Supplementary material

The beneficial and harmful effects of duloxetine versus placebo for adults with major depressive disorder: A

systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

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Remission46
Supplementary Fig S35: Meta-analysis of duloxetine vs. placebo on the outcome remission rates
References

Search strategies for 'Duloxetine for major depressive disorder' (Faiza Siddiqui) Searches performed 23 January 2023

Total number of records identified:	4715 records
Number of duplicates excluded:	1314 records
Number of records in final list:	3401 records
Number of new records sent to authors:	173 records

Cochrane Central Register of Controlled Trials (2023, Issue 1) in the Cochrane Library (23 January 2023) (867 hits)

#1 MeSH descriptor: [Duloxetine Hydrochloride] explode all trees

#2 (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox)

- #3 #1 or #2
- #4 MeSH descriptor: [Depressive Disorder, Major] explode all trees
- #5 MeSH descriptor: [Depressive Disorder] this term only
- #6 MeSH descriptor: [Seasonal Affective Disorder] explode all trees
- #7 MeSH descriptor: [Dysthymic Disorder] explode all trees
- #8 MeSH descriptor: [Depression] explode all trees
- #9 MeSH descriptor: [Affective Symptoms] this term only

#10 (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*))

- #11 #4 or #5 or #6 or #7 or #8 or #9 or #10
- #12 #3 and #11

MEDLINE Ovid (1946 to 23 January 2023) (597 hits)

1. exp Duloxetine Hydrochloride/

2. (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

- 3. 1 or 2
- 4. exp Depressive Disorder, Major/
- 5. Depressive Disorder/

- 6. exp Seasonal Affective Disorder/
- 7. exp Dysthymic Disorder/
- 8. exp Depression/
- 9. Affective Symptoms/

10. (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

- 11. 4 or 5 or 6 or 7 or 8 or 9 or 10
- 12. 3 and 11
- 13. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.

14. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

15. 12 and (13 or 14)

Embase Ovid (1974 to 23 January 2023) (2253 hits)

1. exp duloxetine/

2. (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

- 3. 1 or 2
- 4. exp major depression/
- 5. depression/
- 6. exp seasonal affective disorder/
- 7. exp dysthymia/
- 8. emotional disorder/

9. (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

10. 4 or 5 or 6 or 7 or 8 or 9

11. 3 and 10

12. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.ne.

13. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

14. 11 and (12 or 13)

PsycINFO (EBSCOhost; 1806 to 3 June 2022) (438 hits)

S14 S12 AND S13

S13 TX (random* or blind* or placebo* or trial*)

- S12 S3 AND S11
- S11 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10

S10 TX (MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*))

- S9 MA affective symptoms
- S8 MA depression
- S7 MA dysthymic disorder
- S6 MA seasonal affective disorder
- S5 MA depressive disorder
- S4 MA Depressive Disorder, Major
- S3 S1 OR S2 Expanders Apply equivalent subjects

S2 TX (duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex * or dureep or dutin* or duzet or duze or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox)

S1 MA Duloxetine

LILACS (VHL Regional Portal; 1982 to 23 January 2023) (20 hits)

((duloxetin* OR cymbalta* OR irenka* OR ariclaim OR xeristar OR yentreve OR duzela OR c-pact OR combac OR delok OR deneurone OR detine OR dimorex OR dlx OR dulane OR dulex OR dulojoy OR dulok OR dulomax OR dulonix OR dulot* OR dulox* OR dultin OR dulx OR dumore OR duonex* OR dureep OR dutin* OR duxet OR duzet OR duzela OR dxt OR neuroxetin OR nudep OR sylonex OR symbal OR sympta OR ulozet OR verlox)) AND ((mdd OR depress* OR ((affective OR adjustment OR dysthym* OR mood) AND (disorder* OR disease* OR symptom*)) OR dysthymia OR alexithymia OR (involutional AND (melancholia OR paraphrenia* OR psychos*)) OR (emotion* AND disturbance*))) AND (db:("LILACS"))

Science Citation Index Expanded (Web of Science; 1900 to 23 January 2023) and Conference Proceedings Citation Index – Science (Web of Science; 1990 to 23 January 2023) (978 hits)

#5 #3 AND #4

#4 TI=(random* or blind* or placebo* or trial*) OR TS=(random* or blind* or placebo*)

#3 #2 AND #1

#2 TS=(MDD or depress* or ((affective or adjustment or dysthym* or mood) and (disorder* or disease* or symptom*)) or dysthymia or alexithymia or (involutional and (melancholia or paraphrenia* or psychos*)) or (emotion* and disturbance*))

#1 TS=(duloxetin* or cymbalta* or Irenka* or ariclaim or xeristar or yentreve or duzela or c-pact or combac or delok or deneurone or detine or dimorex or DLX or dulane or dulex or dulife or dulojoy or dulok or dulomax or dulonix or dulot* or dulox* or dultin or dulx or dumore or duonex* or dureep or dutin* or duxet or duzac or duzela or DXT or neuroxetin or nudep or sylonex or symbal or sympta or ulozet or verlox)

Trial	Participants receiving	duloxetine	Participants receiving placebo			
	Types of SAEs	Proportion of participants with SAEs	Types of SAEs	Proportion of participants with SAEs		
Baldwin 2012	Middle ear effusion, serotonin syndrome	2 out of 155	Serotonin syndrome, adenomyosis, pulmonary embolism	3 out of 148		
Boulenger 2014	Suicidal behavior and self harm, intentional overdose, vaginal haemorrhage	3 out of 147		0 out of 158		
Detke 2002 A		0 out of 123	Umblical hernia, emphysema with pneumonia, chest pain	3 out of 122		
Detke 2002 B	Breast carcinoma	1 out of 128		0 out of 139		
Goldstein 2004 B	Accidental injury falling from a horse, suffering a concussion and a subsequent seizure.	1 out of 91		0 out of 45		
Katona 2012	Prostate cancer, suicide attempt	2 out of 151	Hip fracture, bile duct cancer, depression, transient ischemic attack	4 out of 145		
Mahableshwarkar 2013	Myocardial infarction, panic attack	2 out of 150	Elective abortion, worsening of depression	2 out of 151		
Mahableshwarkar 2015 B	Craniocerebral injury	1 out of 207	Acute myocardial infarction, worsening of depression	2 out of 191		
Nierenberg 2007	Not specified	3 out of 273	Not specified	2 out of 137		

Supplementary table S2: Summary of serious adverse events in the included trials.

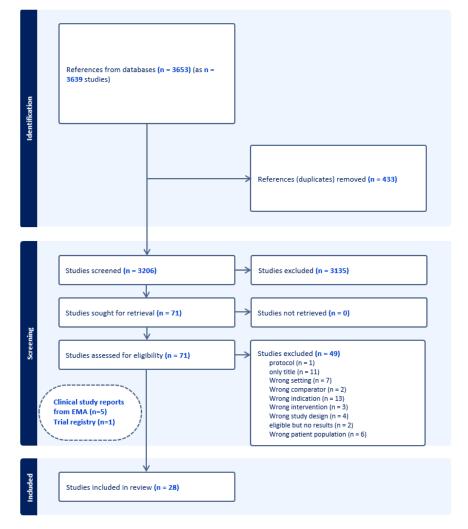
Oakes 2012 A	Not specified	6 out of 257	Suicide attempt, others not specified	3 out of 127
Oakes 2012 B	Ruptured cerebral aneurysm, suicide attempt	2 out of 261	Suicide, others not specified	7 out of 131
Perahia 2006 B	Major depression	1 out of 103		0 out of 50
Raskin 2007	Not specified	1 out of 207	Not specified	4 out of 104
Tourian 2009	Suicide attempts	2 out of 157	Accidental injury, asthma	2 out of 161
F1J-MC-HMAI (A)	Suicide attempt	1 out of 130		0 out of 41
F1J-MC-HMAI (C)	Suicide attempt	1 out of 131	Suicide attempt	1 out of 41
F1J-MC-HMAQ b (B)		0 out of 82	Infectious colitis, food poisoning	2 out of 75
11918A	Not specified	1 out of 133	Not specified	1 out of 136
F1J-MC-HMAT a (B)	Cardiopulmonary arrest leading to death	1 out of 84	Hospitalization due to exacerbation of asthma	1 out of 45
F1J-MC-HMAH	Maniac episode, overdose	9 out of 89	Accidental injury, hostility, overdose	8 out of 88

Supplementary	/ Table S3: Meta-anal	vsis of individual	non-serious adverse events.
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Non-serious adverse events	No of	n* duloxetine	N** duloxetine	n* control	N**	RR⁼	95% CI	P-value	NNH
	trials	group	group	group	control				
					group				
Nausea	30	957	3982	244	2856	2.92	2.38-3.58	<0.0001	6.46
Dry mouth	30	627	3982	222	2856	2.05	1.67-2.52	<0.0001	12.54
Somnolence	26	306	3110	96	2249	2.4	1.81-3.18	<0.0001	17.95
Sweating	27	252	3521	55	2517	2.88	1.95-4.26	<0.0001	20.11
Dizziness	30	399	3982	156	2856	1.88	1.49-2.38	<0.0001	21.94
Yawn	11	45	1569	1	1177	5.54	2.32-13.22	0.0001	35.93
Appetite decreased	9	83	1469	18	1129	3.33	1.8-6.15	0.0001	24.66
Insomnia	25	304	3113	133	2097	1.64	1.27-2.11	0.0001	29.21
Anorexia	15	100	1671	22	1043	2.85	1.6-5.06	0.0004	25.81
Constipation	28	359	3628	132	2507	1.79	1.3-2.47	0.0004	21.6
Withdrawal syndrome	1	49	334	24	250	2.09	1.35-3.24	0.0009	19.72
Vomiting	22	135	2556	39	1799	2.28	1.4-3.71	0.0009	32.11
Diarrhea	30	376	3982	203	2856	1.38	1.12-1.71	0.0028	42.83
Fatigue	13	143	2284	48	1609	2.06	1.28-3.3	0.0029	30.51
Libido decreased	13	54	1671	13	1043	2.37	1.22-4.61	0.0111	50.37
Vasodilatation	13	55	1287	16	851	2.08	1.11-3.89	0.0215	41.78
Back pain	20	62	2128	65	1514	0.64	0.42-0.95	0.0288	-72.48
Hyperventilation	3	0	460	4	196	0.14	0.02-0.82	0.0299	-49
Pain	16	64	1782	77	1264	0.65	0.43-0.97	0.0352	-40
Breast pain	8	3	1055	8	600	0.33	0.11-0.99	0.048	-95.33

*n= no of events

**N= no analyzed RR= relative risk



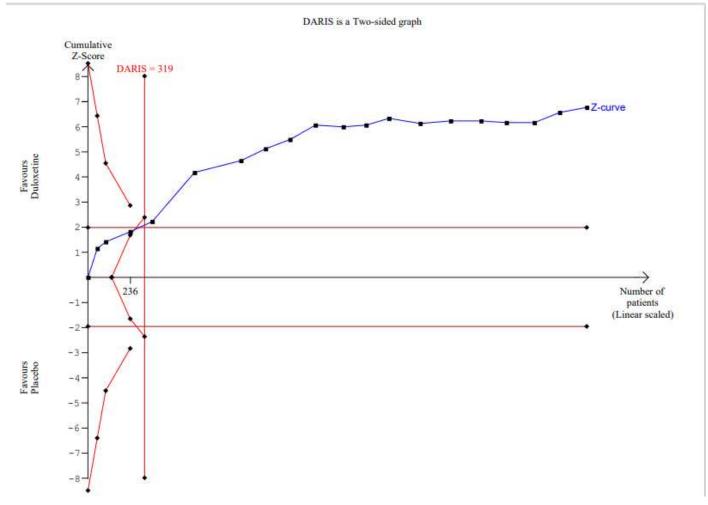
Supplementary Fig S1: PRISMA flow chart.

