 600mg (B	etter indicated by	lower values)								
				no serious indirectness	serious ¹	none	69	61	-	MD 2.28 higher (0.58 to 3.98 higher)	□□□□ MODERATE	

IAM-A	- Pregablin 200	mg vs 400mg (Better indicated b	y lower values)						
		U (
	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)	MODERATE
AM-A	- Pregablin 300	mg vs 450mg (Better indicated b	y lower values)						
	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)	MODERATE
AM-A	- Pregablin 400	mg vs 450mg (Better indicated b	y 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)	MODERATE
AM-A	- Pregablin 400	mg vs 600mg (Better indicated b	y lower values)			l			
	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
AM-A	- Pregablin 450	mg vs 600mg (Better indicated b	y lower values)						
	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)	MODERATE
ADS-	A - Pregablin 40	0mg vs 600mg	(Better indicated	by lower value	s)						
	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)	MODERATE
on Re	sponse - Pregab	lin 300mg vs 4	50mg								
	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	HIGH

	1	+	_	+	_	1	-			1		
										0 more)		
n.		1: 450	20									
ке	sponse - Pregab	iin 450mg vs 60	Jumg									
	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)	□□□□ MODERATE	
ont	inuation due to	Adverse Event	ts - Pregablin 150	ng vs 600mg								
	1 1 1	<u> </u>	T .	1 .	T .	1	1		DD 0.06	100 (1000	T	
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/69 (10.1%)	28.6%	RR 0.36 (0.16 to 0.79)	183 fewer per 1000 (from 60 fewer to 240 fewer)	HIGH	
cont	inuation due to	Adverse Event	ts - Pregablin 300	ng vs 450mg							L	
	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)	□□□□ MODERATE	
cont	inuation due to	Adverse Event	ts - Pregablin 400	ng vs 600mg								
	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)	□□□□ MODERATE	
cont	inuation due to	Adverse Event	ts - Pregablin 450	ng vs 600mg							L	
	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)	□□□□ MODERATE	
scont	inuation for any	reason - Prega	ablin 400mg vs 60	0mg								
	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)		
ınol	ence - Pregablin	150mg vs 600r	mg									

			,				(23.2%)		to 1.01)	4 more)	MODERATE	
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	16/69	38.6%	RR 0.6 (0.36	154 fewer per 1000 (from 247 fewer to		
Dizzine	ss - Pregablin 15	0mg vs 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)	□□□□ MODERATE	
Somnol	ence - Pregablin			1								
	trials	limitations	inconsistency	indirectness			13/97 (13.4%)	13.6%	(0.49 to 1.96)	(from 69 fewer to 131 more)	□□□□ MODERATE	
Somnol	ence - Pregablin	400mg vs 600m	no serious	no serious	serious ¹	none			RR 0.98	3 fewer per 1000		
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	
Somnol	ence - Pregablin											
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)	□□□□ MODERATE	
Somnol	ence - Pregablin	300mg vs 450m	ng									
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	none	24/78 (30.8%)	37.1%	RR 0.83 (0.54 to 1.27)	63 fewer per 1000 (from 171 fewer to 100 more)	□□□□ MODERATE	
Somnol	ence - Pregablin	200mg vs 400m	ng									
	trials	limitations	inconsistency	indirectness	imprecision		(14.5%)	35.7%	(0.21 to 0.78)	(from 79 fewer to 282 fewer)	HIGH	
1	randomised	no serious	no serious	no serious	no serious	none	10/69		RR 0.41	211 fewer per 1000		

lizzina	ess - Pregablin 20	10mg ve 400mg	•									
1221110	.oo - 1 1egavilli 20	Joing vs Tooling	•									
	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)		
zzine	ess - Pregablin 30	00mg vs 450mg	5		-							
	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)	MODERATE	
izzine	ess - Pregablin 40	00mg vs 450mg	3									
	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)	MODERATE	
izzine	ess - Pregablin 40	00mg vs 600mg	5		•			,				
	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)	MODERATE	
izzine	ess - Pregablin 4	50mg vs 600mg	;									
	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)	MODERATE	
ausea	- Pregablin 1501	ng vs 600mg			1				l			
	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)	MODERATE	
ausea	- Pregablin 3001	ng vs 450mg		•								
	randomised	no serious	no serious	no serious	serious ¹	none	10/91	14.4%	RR 0.76	35 fewer per 1000		