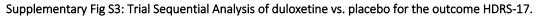
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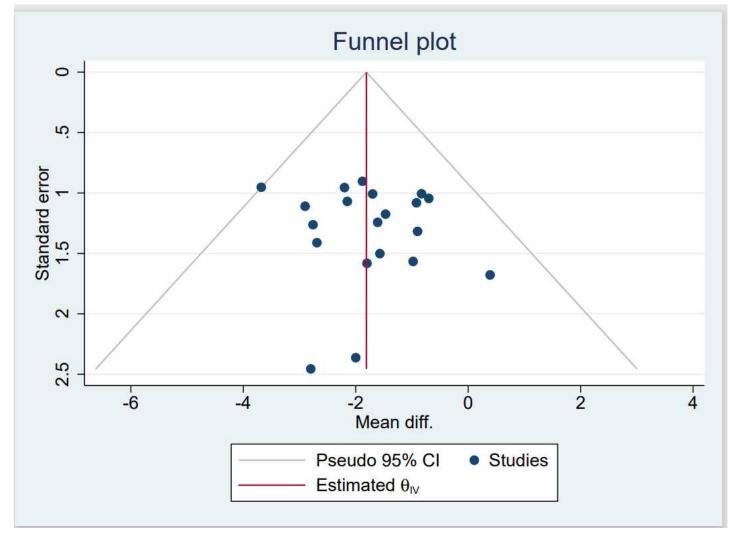
	Duloxetine				Placebo			Mean Diff.	
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
HDRS-17 change scores									
F1J-MC-HMAG (A)	26	-8.7	9.1	26	-5.9	8.6		-2.80 [-7.61, 2.01]	1.19
F1J-MC-HMAG (B)	24	-7.8	9	25	-5.8	7.5		-2.00 [-6.63, 2.63]	1.29
Higuchi 2009 A	73	-10.5	5.7	72	-8.3	5.8		-2.20 [-4.07, -0.33]	7.90
Higuchi 2009 B	74	-10	6.4	73	-8.3	5.8		-1.70 [-3.68, 0.28]	7.09
Heterogeneity: I ² = 0.00%,	$H^2 = 1$.00					-	-2.02 [-3.28, -0.76]	
Test of $\theta_i = \theta_i$: Q(3) = 0.24,	p = 0.	97							
HDRS-17 end scores									
Detke 2002 A	121	12.25	7.6	115	15.93	7	-	-3.68 [-5.55, -1.81]	7.94
Detke 2002 B	123	11.37	7.1	136	13.25	7.4		-1.88 [-3.65, -0.11]	8.83
Detke 2004 A	93	9.6	5.8	46	11.75	6.2	_8_	-2.15 [-4.25, -0.05]	6.29
Detke 2004 B	93	8.85	6.2	47	11.75	6.2		-2.90 [-5.07, -0.73]	5.85
Goldstein 2004 A	84	11.46	8	44	13.03	8.2		-1.57 [-4.51, 1.37]	3.19
Goldstein 2004 B	86	10.34	7.3	44	13.03	8.2		-2.69 [-5.46, 0.08]	3.62
Goldstein 2002	68	10.6	7.5	66	13.36	7.1		-2.76 [-5.23, -0.29]	4.52
Perahia 2006 A	93	9.76	5.8	49	10.59	5.5		-0.83 [-2.80, 1.14]	7.12
Perahia 2006 B	102	9.67	6.6	50	10.59	5.5		-0.92 [-3.04, 1.20]	6.16
F1J-MC-HMAI (A)	129	13.45	9.5	41	13.06	8.9		0.39 [-2.90, 3.68]	2.56
F1J-MC-HMAI (B)	129	11.26	8.8	41	13.06	8.9		-1.80 [-4.90, 1.30]	2.88
F1J-MC-HMAI (C)	130	12.08	8.8	42	13.06	8.9		-0.98 [-4.05, 2.09]	2.94
F1J-MC-HMAQ (B)	81	11.63	8.5	72	12.53	7.7		-0.90 [-3.48, 1.68]	4.15
F1J-MC-HMAT a (A)	90	12.04	6.3	45	13.51	6.7		-1.47 [-3.77, 0.83]	5.22
F1J-MC-HMAT a (B)	81	11.9	6.6	44	13.51	6.7		-1.61 [-4.05, 0.83]	4.66
F1J-MC-HMAH	86	13.7	6.8	86	14.4	6.9		-0.70 [-2.75, 1.35]	6.60
Heterogeneity: I ² = 0.00%,	$H^2 = 1$.00					•	-1.77 [-2.34, -1.19]	
Test of $\theta_i = \theta_j$: Q(15) = 11.3	23, p =	0.74							
Overall							٠	-1.8 <mark>1 [-2.34</mark> , -1.28]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1$.00							
Test of $\theta_i = \theta_j$: Q(19) = 11.0	60, p =	0.90							
Test of group differences:	Q _b (1) :	= 0.13, I	p = 0	.72					
						-10	-5 0	5	

Supplementary Fig S2: Meta-analysis of duloxetine vs. placebo for the outcome HDRS-17 scores.

11







Supplementary Fig S4: Funnel plot of duloxetine vs. placebo for the outcome HDRS-17 scores.

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		freatmen			Control			Mean Diff.	Weight
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
Baseline HDRS-17 scores < 23									
Detke 2002 A	121	12.25	7.6	115	15.93	7		-3.68 [-5.55, -1.81]	7.94
Detke 2002 B	123	11.37	7.1	136	13.25	7.4		-1.88 [-3.65, -0.11]	8.83
Detke 2004 A	93	9.6	5.8	46	11.75	6.2		-2.15 [-4.25, -0.05]	6.29
Detke 2004 B	93	8.85	6.2	47	11.75	6.2		-2.90 [-5.07, -0.73]	5.85
Goldstein 2004 A	84	11.46	8	44	13.03	8.2		-1.57 [-4.51, 1.37]	3.19
Goldstein 2004 B	86	10.34	7.3	44	13.03	8.2		-2.69 [-5.46, 0.08]	3.62
Goldstein 2002	68	10.6	7.5	66	13.36	7.1		-2.76 [-5.23, -0.29]	4.52
Perahia 2008 A	93	9.76	5.8	49	10.59	5.5		-0.83 [-2.80, 1.14]	7.12
Perahia 2008 B	102	9.67	6.6	50	10.59	5.5		-0.92 [-3.04, 1.20]	6.16
F1J-MC-HMAQ (B)	81	11.63	8.5	72	12.53	7.7		-0.90 [-3.48, 1.68]	4.15
F1J-MC-HMAT a (A)	90	12.04	6.3	45	13.51	6.7		-1.47 [-3.77, 0.83]	5.22
F1J-MC-HMAT a (B)	81	11.9	6.6	44	13.51	6.7		-1.61 [-4.05, 0.83]	4.66
F1J-MC-HMAG (A)	26	-8.7	9.1	26	-5.9	8.6		-2.80 [-7.61, 2.01]	1.19
F1J-MC-HMAG (B)	24	-7.8	9	25	-5.8	7.5		-2.00 [-6.63, 2.63]	1.29
F1J-MC-HMAH	88	13.7	6.8	86	14.4	6.9		-0.70 [-2.75, 1.35]	6.60
Higuchi 2009 A	73	-10.5	5.7	72	-8.3	5.8		-2.20 [-4.07, -0.33]	7.90
Higuchi 2009 B	74	-10	6.4	73	-8.3	5.8		-1.70 [-3.68, 0.28]	7.09
Heterogeneity: I ² = 0.00%, H ² =	1.00						•	-1.90 [-2.45, -1.35]	
Test of $\theta_1 = \theta_1$: Q(18) = 9.50, p =	0.89								
Baseline HDRS-17 scores ≥ 23									
F1J-MC-HMAI (A)	129	13.45	9.5	41	13.06	8.9		0.39 [-2.90, 3.68]	2.56
F1J-MC-HMAI (B)	129	11.26	8.8	41	13.06	8.9		-1.80 [-4.90, 1.30]	2.88
F1J-MC-HMAI (C)	130	12.08	8.8	42	13.06	8.9		-0.98 [-4.05, 2.09]	2.94
Heterogeneity: I ² = 0.00%, H ² =	1.00						-	-0.84 [-2.66, 0.97]	
Test of $\theta_1 = \theta_1$: Q(2) = 0.91, p = 0	0.63								
Overall							•	-1.81 [-2.34, -1.28]	
Heterogeneity: $I^2 = 0.00\%$, $H^2 =$	1.00								
Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p	= 0.90								
Test of group differences: Q _b (1)	= 1.19,	p = 0.2	В			_		_	
						-10	-5 0	5	
ixed-effects inverse-variance mo	del								

Supplementary Fig S5: Subgroup analysis of duloxetine vs. placebo on HDRS-17 for baseline HDRS-17 scores.

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		reatme			Control			Mean Diff.	Weigh
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
Excluded participants with chronic treatment resistant depression									
Detke 2002 A	121	12.25	7.6	115	15.93	7		-3.68 [-5.55, -1.81]	7.94
Detke 2002 B	123	11.37	7.1	136	13.25	7.4		-1.88 [-3.65, -0.11]	8.83
Detke 2004 A	93	9.6	5.8	46	11.75	6.2		-2.15 [-4.25, -0.05]	6.29
Detke 2004 B	93	8.85	6.2	47	11.75	6.2		-2.90 [-5.07, -0.73]	5.85
Goldstein 2004 A	84	11.46	8	44	13.03	8.2		-1.57 [-4.51, 1.37]	3.19
Goldstein 2004 B	86	10.34	7.3	44	13.03	8.2		-2.69 [-5.46, 0.08]	3.62
Goldstein 2002	68	10.6	7.5	66	13.36	7.1		-2.76 [-5.23, -0.29]	4.52
Perahia 2008 A	93	9.76	5.8	49	10.59	5.5		-0.83 [-2.80, 1.14]	7.12
Perahia 2006 B	102	9.67	6.6	50	10.59	5.5		-0.92 [-3.04, 1.20]	6.16
F1J-MC-HMAT a (A)	90	12.04	6.3	45	13.51	6.7		-1.47 [-3.77, 0.83]	5.22
F1J-MC-HMAT a (B)	81	11.9	6.6	44	13.51	6.7		-1.61 [-4.05, 0.83]	4.66
F1J-MC-HMAG (A)	26	-8.7	9.1	26	-5.9	8.6		-2.80 [-7.61, 2.01]	1.19
F1J-MC-HMAG (B)	24	-7.8	9	25	-5.8	7.5		-2.00 [-6.63, 2.63]	1.29
F1J-MC-HMAH	86	13.7	6.8	86	14.4	6.9		-0.70 [-2.75, 1.35]	6.60
Heterogeneity: 1 ² = 0.00%, H ² = 1.00							•	-1.94 [-2.56, -1.32]	
Test of $\theta_i = \theta_j$: Q(13) = 8.76, p = 0.79									
Participants with chronic treatment resistant depression not excluded	Н								
F1J-MC-HMAI (A)	129	13.45	9.5	41	13.06	8.9		0.39 [-2.90, 3.68]	2.56
F1J-MC-HMAI (B)	129	11.26	8.8	41	13.06	8.9		-1.80 [-4.90, 1.30]	2.88
F1J-MC-HMAI (C)	130	12.08	8.8	42	13.06	8.9		-0.98 [-4.05, 2.09]	2.94
F1J-MC-HMAQ (B)	81	11.63	8.5	72	12.53	7.7		-0.90 [-3.48, 1.68]	4.15
Heterogeneity: 1 ² = 0.00%, H ² = 1.00							-	-0.86 [-2.35, 0.62]	
Test of $\theta_i = \theta_i$: Q(3) = 0.91, p = 0.82									
Overall							•	-1.78 [-2.35, -1.21]	
Heterogeneity: I ² = 0.00%, H ² = 1.00									
Test of $\theta_i = \theta_j$: Q(17) = 11.41, p = 0.83									
Test of group differences: $Q_{\rm b}(1)$ = 1.73, p = 0.19						-		_	
						-10) -5 0	5	

Supplementary Fig S6: Subgroup analysis of duloxetine vs. placebo on HDRS-17 for chronic or treatment resistant depression.