	trials	limitations	inconsistency	indirectness			(11%)		(0.35 to	(from 94 fewer to	MODERATE	
									1.65)	94 more)		
Nausea -	- Pregablin 400m	ng vs 600mg										
	o .	0										
1	randomised	no serious	no serious	no serious	serious ¹	none	9/97		RR 0.73	34 fewer per 1000	пппп	
	trials	limitations	inconsistency	indirectness			(9.3%)	12.7%	(0.33 to	(from 85 fewer to	MODERATE	
							()		1.61)	77 more)		
Nausea -	- Pregablin 450m	ng vs 600mg										
1	randomised	no serious	no serious	no serious	serious ¹	none	13/90		RR 1.29	32 more per 1000		
	trials	limitations	inconsistency	indirectness			(14.4%)	11.2%	(0.59 to	(from 46 fewer to	MODERATE	
									2.78)	199 more)		
Headach	ne - Pregablin 15	Omg vs 600mg			1					<u> </u>	<u> </u>	
	G	0 0										
1	randomised	no serious	no serious	no serious	serious1	none	13/69		RR 0.88	26 fewer per 1000	ПППП	
	trials	limitations	inconsistency	indirectness			(18.8%)	21.4%	(0.45 to	(from 118 fewer to	MODERATE	
							(10.070)		1.71)	152 more)	, , , , , , , , , , , , , , , , , , ,	
Headach	l ne - Pregablin 40	Omg vs 600mg										
	Ö	0 0										
1	randomised	no serious	no serious	no serious	serious1	none	7/97		RR 0.88	10 fewer per 1000		
	trials	limitations	inconsistency	indirectness			(7.2%)	8.2%	(0.34 to	(from 54 fewer to	MODERATE	
							(7.270)		2.28)	105 more)	WIODEIGTTE	
ncomni	a - Pregablin 400	0ma ve 600ma										
11150111111	a - 1 legaviiii 400	onig vs ooonig										
1	randomised	no serious	no serious	no serious	serious ¹	none			RR 0.38	17 fewer per 1000	ПППП	
	trials	limitations	inconsistency	indirectness			1/97 (1%)	2.7%	(0.04 to	(from 26 fewer to	MODERATE	
									3.57)	69 more)	ODERUITE	

¹ Wide confidence interval

3 Maintenance treatment

3.1 Pregabalin versus Placebo for GAD

			Quality assess	sment					Summary o	f findings				
			Quarty 100 cos				No of patie	ents		Effect		Importance		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin versus Placebo	control	Relative (95% CI)	Absolute	Quality			
Relapse			L											
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)				
HAM-A (Better indicated by lower values)														
	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)	□□□□ MODERATE			
Discontin	nuation for ar	ny reason		l										
	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)	DDDERATE			
Disconti	nuation due to	o adverse even	ts											
	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)	DDDERATE			

¹ Only one study

² Wide confidence interval

3.2 Duloxetine versus Placebo for GAD

			Quality assess	sment					Summary of	findings		
			~ ,				No of patie	ents		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine versus Placebo	control	Relative (95% CI)	Absolute	Quality	
Relapse												
	randomised trials		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)	DDD MODERATE	
Non-rem	ission						L					
			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)	DDD MODERATE	
HAM-A	(Better indica	ted by lower v	alues)									
	randomised trials		no serious inconsistency	no serious indirectness	serious ^{1,2,3}	none	213	211	-	SMD 0.7 lower (0.9 to 0.51 lower)	□□□□ MODERATE	
Q-LES-Q	-SF (Better in	dicated by low	ver values)									
	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)	MODERATE	
Disconti	nuation for ar	ny 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)	□□□□ MODERATE	
Disconti	nuation due to	o adverse even	ts									l

-	1	randomised	no serious	no serious	no serious	serious ³	none			RR 1.97	9 more per 1000		
		trials	limitations	inconsistency	indirectness			4/216 (1.9%)	0.9%	(0.37 to	(from 6 fewer to 87	MODERATE	
										10.65)	more)	MODERATE	

¹ High drop out

3.3 Paroxetine versus Placebo for GAD

									Summary o	of findings		
			Quality assess	ment					Summary C	n iniunigs		
			Quality about				No of patie	ents		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetine versus Placebo	control	Relative (95% CI)	Absolute	Quality	
Relapse												
				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)	□□□□ MODERATE	
Non-rem	ission					<u>'</u>				<u>'</u>		
		no serious limitations		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)	□□□□ MODERATE	
HAM-A	Better indicat	ed by lower va	alues)									
		no serious limitations		no serious indirectness	serious ^{1,2}	none	274	287	-	SMD 1.03 lower (1.2 to 0.85 lower)	□□□□ MODERATE	
Discontin	nuation for an	y reason		_	,					<u>'</u>		
1	randomised	no serious	no serious	no serious	serious ^{1,2}	none	62/278 (22.3%)	49%	RR 0.46 (0.36 to	265 fewer per 1000 (from 206 fewer to	0000	