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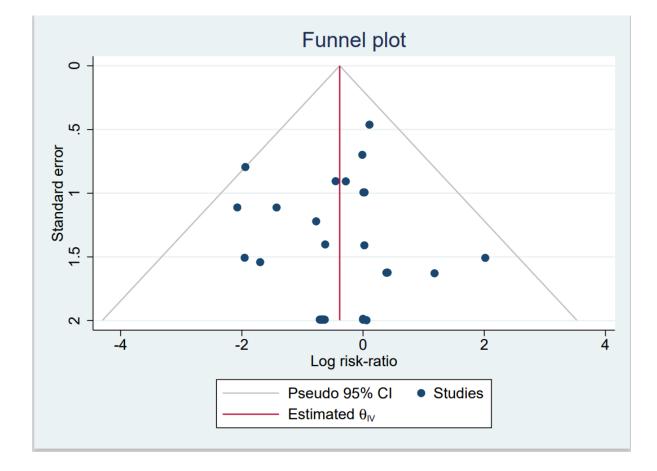
Study N Mean SD with 95% CI (%) Duloxetine dose $\leq 60mg/day$ 121 12.25 7.6 115 15.93 7 Delke 2002 A 121 12.25 7.6 115 15.93 7 Delke 2002 B 123 11.37 7.1 136 13.26 7.4 Goldstein 2004 A 84 11.46 8 44 13.06 8.9 F1J-MC-HMAI (B) 129 11.26 8.8 41 13.06 8.9 F1J-MC-HMAG (B) 26 -8.7 9.1 26 -5.8 7.5 F1J-MC-HMAG (B) 26 -8.7 9.25 -5.8 7.5 -7.6 -2.00 [-6.63, 2.63] 1.29 F1J-MC-HMAG (B) 24 -7.8 9.25 -5.8 7.5 -2.00 [-6.63, 2.63] 1.29 F1J-MC-HMAG (B) 24 -7.8 9.25 -5.8 7.5 -2.00 [-6.63, 2.63] 1.29 Playchi PMAG 10.6 4 7.3 -8.3 5.8 -7.10 [-2.75, 1.36] 6.60 Deloxetine dose > 60mg/day -0.02		Т	reatme	nt		Control			Mean Diff.	Weight
Detke 2002 A 121 12.25 7.6 115 15.93 7 Detke 2002 B 123 11.37 7.1 136 13.25 7.4 Goldstein 2004 A 84 11.46 8 44 13.03 8.2 F1.J-MC-HMAI (A) 129 13.45 9.5 41 13.06 8.9 F1.J-MC-HMAI (B) 129 11.26 8.8 41 13.06 8.9 F1.J-MC-HMAI (C) 130 12.06 8.8 42 13.06 8.9 F1.J-MC-HMAI (C) 130 12.06 8.8 42 13.06 8.9 F1.J-MC-HMAI (C) 130 12.06 8.8 42 13.06 8.9 F1.J-MC-HMAG (B) 24 7.8 9 25 6.8 7.5 F1.J-MC-HMAG (B) 24 7.8 9 25 6.5 7.7 F1.J-MC-HMAG (B) 24 7.8 9 25 6.5 7.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 7.44, p = 0.76 Duloxetine dose $> 60mg/day$ Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Detke 2004 B 93 9.76 5.8 46 11.75 6.2 Detke 2004 B 93 9.76 5.8 46 11.75 6.2 Detke 2004 B 93 9.76 5.8 49 10.59 5.5 F1.J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 7.44, p = 0.76 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1.J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.99 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1.J-MC-HMAT a (B) 81 11.93 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.99 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1.J-MC-HMAT a (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.40, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(2) = 0.02, p = 0.99	Study	N	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Detke 2002 B 123 11.37 7.1 136 13.25 7.4 Goldstein 2004 A 84 11.46 8 44 13.03 8.2 F1J-MC-HMAI (A) 129 13.45 9.5 41 13.06 8.9 F1J-MC-HMAI (B) 129 11.26 8.8 41 13.06 8.9 F1J-MC-HMAI (C) 130 12.08 8.4 24 13.06 8.9 F1J-MC-HMAI (C) 130 12.08 8.4 24 13.06 8.9 F1J-MC-HMAG (A) 26 8.7 9.1 26 -5.9 8.6 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.6 5.7 72 -8.3 5.8 Higuchi 2009 A 73 -10.6 4. 73 -8.3 5.8 Higuchi 2009 A 73 -10.6 4. 73 -8.3 5.8 Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i \in Q_i(11) = 7.44$, $p = 0.76$ Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Dotate 2004 A 93 9.76 5.8 49 10.59 5.5 F1-JMC-HMAG (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i: Q_i(1) = 1.04$, $p = 0.31$ Overall Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i: Q_i(1) = 1.04$, $p = 0.31$ Overall Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i: Q_i(1) = 1.04$, $p = 0.31$ Overall Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i: Q_i(1) = 1.160$, $p = 0.90$ Test of $\theta_i = \theta_i: Q_i(2) = 1.160$, $p = 0.90$	Duloxetine dose ≤ 60mg/day									
Goldstein 2004 A 84 11.46 8 44 13.03 8.2 F1J-MC-HMAI (A) 129 13.45 9.5 41 13.06 8.9 F1J-MC-HMAI (B) 129 11.26 8.8 41 13.06 8.9 F1J-MC-HMAI (C) 130 12.08 8.8 42 13.06 8.9 F1J-MC-HMAI (C) 130 12.08 8.8 42 13.06 8.9 F1J-MC-HMAG (A) 26 8.7 9.1 26 -5.9 8.6 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 A 93 9.6 5.8 46 11.75 6.2 Duloxetine dose > 60mg/day Detke 2004 A 93 9.76 5.8 46 11.75 6.2 Duloxetine dose > 60mg/day Detke 2004 A 93 9.76 5.8 49 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.16, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.16, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.16, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.16, p = 0.90 Test of $\theta_i = \theta_i$; Q(1) = 1.16, p = 0.90 Test of $\theta_i = \theta_i$; Q(2) = 0.02, p = 0.99	Detke 2002 A	121	12.25	7.6	115	15.93	7		-3.68 [-5.55, -1.81]	7.94
F1J-MC-HMAI (A) 129 13.45 9.5 41 13.06 8.9 F1J-MC-HMAI (B) 129 11.26 8.8 41 13.06 8.9 F1J-MC-HMAI (C) 130 12.08 8.8 42 13.06 8.9 F1J-MC-HMAG (A) 90 12.04 6.3 45 13.51 6.7 F1J-MC-HMAG (A) 26 8.7 9.1 26 5.9 8.6 F1J-MC-HMAG (B) 24 7.8 9 25 5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 B 72 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_2$; Q(2) = 0.02, p = 0.99	Detke 2002 B	123	11.37	7.1	136	13.25	7.4		-1.88 [-3.65, -0.11]	8.83
F1J-MC-HMAI (B) 129 11.26 8.8 41 13.06 8.9 F1J-MC-HMAI (C) 130 12.08 8.8 42 13.06 8.9 F1J-MC-HMAT (A) 90 12.04 6.3 45 13.51 6.7 F1J-MC-HMAG (A) 26 -8.7 9.1 26 -5.9 8.6 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2004 B 93 8.85 6.2 47 11.75 6.2 Duloxetine dose > 60mg/day Detke 2004 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: I ² = 0.00%, H ² = 1.00 Test of $\theta_1 = \theta_1$, Q(1) = 1.04, p = 0.31 Overall Heterogeneity: I ² = 0.00%, H ² = 1.00 Test of $\theta_1 = \theta_1$, Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$, Q(1) = 1.160, p = 0.99 Test of $\theta_1 = \theta_1$, Q(2) = 0.02, p = 0.99	Goldstein 2004 A	84	11.46	8	44	13.03	8.2		-1.57 [-4.51, 1.37]	3.19
F1J-MC-HMA1 (C) 130 12.08 8.8 42 13.06 8.9 F1J-MC-HMAT a (A) 90 12.04 6.3 45 13.51 6.7 F1J-MC-HMAG (A) 26 -8.7 9.1 26 -5.9 8.6 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Derka 2004 B 93 8.85 6.2 47 11.75 6.2 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.91 Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.16, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.16, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.16, p = 0.90	F1J-MC-HMAI (A)	129	13.45	9.5	41	13.06	8.9		0.39 [-2.90, 3.68]	2.56
F1J-MC-HMAT a (A) 90 12.04 6.3 45 13.51 6.7 F1J-MC-HMAG (A) 26 -8.7 9.1 26 -5.9 8.6 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2004 B 93 8.85 6.2 47 11.75 6.2 Duloxetine dose > 60mg/day Detke 2004 B 93 9.6 5.8 46 11.75 6.2 Duloxetine dose > 60mg/day Detke 2004 B 93 9.76 5.8 49 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: I ² = 0.00%, H ² = 1.00 Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: I ² = 0.00%, H ² = 1.00 Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: I ² = 0.00%, H ² = 1.00 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(2) = 0.02, p = 0.99	F1J-MC-HMAI (B)	129	11.26	8.8	41	13.06	8.9		-1.80 [-4.90, 1.30]	2.88
F1J-MC-HMAG (A) 26 -8.7 9.1 26 -5.9 8.6 F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Detail 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.99 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.00, p = 0.90	F1J-MC-HMAI (C)	130	12.08	8.8	42	13.06	8.9		0.98 [-4.05, 2.09]	2.94
F1J-MC-HMAG (B) 24 -7.8 9 25 -5.8 7.5 F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAT a (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$: Q(1) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(2) = 0.02, p = 0.99	F1J-MC-HMAT a (A)	90	12.04	6.3	45	13.51	6.7		-1.47 [-3.77, 0.83]	5.22
F1J-MC-HMAH 86 13.7 6.8 86 14.4 6.9 Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90	F1J-MC-HMAG (A)	26	-8.7	9.1	26	-5.9	8.6		2.80 [-7.61, 2.01]	1.19
Higuchi 2009 A 73 -10.5 5.7 72 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.30 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.00, p = 0.90	F1J-MC-HMAG (B)	24	-7.8	9	25	-5.8	7.5		-2.00 [-6.63, 2.63]	1.29
Higuchi 2009 B 74 -10 6.4 73 -8.3 5.8 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90	F1J-MC-HMAH	86	13.7	6.8	86	14.4	6.9		-0.70 [-2.75, 1.35]	6.60
Heterogeneity: $l^{2} = 0.00\%$, $H^{2} = 1.00$ Test of $\theta_{1} = \theta_{1}$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^{2} = 0.00\%$, $H^{2} = 1.00$ Test of $\theta_{1} = \theta_{1}$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^{2} = 0.00\%$, $H^{2} = 1.00$ Test of $\theta_{1} = \theta_{1}$: Q(1) = 1.04, p = 0.90 Test of $\theta_{1} = \theta_{1}$: Q(1) = 1.160, p = 0.99 Test of $\theta_{1} = \theta_{1}$: Q(1) = 1.160, p = 0.99	Higuchi 2009 A	73	-10.5	5.7	72	-8.3	5.8		-2.20 [-4.07, -0.33]	7.90
Test of $\theta_{1} = \theta_{1}$: Q(11) = 7.44, p = 0.76 Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^{2} = 0.00\%$, $H^{2} = 1.00$ Test of $\theta_{1} = \theta_{1}$: Q(1) = 1.04, p = 0.31 Dverall Heterogeneity: $l^{2} = 0.00\%$, $H^{2} = 1.00$ Test of $\theta_{1} = \theta_{1}$: Q(1) = 1.04, p = 0.90 Test of $\theta_{1} = \theta_{1}$: Q(19) = 11.60, p = 0.90 Test of $\theta_{1} = \theta_{1}$: Q(19) = 11.60, p = 0.90 Test of $\theta_{1} = \theta_{1}$: Q(19) = 11.60, p = 0.90 Test of $\theta_{1} = \theta_{1}$: Q(19) = 11.60, p = 0.99	Higuchi 2009 B	74	-10	6.4	73	-8.3	5.8		-1.70 [-3.68, 0.28]	7.09
Duloxetine dose > 60mg/day Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Soldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 Perahia 2008, H ² = 1.00 Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.69 Variable duloxetine dose Soldstein 2002 68 10.6 7.5 66 13.36 7.1 Perator $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.69 Variable duloxetine dose Soldstein 2002 68 10.6 7.5 66 13.36 7.1 Perator $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.31 Dverall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90	Heterogeneity: I ² = 0.00%, H ²	= 1.00)					•	-1.83 [-2.52, -1.14]	
Detke 2004 A 93 9.6 5.8 46 11.75 6.2 Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 1.160, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90 Test of $\theta_i = \theta_i$: Q(1) = 11.60, p = 0.90	Test of $\theta_i = \theta_j$: Q(11) = 7.44, p	= 0.76	6							
Detke 2004 B 93 8.85 6.2 47 11.75 6.2 Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $1^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $1^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90 Test of $\theta_1 = \theta_1$: Q(1) = 1.160, p = 0.90	Duloxetine dose > 60mg/day									
Goldstein 2004 B 86 10.34 7.3 44 13.03 8.2 -2.69 -5.46 0.08 3.62 Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 -0.83 [-2.80, 1.14] 7.12 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 -0.92 [-3.04, 1.20] 6.16 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 -0.92 [-3.04, 1.20] 6.16 Heterogeneity: I ² = 0.00%, H ² = 1.00 Test of $\theta_1 = \theta_1$; Q(5) = 3.10, p = 0.69 -1.76 [-2.67, -0.85] -2.76 [-5.23, -0.29] 4.52 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 -2.76 [-5.23, -0.29] 4.52 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 -0.90 [-3.48, 1.68] 4.15 Heterogeneity: I ² = 3.77%, H ² = 1.04 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81 -1.81<	Detke 2004 A	93	9.6	5.8	46	11.75	6.2		-2.15 [-4.25, -0.05]	6.29
Perahia 2006 A 93 9.76 5.8 49 10.59 5.5 Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.90 Test of $\theta_i = \theta_i$: Q(19) = 11.60, p = 0.90 Test of $g_i = \theta_i$: Q(19) = 11.60, p = 0.99	Detke 2004 B	93	8.85	6.2	47	11.75	6.2		-2.90 [-5.07, -0.73]	5.85
Perahia 2006 B 102 9.67 6.6 50 10.59 5.5 F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.99 Test of group differences: Q _b (2) = 0.02, p = 0.99	Goldstein 2004 B	86	10.34	7.3	44	13.03	8.2		-2.69 [-5.46, 0.08]	3.62
F1J-MC-HMAT a (B) 81 11.9 6.6 44 13.51 6.7 Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(19) = 11.60, p = 0.99 Test of group differences: Q _b (2) = 0.02, p = 0.99	Perahia 2006 A	93	9.76	5.8	49	10.59	5.5		-0.83 [-2.80, 1.14]	7.12
Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(19) = 11.60, p = 0.99 Test of group differences: Q _b (2) = 0.02, p = 0.99	Perahia 2006 B	102	9.67	6.6	50	10.59	5.5		-0.92 [-3.04, 1.20]	6.16
Test of $\theta_1 = \theta_1$; Q(5) = 3.10, p = 0.69 Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(19) = 11.60, p = 0.99 Test of group differences: Q _b (2) = 0.02, p = 0.99	F1J-MC-HMAT a (B)	81	11.9	6.6	44	13.51	6.7		-1.61 [-4.05, 0.83]	4.66
Variable duloxetine dose Goldstein 2002 68 10.6 7.5 66 13.36 7.1 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_1 = \theta_1$; Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_1 = \theta_1$; Q(19) = 11.60, p = 0.90 Test of group differences: Q _b (2) = 0.02, p = 0.99	Heterogeneity: I ² = 0.00%, H ²	= 1.00)					•	-1.76 [-2.67, -0.85]	
Goldstein 2002 68 10.6 7.5 66 13.36 7.1 -2.76 [-5.23, -0.29] 4.52 F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 -0.90 [-3.48, 1.68] 4.15 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ -1.87 [-3.66, -0.08] -1.87 [-3.66, -0.08] Overall -1.81 [-2.34, -1.28] -1.81 [-2.34, -1.28] -1.81 [-2.34, -1.28] Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ -0.90 -1.81 [-2.34, -1.28] -1.81 [-2.34, -1.28] Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 -0.90 -0.90 -1.81 [-2.34, -1.28] -1.81 <	Test of $\theta_i = \theta_j$: Q(5) = 3.10, p =	= 0.69								
F1J-MC-HMAQ (B) 81 11.63 8.5 72 12.53 7.7 -0.90 [-3.48, 1.68] 4.15 Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ -1.87 [-3.66, -0.08] -1.87 [-3.66, -0.08] -1.87 [-3.66, -0.08] Overall -1.81 [-2.34, -1.28] -1.81 [-2.34, -1.28] -1.81 [-2.34, -1.28] Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ -1.80 [-2.34, -1.28] -1.81 [-2.34, -1.28] Test of $\theta_1 = \theta_1$: Q(19) = 11.60, p = 0.90 -1.81 [-2.34, -1.28] -1.81 [-2.34, -1.28]	Variable duloxetine dose									
Heterogeneity: $l^2 = 3.77\%$, $H^2 = 1.04$ Test of $\theta_i = \theta_i$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(19) = 11.60, p = 0.90 Test of group differences: Q _b (2) = 0.02, p = 0.99	Goldstein 2002	68	10.6	7.5	66	13.36	7.1		-2.76 [-5.23, -0.29]	4.52
Test of $\theta_i = \theta_j$: Q(1) = 1.04, p = 0.31 Overall Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: Q(19) = 11.60, p = 0.90 Test of group differences: Q _b (2) = 0.02, p = 0.99	F1J-MC-HMAQ(B)	81	11.63	8.5	72	12.53	7.7		0.90 [-3.48, 1.68]	4.15
Overall -1.81 [-2.34, -1.28] Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: Q(19) = 11.60, p = 0.90 Test of group differences: Q _b (2) = 0.02, p = 0.99	Heterogeneity: I ² = 3.77%, H ²	= 1.04	Ļ					-	-1.87 [-3.66, -0.08]	
Heterogeneity: $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_i$: Q(19) = 11.60, p = 0.90 Test of group differences: Q _b (2) = 0.02, p = 0.99	Test of $\theta_i = \theta_j$: Q(1) = 1.04, p =	= 0.31								
Test of θ _i = θ _j : Q(19) = 11.60, p = 0.90 Test of group differences: Q _b (2) = 0.02, p = 0.99								•	-1.81 [-2.34, -1.28]	
Test of group differences: $Q_b(2) = 0.02$, p = 0.99	Heterogeneity: I ² = 0.00%, H ²	= 1.00)							
	Test of $\theta_i = \theta_j$: Q(19) = 11.60, p	p = 0.9	00							
-10 -5 0 5	Test of group differences: $Q_b(2)$	2) = 0.0	02, p =	0.99			r			
ixed-effects inverse-variance model	ixed-effects inverse-variance	model					-1() -5 0	5	

Supplementary Fig S7: Subgroup analysis of duloxetine vs. placebo on HDRS-17 for duloxetine dose.

Study		reatme		N	Control				Mean Dif		Weigh
Study	N	Mean	SD	Ν	Mean	SD			with 95%	CI	(%)
Placebo washout period							_				
Detke 2002 A	121					7			3.68 [-5.55,		
Detke 2002 B	123	11.37	7.1	136	13.25	7.4			1.88 [-3.65,		
Detke 2004 A	93	9.6	5.8	46	11.75	6.2			2.15 [-4.25,		
Detke 2004 B	93	8.85	6.2	47	11.75	6.2			2.90 [-5.07,		
Goldstein 2004 A	84	11.46	8	44	13.03	8.2		-	1.57 [-4.51,	1.37]	3.19
Goldstein 2004 B	86	10.34	7.3	44	13.03	8.2		12-	2.69 [-5.46,	0.08]	3.62
Goldstein 2002	68	10.6	7.5	66	13.36	7.1		-	2.76 [-5.23,	-0.29]	4.52
Perahia 2006 A	93	9.76	5.8	49	10.59	5.5		-	0.83 [-2.80,	1.14]	7.12
Perahia 2006 B	102	9.67	6.6	50	10.59	5.5			0.92 [-3.04,	1.20]	6.16
F1J-MC-HMAI (A)	129	13.45	9.5	41	13.06	8.9			0.39 [-2.90,	3.68]	2.56
F1J-MC-HMAI (B)	129	11.26	8.8	41	13.06	8.9		-	1.80 [-4.90,	1.30]	2.88
F1J-MC-HMAI (C)	130	12.08	8.8	42	13.06	8.9			0.98 [-4.05,	2.09]	2.94
F1J-MC-HMAQ(B)	81	<mark>11.6</mark> 3	8.5	72	12.53	7.7		-	0.90 [-3.48,	1.68]	4.15
⁼ 1J-MC-HMAT a (A)	90	12.04	6.3	45	13.51	6.7		-	1.47 [-3.77,	0.83]	5.22
F1J-MC-HMAT a (B)	81	11.9	6.6	44	13.51	6.7		-	1.61 [-4.05,	0.83]	4.66
F1J-MC-HMAH	86	13.7	6.8	86	14.4	6.9			0.70 [-2.75,	1.35]	6.60
Higuchi 2009 A	73	-10.5	5.7	72	<mark>-8.3</mark>	5.8		-	2.20 [-4.07,	-0.33]	7.90
Higuchi 2009 B	74	-10	6.4	73	-8.3	5.8		-	1.70 [-3.68,	0.28]	7.09
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$							•	-	1.80 [-2.33,	-1.26]	
Fest of $\theta_i = \theta_j$: Q(17) = 11.43, p = 0.83											
Only some participants had placebo washout period											
F1J-MC-HMAG (A)	26	-8.7	9.1	26	-5.9	8.6			2.80 [-7.61,	2.01]	1.19
F1J-MC-HMAG (B)	24	-7.8	9	25	-5.8	7.5			2.00 [-6.63,	2.63]	1.29
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$								-	2.38 [-5.72,	0.95]	
Fest of $\theta_i = \theta_j$: Q(1) = 0.06, p = 0.81											
Overall							•	_	1.81 [-2.34,	-1.28]	
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$											
Test of $\theta_i = \theta_j$: Q(19) = 11.60, p = 0.90											
Test of group differences: $Q_b(1) = 0.12$, $p = 0.73$						-		1			
xed-effects inverse-variance model						-10	-5 0	5			

Fixed-effects inverse-variance model

Supplementary Fig S8: Subgroup analysis of placebo washout period on HDRS-17.



Supplementary Fig S9: Funnel plot of duloxetine vs. placebo for the outcome serious adverse events.

		oxetine		acebo					Odds r		Weigh
Study		No events	Events	No event	s				with 959	% CI	(%)
Baseline HDRS-17 scores < 23											
Detke 2002 A	0	123	3	119			+-		0.14 [0.01,	2.70]	6.55
Detke 2002 B	1	127	0	139					3.11 [0.13,	-	0.92
Goldstein 2004 B	1	90	0	45					2.52 [0.06,	106.89]	0.81
Katona 2012	2	149	4	141			+-		0.47 [0.09,	2.62]	7.54
Nierenberg 2007	3	270	2	135			-		0.75 [0.12,	4.54]	4.93
Oakes 2012 A	6	251	3	124			•		0.99 [0.24,	4.02]	7.34
Oakes 2012 B	2	259	7	124	-	_			0.14 [0.03,	0.67]	17.3
Perahia 2006 B	1	102	0	50					- 2.51 [0.06,	108.17]	0.81
Raskin 2007	1	206	4	100			+		0.12 [0.01,	1.10]	9.92
F1J-MC-HMAQ(B)	0	82	2	73		-			0.19 [0.01,	3.77]	4.8
F1J-MC-HMAT a (B)	1	83	1	44	-	-	+		0.53 [0.03,	8.68]	2.4
F1J-MC-HMAH	9	80	8	80		-	—		1.13 [0.41,	3.06]	13.5
Heterogeneity: I ² = 1.93%, H ² =	1.02					•			0.56 [0.34,	0.93]	
Test of $\theta_i = \theta_j$: Q(11) = 11.22, p	= 0.43										
Test of θ = 0: z = -2.26, p = 0.02	2										
Baseline HDRS-17 scores ≥ 23											
Baldwin 2012	2	153	3	145			-		0.63 [0.10,	3.84]	5.6
Tourian 2009	2	155	2	159			•		1.03 [0.14,	7.37]	3.6
F1J-MC-HMAI (A)	1	129	0	41	-				-2.33 [0.03,	168.72]	0.6
F1J-MC-HMAI (C)	1	130	1	41	-	-			0.32 [0.02,	5.16]	2.8
Heterogeneity: I ² = 0.00%, H ² =	1.00								0.76 [0.25,	2.36]	
Test of $\theta_i = \theta_j$: Q(3) = 0.77, p = 0	0.86										
Test of θ = 0: z = -0.47, p = 0.64	4										
Overall									0.59 [0.38,	0.93]	
Heterogeneity: I ² = 0.00%, H ² =	1.00										
Test of $\theta_i = \theta_j$: Q(15) = 12.06, p	= 0.67										
Test of θ = 0: z = -2.26, p = 0.02	2										
Test of group differences: Q _b (1)	= 0.23, p =	0.63					<u> </u>		_		
					1/128	1/8	ż	32			
ixed-effects Mantel-Haenszel n	nodel										

Supplementary Fig S10: Subgroup analysis of baseline HDRS scores on serious adverse events.

Shudu		oxetine		acebo	_	Odds ratio	Weigh
Study	Events	No events	Events	No event	S	with 95% CI	(%)
Participants with chronic/treatment resistant depression excluded							
Baldwin 2012	2	153	3	145		0.63 [0.10, 3.84	
Detke 2002 A	0	123	3	119		0.14 [0.01, 2.70	-
Detke 2002 B	1	127	0	139		3.11 [0.13, 73.86] 0.92
Goldstein 2004 B	1	90	0	45		- 2.52 [0.06, 106.89] 0.81
Katona 2012	2	149	4	141		0.47 [0.09, 2.62] 7.54
Mahableshwarkar 2013	2	148	2	149		1.01 [0.14, 7.24] 3.68
Mahableshwarkar 2015 B	1	206	2	189		0.46 [0.04, 5.10] 3.87
Nierenberg 2007	3	270	2	135		0.75 [0.12, 4.54] 4.93
Oakes 2012 A	6	251	3	124		0.99 [0.24, 4.02	7.34
Oakes 2012 B	2	259	7	124		0.14 [0.03, 0.67] 17.31
Perahia 2006 B	1	102	0	50		- 2.51 [0.06, 108.17] 0.81
11918A	1	132	1	135		1.02 [0.06, 16.52] 1.84
F1J-MC-HMAT a (B)	1	83	1	44		0.53 [0.03, 8.68	2.41
F1J-MC-HMAH	9	80	8	80		1.13 [0.41, 3.06] 13.53
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$					•	0.68 [0.42, 1.09]
Test of $\theta_i = \theta_j$: Q(13) = 8.65, p = 0.80							
Test of θ = 0: z = -1.62, p = 0.11							
Participants with chronic/treatment resistant depression not excluded							
Boulenger 2014	3	144	0	158		- 7.37 [0.39, 137.75] 0.91
Raskin 2007	1	206	4	100		0.12 [0.01, 1.10] 9.92
Tourian 2009	2	155	2	159		1.03 [0.14, 7.37] 3.65
F1J-MC-HMAI (A)	1	129	0	41		-2.33 [0.03, 168.72] 0.67
F1J-MC-HMAI (C)	1	130	1	41		0.32 [0.02, 5.16] 2.81
F1J-MC-HMAQ(B)	0	82	2	73		0.19 [0.01, 3.77] 4.81
Heterogeneity: I ² = 21.24%, H ² = 1.27					-	0.66 [0.27, 1.58]
Test of $\theta_i = \theta_i$: Q(5) = 6.35, p = 0.27							
Test of θ = 0: z = -0.93, p = 0.35							
Overall					•	0.67 [0.44, 1.02]
Heterogeneity: I ² = 0.00%, H ² = 1.00							
Test of θ _i = θ _j : Q(19) = 15.03, p = 0.72							
Test of θ = 0: z = -1.87, p = 0.06							
Test of group differences: $Q_b(1) = 0.00$, p = 0.96						_	
ixed-effects Mantel-Haenszel model				1	1/128 1/8 2 32		

Supplementary Fig S11: Subgroup analysis of chronic treatment resistant depression on serious adverse events.