² Only one study ³ Wide confidence interval

	trials	limitations	inconsistency	indirectness					0.58)	314 fewer)	MODERATE	
Disconti	nuation due to	o adverse even	ts									
1	randomised trials			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)	□□□□ MODERATE	

¹ Large drop out

3.4 Escitalopram versus Placebo for GAD

			40114000101					S	ummary of	findings		
			Quality assess	ment			No of paties	• t o	1	Effect		
							No or paties	iiis		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Escitalopram versus Placebo	control	Relative (95% CI)	Absolute	Quality	
Relapse												
	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)	□□□□ MODERATE	
Disconti	nuation for ar	ny reason										
1			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)		
Disconti	nuation due t	o adverse even	its									
	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious¹	none	13/187 (7%)	8.5%	RR 0.82 (0.4 to 1.65)	15 fewer per 1000 (from 51 fewer to 55 more)	□□□□ MODERATE	

¹ Only one study

² Only one study

4 Augmentation

4.1 Olanzapine vs Placebo for GAD

			Quality assess	sment				Sumi	nary of find	lings		
							No of patie	nts		Effect		Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Olanzapine	Placebo	Relative (95% CI)	Absolute	Quality	
HAM-A	Better indica	ted by lower v	alues)									
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)	LOW	
Non-rem	lission			Į.								
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	247 fewer per 1000 (from 486 fewer to 110 more)	LOW	
								91.7%	1.12)	248 fewer per 1000 (from 486 fewer to 110 more)		
Non-resp	oonse											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious¹	none	7/12 (58.3%)	11/12 (91.7%)	RR 0.64 (0.38 to	330 fewer per 1000 (from 568 fewer to 55 more)	LOW	
								91.7%	1.06)	330 fewer per 1000 (from 569 fewer to 55 more)		
Disconti	nuation due t	o adverse even	ts					_				
1	randomised	no serious	no serious	no serious	very	none	4/12 (33.3%)	8.3%	RR 4 (0.52	249 more per 1000 (from 40 fewer to	0000	

trials	limitations	inconsistency	indirectness	serious¹		to 30.76)	2470 more)	LOW	

¹ 1 small study

4.2 Risperidone vs Placebo for GAD

4.2	Kispei	iluone vs i	lacebo for GA	1D								
			Quality asse	ssment				Sum	ımary of fii	ndings		
							No of patie	ents		Effect	Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Risperidone	Placebo	Relative (95% CI)	Absolute	Quanty	
HAM-A	(Better indica	ated by lower	values)	l								
2	randomised trials	no serious limitations	serious ²	no serious indirectness	serious¹	none	215	214	-	SMD 0.27 lower (0.9 lower to 0.36 higher)	LOW	
Non-rem	nission											
1		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-res	ponse											
1		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)		□□□□ MODERATE	
								60.3%	1.10)	6 fewer per 1000 (from 96 fewer to 96 more)		
Disconti	nuation due	to adverse eve	nts									
2	randomised	no serious	no serious	no serious	serious ¹	none	24/215 (11.2%)	11/214	RR 2.17 (1.09 to	60 more per		
										1000 (from 5		

trials	limitations	inconsistency	indirectness		(5.1%)		more to 171 more)		
					5.1%	4.32)	60 more per 1000 (from 5	MODERATE	
							more to 169 more)		

¹ CIs compatible with benefit and no benefit

4.3 Antipsychotics vs Placebo for GAD

Quality assessment							Summary of findings					
							No of patients		Effect			Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation: Antipsychotics	Placebo	Relative (95% CI)	Absolute	Quality	
HAM-A	(Better indica	ated by lower	values)									
		no serious limitations		no serious indirectness	serious¹	none	245	244	-	MD 1.04 lower (2.49 lower to 0.41 higher)	□□□□ MODERATE	
Non-resp	oonse	ı										
		no serious serious³ limitations		no serious indirectness	serious ²	none	124/208 (59.6%)	128/206 (62.1%)	RR 0.85 (0.56 to	93 fewer per 1000 (from 273 fewer to 174 more)	LOW	
								76%	1.28)	114 fewer per 1000 (from 334 fewer to 213 more)		
Non-rem	ission											
3	randomised	no serious	no serious	no serious	serious ¹	none	173/219 (79%)	179/217	RR 0.93	58 fewer per		

²I-squared >50%

	trials	limitations	inconsistency	indirectness				(82.5%)	(0.78 to 1.09)	1000 (from 181 fewer to 74 more)	MODERATE	
								82%	,	57 fewer per 1000 (from 180 fewer to 74 more)		
Disconti	nuation due	to adverse eve	ents									
5		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 CIs compatible with benefit for treatment or placebo

² 1 small study and 1 large study

³I-squared > 50%