		oxetine		acebo					Odds n		Weight
Study	Events	No events	Events	No event	ts				with 959	% CI	(%)
Participants' age ≤65 years											
Baldwin 2012	2	153	3	145			<u> </u>		0.63 [0.10,	3.84]	5.67
Boulenger 2014	3	144	0	158			-		- 7.37 [0.39,	137.75]	0.91
Detke 2002 A	0	123	3	119			-		0.14 [0.01,	2.70]	6.55
Detke 2002 B	1	127	0	139					3.11 [0.13,	73.86]	0.92
Goldstein 2004 B	1	90	0	45					- 2.52 [0.06,	106.89]	0.81
Mahableshwarkar 2013	2	148	2	149					1.01 [0.14,	7.24]	3.68
Mahableshwarkar 2015 B	1	206	2	189					0.46 [0.04,	5.10]	3.87
Nierenberg 2007	3	270	2	135			<u> </u>		0.75 [0.12,	4.54]	4.93
Oakes 2012 A	6	251	3	124		—	—		0.99 [0.24,	4.02]	7.34
Oakes 2012 B	2	259	7	124	-	_			0.14 [0.03,	0.67]	17.31
Perahia 2006 B	1	102	0	50					- 2.51 [0.06,	108.17]	0.81
Tourian 2009	2	155	2	159			•——		1.03 [0.14,	7.37]	3.65
F1J-MC-HMAI (A)	1	129	0	41					-2.33 [0.03,	168.72]	0.67
F1J-MC-HMAI (C)	1	130	1	41	_				0.32 [0.02,	5.16]	2.81
F1J-MC-HMAQ(B)	0	82	2	73		-			0.19 [0.01,	3.77]	4.81
11918A	1	132	1	135				_	1.02 [0.06,	16.52]	1.84
F1J-MC-HMAT a (B)	1	83	1	44					0.53 [0.03,	8.68]	2.41
F1J-MC-HMAH	9	80	8	80		-	-		1.13 [0.41,	3.06]	13.53
Heterogeneity: I ² = 0.00%, H	² = 1.00								0.76 [0.48,	1.18]	
Test of $\theta_1 = \theta_1$: Q(17) = 12.29	p = 0.78								•		
Test of θ = 0: z = -1.23, p = 0).22										
Participants' age > 65 years											
Katona 2012	2	149	4	141			<u> </u>		0.47 [0.09,	2.62]	7.54
Raskin 2007	1	206	4	100		_	+		0.12 [0.01,	1.10]	9.92
Heterogeneity: I ² = 0.00%, H	² = 1.00						•		0.27 [0.07,	1.02]	
Test of $\theta_i = \theta_i$: Q(1) = 0.92, p	= 0.34										
Test of θ = 0: z = -1.93, p = 0	0.05										
Overall						•			0.67 [0.44,	1.02]	
Heterogeneity: I ² = 0.00%, H	² = 1.00										
Test of $\theta_1 = \theta_1$: Q(19) = 15.03	, p = 0.72										
Test of θ = 0: z = -1.87, p = 0											
Test of group differences: Q	₀ (1) = 2.06,	p = 0.15							_		
					1/128	1/8	ż	32			
ixed-effects Mantel-Haensze	el model										

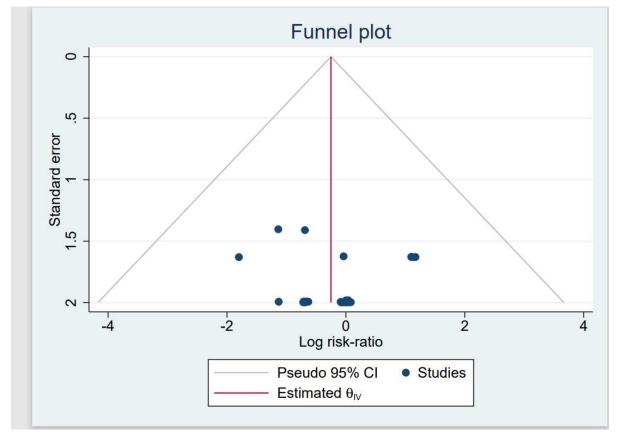
Supplementary Fig S12: Subgroup analysis of participants' age on serious adverse events.

Study Duloxetine dose ≤ 60 mg/day Baldwin 2012	Events	No events	Events	No evente		with 95% CI	
• ,			2101110	NO EVENIS		with 3570 Ci	(%)
Baldwin 2012							
	2	153	3	145			.84] 5.67
Boulenger 2014	3	144	0	158		- 7.37 [0.39, 137	.75] 0.91
Detke 2002 A	0	123	3	119		0.14 [0.01, 2	.70] 6.55
Detke 2002 B	1	127	0	139		3.11 [0.13, 73	.86] 0.92
Katona 2012	2	149	4	141		0.47 [0.09, 2	.62] 7.54
Mahableshwarkar 2013	2	148	2	149		1.01 [0.14, 7	.24] 3.68
Mahableshwarkar 2015 B	1	206	2	189		0.46 [0.04, 5	.10] 3.87
Nierenberg 2007	3	270	2	135		0.75 [0.12, 4	.54] 4.93
Oakes 2012 A	6	251	3	124		0.99 [0.24, 4	.02] 7.34
Oakes 2012 B	2	259	7	124		0.14 [0.03, 0	.67] 17.31
Raskin 2007	1	206	4	100		0.12[0.01, 1	.10] 9.92
Tourian 2009	2	155	2	159		1.03 [0.14, 7	.37] 3.65
F1J-MC-HMAI (A)	1	129	0	41		-2.33 [0.03, 168	.72] 0.67
F1J-MC-HMAI (C)	1	130	1	41		0.32 [0.02, 5	.16] 2.81
11918A	1	132	1	135		1.02 [0.06, 16	.52] 1.84
F1J-MC-HMAH	9	80	8	80		1.13 [0.41, 3	.06] 13.53
Heterogeneity: I ² = 0.00%, H ² =	1.00				•	0.67 [0.43, 1	.04]
Test of $\theta_i = \theta_j$: Q(15) = 13.36, p =	= 0.57						
Test of θ = 0: z = -1.80, p = 0.07	7						
duloxetine dose > 60 mg/day							
Goldstein 2004 B	1	90	0	45		2.52 [0.06, 106	.89] 0.81
Perahia 2006 B	1	102	0	50		2.51 [0.06, 108	.17] 0.81
F1J-MC-HMAT a (B)	1	83	1	44		0.53 [0.03, 8	.68] 2.41
Heterogeneity: I ² = 0.00%, H ² =	1.00				-	1.33 [0.22, 8	.10]
Test of $\theta_i = \theta_j$: Q(2) = 0.64, p = 0).73						
Test of θ = 0: z = 0.31, p = 0.76							
Variable duloxetine dose							
F1J-MC-HMAQ(B)	0	82	2	73		0.19[0.01, 3	.77] 4.81
Heterogeneity: I ² = 0.00%, H ² =	1.00					0.19[0.01, 3	.77]
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .							
Test of θ = 0: z = -1.09, p = 0.27	7						
Overall					•	0.67 [0.44, 1	.02]
Heterogeneity: I ² = 0.00%, H ² =	1.00						
Test of $\theta_i = \theta_j$: Q(19) = 15.03, p	= 0.72						
Test of θ = 0: z = -1.87, p = 0.06							
Test of group differences: Q _b (2)	= 1.24, j	o = 0.54				_	
ixed-effects Mantel–Haenszel m				1.	128 1/8 2 32		

Supplementary Fig S13: Subgroup analysis of duloxetine dose on serious adverse events.

		oxetine		acebo					Odds r		Weigh
Study	Events	No events	Events	No event	s				with 95	% CI	(%)
Trials with no placebo washout period											
Boulenger 2014	3	144	0	158					7.37 [0.39,	137.75]	0.91
Katona 2012	2	149	4	141			-		0.47 [0.09,	2.62]	7.54
Mahableshwarkar 2013	2	148	2	149			-		1.01 [0.14,	7.24]	3.68
Mahableshwarkar 2015 B	1	206	2	189	-	-	<u> </u>		0.46 [0.04,	5.10]	3.87
Oakes 2012 A	6	251	3	124			—		0.99 [0.24,	4.02]	7.34
Oakes 2012 B	2	259	7	124	-				0.14 [0.03,	0.67]	17.31
Tourian 2009	2	155	2	159			• · · · ·		1.03 [0.14,	7.37]	3.65
11918A	1	132	1	135					1.02 [0.06,	16.52]	1.84
Heterogeneity: I ² = 5.61%, H ² = 1.06						-			0.67 [0.36,	1.24]	
Test of $\theta_i = \theta_j$: Q(7) = 7.42, p = 0.39											
Test of θ = 0: z = -1.27, p = 0.20											
Trials with placebo washout period											
Baldwin 2012	2	153	3	145			-		0.63 [0.10,	3.84]	5.67
Detke 2002 A	0	123	3	119		-	-		0.14 [0.01,	2.70]	6.55
Detke 2002 B	1	127	0	139					3.11 [0.13,	73.86]	0.92
Goldstein 2004 B	1	90	0	45					2.52 [0.06,	106.89]	0.81
Nierenberg 2007	3	270	2	135			-		0.75 [0.12,	4.54]	4.93
Perahia 2006 B	1	102	0	50			•		2.51 [0.06,	108.17]	0.81
Raskin 2007	1	206	4	100		-	+		0.12 [0.01,	1.10]	9.92
F1J-MC-HMAI (A)	1	129	0	41	-		•		2.33 [0.03,	168.72]	0.67
F1J-MC-HMAI (C)	1	130	1	41	-	-			0.32 [0.02,	5.16]	2.81
F1J-MC-HMAQ(B)	0	82	2	73		-	<u> </u>		0.19 [0.01,	3.77]	4.81
F1J-MC-HMAT a (B)	1	83	1	44	-	-			0.53 [0.03,	8.68]	2.41
F1J-MC-HMAH	9	80	8	80		-	-		1.13 [0.41,	3.06]	13.53
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$						-			0.67 [0.38,	1.19]	
Test of $\theta_i = \theta_j$: Q(11) = 7.61, p = 0.75											
Test of θ = 0: z = -1.37, p = 0.17											
Overall						•			0.67 [0.44,	1.02]	
Heterogeneity: I ² = 0.00%, H ² = 1.00											
Test of $\theta_i = \theta_j$: Q(19) = 15.03, p = 0.72											
Test of θ = 0: z = -1.87, p = 0.06											
Test of group differences: $Q_b(1) = 0.00$,	p = 1.00				1/128	1/8	2	32			
ixed-effects Mantel–Haenszel model					1/128	1/0	2	32			

Supplementary Fig S14: Subgroup analysis of placebo washout period on serious adverse events.



Supplementary Fig S15: Funnel plot duloxetine vs. placebo for the outcome suicide or suicide attempt.

	Dul	oxetine	PI	acebo					Odds r	atio	Weight
Study	Events	No events	Events	No events	5				with 959	% CI	(%)
Baseline HDRS-17 scores < 23											
Katona 2012	1	113	0	114					3.03 [0.12,	75.08]	7.66
Oakes 2012 A	0	257	1	126		_			0.25 [0.01,	4.69]	27.56
Oakes 2012 B	1	260	1	130		_			0.50 [0.03,	8.06]	20.58
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1$.00								0.72 [0.15,	3.46]	
Test of $\theta_i = \theta_j$: Q(2) = 1.34, p = 0.5	51										
Test of θ = 0: z = -0.41, p = 0.68											
Baseline HDRS-17 scores ≥ 23											
Tourian 2009	2	155	0	161			-		5.12 [0.25,	105.81]	7.63
F1J-MC-HMAI (A)	1	129	0	41					-2.33 [0.03,	168.72]	5.58
F1J-MC-HMAI (C)	1	130	1	41	-	-	-		0.32 [0.02,	5.16]	23.32
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1$.00					-			1.63 [0.30,	8.70]	
Test of $\theta_i = \theta_j$: Q(2) = 1.90, p = 0.3	39										
Test of θ = 0: z = 0.57, p = 0.57											
Overall						<			1.08 [0.35,	3.31]	
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1$.00										
Test of $\theta_i = \theta_j$: Q(5) = 3.54, p = 0.6	62										
Test of $\theta = 0$: z = 0.13, p = 0.89											
Test of group differences: $Q_b(1) =$	0.48, p =	= 0.49			1/64	1/4	4	64	4		
- ixed-effects Mantel–Haenszel mo	del				1/64	1/4	4	64			

Supplementary Fig S16: Subgroup analysis of baseline HDRS scores on suicide and suicide attempts.

	1.	oxetine		acebo		Odds ra	CALL STORE	Weight
Study	Events	No events	Events	No events	3	with 95%	% CI	(%)
Excluded participants with chronic treatment resistant depression								
Katona 2012	1	113	0	114	-	- 3.03 [0.12,	75.08]	7.66
Oakes 2012 A	0	257	1	126		0.25 [0.01,	4.69]	27.56
Oakes 2012 B	1	260	1	130		0.50 [0.03,	8.06]	20.58
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$						0.72 [0.15,	3.46]	
Test of $\theta_i = \theta_i$: Q(2) = 1.34, p = 0.51								
Test of θ = 0: z = -0.41, p = 0.68								
Participants with chronic treatment resistant depression not excluded								
Boulenger 2014	1	146	0	158		- 3.10 [0.13,	73.81]	7.67
Tourian 2009	2	155	0	161	-	— <u>5.12</u> [0.25,	105.81]	7.63
F1J-MC-HMAI (A)	1	129	0	41		<u> </u>	168.72]	5.58
F1J-MC-HMAI (C)	1	130	1	41		0.32 [0.02,	5.16]	23.32
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$						1.88 [0.43,	8.29]	
Test of $\theta_i = \theta_j$: Q(3) = 2.09, p = 0.55								
Test of θ = 0: z = 0.84, p = 0.40								
Overall					-	1.23 [0.43,	3.53]	
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$								
Test of $\theta_i = \theta_i$: Q(6) = 4.03, p = 0.67								
Test of θ = 0: z = 0.39, p = 0.69								
Test of group differences: $Q_b(1) = 0.76$, p = 0.38					, , , , , ,			
ived offects Mantel Happened model					1/64 1/4 4 6	4		

Fixed-effects Mantel-Haenszel model

Supplementary Fig S17: Subgroup analysis of chronic treatment resistant depression on suicide and suicide attempts.

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	Dul	oxetine	PI	acebo					Odds r	atio	Weight
Study	Events	No events	Events	No events					with 95% CI		(%)
Participants' age ≤65 years											
Boulenger 2014	1	146	0	158					3.10 [0.13,	73.81]	7.67
Oakes 2012 A	0	257	1	126					0.25 [0.01,	4.69]	27.56
Oakes 2012 B	1	260	1	130		-			0.50 [0.03,	8.06]	20.58
Tourian 2009	2	155	0	161					5.12 [0.25,	105.81]	7.63
F1J-MC-HMAI (A)	1	129	0	41	÷		-		-2.33 [0.03,	168.72]	5.58
F1J-MC-HMAI (C)	1	130	1	41	5 <u>7</u>		-		0.32 [0.02,	5.16]	23.32
Heterogeneity: I ² = 0.00%, H ²	= 1.00					-			1.09 [0.35,	3.32]	
Test of $\theta_i = \theta_i$: Q(5) = 3.57, p =	0.61										
Test of θ = 0: z = 0.14, p = 0.8	9										
Participants' age > 65 years											
Katona 2012	1	113	0	114			-		3.03 [0.12,	75.08]	7.66
Heterogeneity: I ² = 0.00%, H ²	= 1.00					-		-	3.03 [0.12,	75.08]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p =	521										
Test of θ = 0: z = 0.68, p = 0.5	60										
Overall									1.23 [0.43,	3.53]	
Heterogeneity: $I^2 = 0.00\%$, H^2	= 1.00										
Test of $\theta_1 = \theta_1$: Q(6) = 4.03, p =	0.67										
Test of θ = 0: z = 0.39, p = 0.6	9										
Test of group differences: Q _b (1) = 0.35,	p = 0.55			1						
ixed-effects Mantel-Haenszel	model			1/	64	1/4	4	64			

Supplementary Fig S18: Subgroup analysis of participants' age on suicide and suicide attempts.

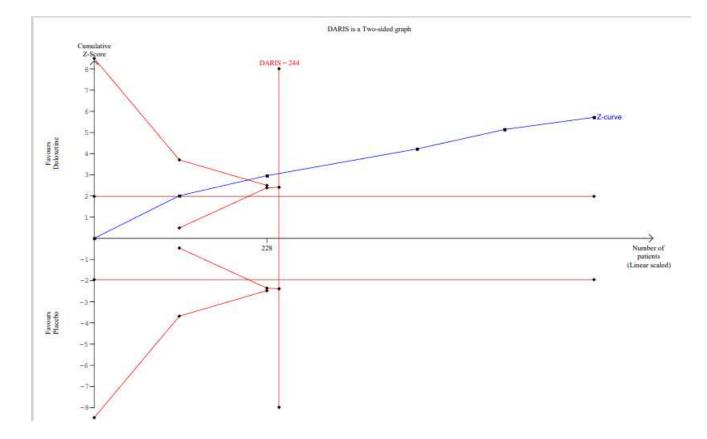
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	Duloxetine		PI	acebo					Odds r	Weight	
Study	Events	No events	Events	No events	8				with 95°	% CI	(%)
No placebo washout period											
Boulenger 2014	1	146	0	158		×	-		3.10 [0.13,	73.81]	7.67
Katona 2012	1	113	0	114		-	-	-	3.03 [0.12,	75.08]	7.66
Oakes 2012 A	0	257	1	126	-	_			0.25 [0.01,	4.69]	27.56
Oakes 2012 B	1	260	1	130	14		-		0.50 [0.03,	8.06]	20.58
Tourian 2009	2	155	0	161		-			5.12 [0.25,	105.81]	7.63
Heterogeneity: I ² = 0.00%, H ²	= 1.00					-			1.45 [0.43,	4.83]	
Test of $\theta_i = \theta_j$: Q(4) = 3.04, p	= 0.55										
Test of θ = 0: z = 0.60, p = 0.	55										
Placebo washout period											
F1J-MC-HMAI (A)	1	129	0	41	12 5.		-		-2.33 [0.03,	168.72]	5.58
F1J-MC-HMAI (C)	1	130	1	41			-		0.32 [0.02,	5.16]	23.32
Heterogeneity: I ² = 0.00%, H ²	= 1.00								0.71 [0.08,	5.95]	
Test of $\theta_i = \theta_j$: Q(1) = 0.62, p	= 0.43										
Test of θ = 0: z = -0.32, p = 0	.75										
Overall						<			1.23 [0.43,	3.53]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00										
Test of $\theta_i = \theta_i$: Q(6) = 4.03, p	= 0.67										
Test of θ = 0: z = 0.39, p = 0.											
Test of group differences: Qb	(1) = 0.33	, p = 0.56			1/64	1/4	4	64	2		
ixed-effects Mantel-Haensze	Imodel				1/04	1/4	-	04			

Supplementary Fig S 19: Subgroup analysis of placebo washout period on suicide and suicide attempts.

	D	uloxetin	e		Placeb	0						Mean Diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD	9					with 95% CI	(%)
Detke 2002 A	103	-8.36	9	95	-4.4	9.3		9	-			-3.96 [-6.51, -1.41]	27.00
Goldstein 2004 A	76	-9.29	8.6	40	-4.3	8.2	-	-		-		-4.99 [-8.23, -1.75]	16.71
Goldstein 2004 B	78	-8.55	9.4	40	-4.3	8.2	4					-4.25 [-7.69, -0.81]	14.87
F1J-MC-HMAT a (A)	73	-8.4	7.2	42	-5.38	7.1				- A		-3.02 [-5.74, -0.30]	23 .74
F1J-MC-HMAT a (B)	73	-8.4	8.7	40	-5.38	7.1		3			-	-3.02 [-6.17, 0.13]	17.68
Overall Heterogeneity: I ² = 0.0)0%, H	1 ² = 1.00	D						-	-		-3.79 [-5.11, -2.46]	
Test of $\theta_i = \theta_j$: Q(4) = 1													
Test of θ = 0: z = -5.60), p =	0.00					-8	-6	-4	-2	0		
ixed-effects inverse-va	arianc	e mode	ñ										

Supplementary Fig S20: Meta-analysis of duloxetine vs. placebo on the outcome quality of life.



Supplementary Fig S21: Trial Sequential Analysis of duloxetine vs. placebo for the outcome quality of life.

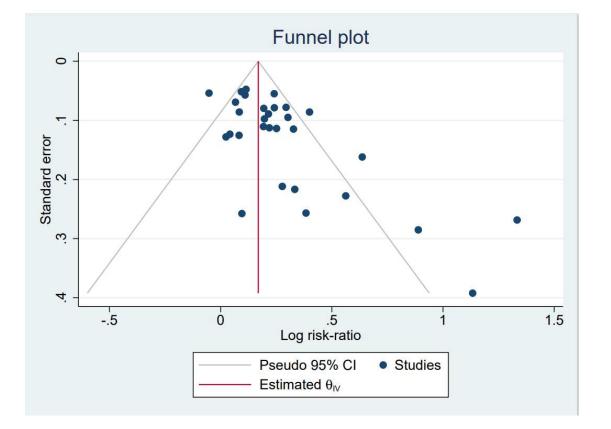
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	Т	reatme	nt		Contro	d		Mean Diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Duloxetine dose < 60 mg/c	day								
Detke 2002 A	103	-8.36	9	95	-4.4	9.3		-3.96 [-6.51, -1.41]	27.00
Goldstein 2004 A	76	-9.29	8.6	40	-4.3	8.2	_	-4.99 [-8.23, -1.75]	16.71
F1J-MC-HMAT a (A)	73	-8.4	7.2	42	-5.38	7.1		-3.02 [-5.74, -0.30]	23.74
Heterogeneity: $I^2 = 0.00\%$,	$H^2 = 1.00$	0						-3.88 [-5.50, -2.27]	
Test of $\theta_i = \theta_j$: Q(2) = 0.84,	p = 0.66								
Duloxetine dose > 60mg/d	ay								
Goldstein 2004 B	78	-8.55	9.4	40	-4.3	8.2		-4.25 [-7.69, -0.81]	14.87
F1J-MC-HMAT a (B)	73	-8.4	8.7	40	-5.38	7.1		-3.02 [-6.17, 0.13]	17.68
Heterogeneity: $I^2 = 0.00\%$,	$H^2 = 1.00$	0						-3.58 [-5.90, -1.26]	
Test of $\theta_i = \theta_j$: Q(1) = 0.27,	p = 0.61								
Overall Heterogeneity: $I^2 = 0.00\%$, Test of $\theta_i = \theta_j$: Q(4) = 1.15,)					-	-3.79 [-5.11, -2.46]	
Test of group differences:	Q _b (1) = 0.	04, p =	0.83				-8 -6 -4 -2 0		
Fixed-effects inverse-varian	ice model								

Supplementary Fig S22: Subgroup analysis of duloxetine dose on quality of life.

	Dulo	cetine	Plac	cebo					Risk R	atio	Weight
Study	Yes	No	Yes	No					with 95°	% CI	(%)
Baldwin 2012	0	155	0	148					0.96 [0.02,	47.83]	4.66
Boulenger 2014	9	138	18	140		-	-		0.54 [0.25,	1.16]	41.38
Katona 2012	7	107	8	106		-	_		0.88 [0.33,	2.33]	34.51
Mahableshwarkar 2015 A	2	148	0	159		14			— 5.30 [0.26,	109.46]	7.40
Mahableshwarkar 2013	2	148	0	151		-	-		- 5.03 [0.24,	103.96]	7.40
Tourian 2009	0	157	0	161	7				1.03 [0.02,	51.36]	4.66
Overall						-			0.94 [0.39,	2.27]	
Heterogeneity: $\tau^2 = 0.33$, I^2	= 31.4	1%, H	² = 1.4	46							
Test of $\theta_i = \theta_j$: Q(5) = 3.97,	p = 0.5	5									
Test of θ = 0: z = -0.14, p =	0.89										
					1/32	1/4	2	16			
Random-effects Sidik-Jonkn	nan mo	del									

Supplementary Fig S23: Meta-analysis of duloxetine vs. placebo on the outcome suicidal ideation.



Supplementary Fig S24: Funnel plot duloxetine vs. placebo for the outcome non-serious adverse events.

Study	Trea Yes	tment No		ntrol No	Risk Rational Risk Rational Risk Rational Risk Rational Research Research Risk Rational Risk Rationa	5
Baseline HDRS-17 scores < 23						()
Detke 2002 A	118	5	92	30	- 1.27 [1.14, 1	1.42] 5.45
Detke 2002 B	111	17	108	31	1.12 [1.00, 1	-
Detke 2004 A	49	46	17	29	1.40 [0.91, 2	
Detke 2004 B	47	46	18	29	1.32 [0.87, 2	-
Goldstein 2004 A	73	13	30	14	1.24 [1.00, 1	
Goldstein 2004 B	76	15	31	14	1.21 [0.98, 1	
Goldstein 2002	62	8	58	12		
Katona 2012	118	33	89	56	- 1.27 [1.09, 1	
Nierenberg 2007	234	39	107	30	1.10 [0.99, 1	
Oakes 2012 A	44	213	7	120	3.11 [1.44, 6	-
Oakes 2012 B	63	198		118	2.43 [1.39, 4	
Perahia 2006 A	39	54	14	35	1.47 [0.89, 2	-
Perahia 2006 B	34	69	15	35	1.10 [0.66, 1	
Raskin 2007	145	62	67	37	1.09 [0.92, 1	
F1J-MC-HMAQ (B)	73	9	55	20		
F1J-MC-HMAT a (A)	78	13	30	15	1.29 [1.03, 1	-
F1J-MC-HMAT a (B)	75	9	33	12	1.22 [1.01, 1	1.47] 2.53
F1J-MC-HMAH	76	12	81	8		-
Heterogeneity: I ² = 62.33%, H ² =	2.65				♦ 1.21 [1.15, 1	1.27]
Test of $\theta_i = \theta_j$: Q(17) = 45.13, p =	0.00					
Baseline HDRS-17 scores ≥ 23						
Baldwin 2012	93	62	64	84		1.74] 3.86
Cutler 2009	54	95	15	142		6.42] 0.86
Tourian 2009	141	16	129	32	1.12 [1.02, 1	1.23] 7.51
F1J-MC-HMAI (A)	93	37	27	14	1.09 [0.85, 1	1.39] 2.42
F1J-MC-HMAI (B)	87	42	27	14	1.02 [0.80, 1	1.32] 2.42
F1J-MC-HMAI (C)	90	41	29	15	1.04 [0.82, 1	1.33] 2.56
Heterogeneity: I ² = 83.56%, H ² =	6.08				1.26 [1.16, 1	1.38]
Test of $\theta_i = \theta_j$: Q(5) = 30.41, p = 0	0.00					
Overall					♦ 1.22 [1.17, 1	1.27]
Heterogeneity: I ² = 69.42%, H ² =	3.27					
Test of θ _i = θ _j : Q(23) = 75.22, p =	0.00					
Test of group differences: $Q_b(1)$:	= 0.82,	p = 0.3	37			
Fixed-effects Mantel-Haenszel mo	odel				1 2 4	

Supplementary Fig S25: Subgroup analysis of baseline HDRS scores on non-serious adverse events.

Obudu		ment	Co Yes	ntrol		Risk Ratio	Weight
Study	Yes	No	res	No		with 95% CI	(%)
Participants' age < 65 yrs					_		
Baldwin 2012	93	62	64	84		1.39 [1.11, 1.74]	3.82
Boulenger 2014	102	45	81	77		1.35 [1.12, 1.63]	4.56
Cutler 2009	54	95	15	142		3.79 [2.24, 6.42]	0.85
Detke 2002 A	118	5	92	30		1.27 [1.14, 1.42]	5.40
Detke 2002 B	111	17	108	31	•	1.12 [1.00, 1.25]	6.05
Detke 2004 A	49	46	17	29		1.40 [0.91, 2.13]	1.34
Detke 2004 B	47	46	18	29		1.32 [0.87, 2.00]	1.40
Goldstein 2004 A	73	13	30	14		1.24 [1.00, 1.55]	2.32
Goldstein 2004 B	76	15	31	14		1.21 [0.98, 1.51]	2.42
Goldstein 2002	62	8	58	12	-	1.07 [0.93, 1.22]	3.39
Mahableshwarkar 2015 A	119	31	94	65		1.34 [1.15, 1.56]	5.33
Mahableshwarkar 2013	120	30	81	70		1.49 [1.26, 1.77]	4.72
Mahableshwarkar 2015 B	84	123	41	150		1.89 [1.38, 2.60]	2.49
Nierenberg 2007	234	39	107	30		1.10 [0.99, 1.21]	8.32
Oakes 2012 A	44	213	7	120		-3.11 [1.44, 6.70]	0.55
Oakes 2012 B	63	198	13	118		2.43 [1.39, 4.25]	1.01
Perahia 2006 A	39	54	14	35		1.47 [0.89, 2.43]	1.07
Perahia 2006 B	34	69	15	35		1.10 [0.66, 1.82]	1.18
Tourian 2009	141	16	129	32		1.12 [1.02, 1.23]	7.44
F1J-MC-HMAI (A)	93	37	27	14		1.09 [0.85, 1.39]	2.40
F1J-MC-HMAI (B)	87	42	27	14		1.02 [0.80, 1.32]	2.39
F1J-MC-HMAI (C)	90	41	29	15		1.04 [0.82, 1.33]	2.54
F1J-MC-HMAQ (B)	73	9	55	20		1.21 [1.04, 1.42]	3.36
11918A	97	36	80	56		1.24 [1.04, 1.48]	4.62
F1J-MC-HMAT a (A)	78	13	30	15		1.29 [1.03, 1.61]	2.35
F1J-MC-HMAT a (B)	75	9	33	12		1.29 [1.03, 1.01]	2.55
F1J-MC-HMAT a (B)	76	12	81	8			4.70
				-	-	0.95 [0.85, 1.05]	
NCT 01145755	30	17	16	28		1.76 [1.12, 2.74]	0.97
Heterogeneity: I ² = 75.12%					•	1.28 [1.23, 1.33]	
Test of $\theta_i = \theta_j$: Q(27) = 108.	53, p =	0.00					
Participants' age ≥ 65 yrs							
Katona 2012	118	33	89	56		1.27 [1.09, 1.49]	5.30
Raskin 2007	145	62	67	37	-	1.09 [0.92, 1.29]	5.21
Heterogeneity: I ² = 45.59%				-		1.18 [1.05, 1.32]	
Test of $\theta_i = \theta_i$: Q(1) = 1.84,					•		
······	- 0.1	-					
Overall						1.27 [1.22, 1.32]	
Heterogeneity: I ² = 73.04%	. H ² = 3	3.71			*		
Test of $\theta_i = \theta_i$: Q(29) = 107.							
			-				
Test of group differences: 0	ג₀(1) =	1.75,	p = 0.	19	1 2 4		
ixed-effects Mantel-Haens	rol mor				1 2 4		
ixeu-enecis maniei-Haensa		iel					

Supplementary Fig S26: Subgroup analysis of participants' age on non-serious adverse events.

Chudu		ment		ntrol		Risk Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Duloxetine dose ≤ 60 mg/day Baldwin 2012	93	62	64	84		1.39 [1.11, 1.74]	3.82
Baldwin 2012 Boulenger 2014	93 102	62 45	81	84 77			3.82 4.56
Boulenger 2014 Cutler 2009	102 54	45 95	81 15	142		1.35 [1.12, 1.63] 3.79 [2.24, 6.42]	4.56 0.85
Detke 2002 A	54 118		15 92	142 30			0.85 5.40
		5		30 31		1.27 [1.14, 1.42]	
Detke 2002 B	111	17	108			1.12 [1.00, 1.25]	6.05
Goldstein 2004 A	73	13	30	14		1.24 [1.00, 1.55]	2.32
Katona 2012	118	33	89	56		1.27 [1.09, 1.49]	5.30
Mahableshwarkar 2015 A	119	31	94	65		1.34 [1.15, 1.56]	5.33
Mahableshwarkar 2013	120	30	81	70		1.49 [1.26, 1.77]	4.72
Mahableshwarkar 2015 B	84	123	41	150		1.89 [1.38, 2.60]	2.49
Nierenberg 2007	234	39	107	30	-	1.10 [0.99, 1.21]	8.32
Oakes 2012 A	44	213	7	120		3.11 [1.44, 6.70]	0.55
Oakes 2012 B	63	198	13	118		2.43 [1.39, 4.25]	1.01
Raskin 2007	145	62	67	37	-	1.09 [0.92, 1.29]	5.21
Tourian 2009	141	16	129	32	•	1.12 [1.02, 1.23]	7.44
F1J-MC-HMAI (A)	93	37	27	14		1.09 [0.85, 1.39]	2.40
F1J-MC-HMAI (B)	87	42	27	14		1.02 [0.80, 1.32]	2.39
F1J-MC-HMAI (C)	90	41	29	15		1.04 [0.82, 1.33]	2.54
11918A	97	36	80	56		1.24 [1.04, 1.48]	4.62
F1J-MC-HMAT a (A)	78	13	30	15		1.29 [1.03, 1.61]	2.35
F1J-MC-HMAH	76	12	81	8	-	0.95 [0.85, 1.05]	4.70
NCT 01145755	30	17	16	28		1.76 [1.12, 2.74]	0.97
Heterogeneity: I ² = 79.75%, H					•	1.28 [1.23, 1.33]	
Test of $\theta_i = \theta_j$: Q(21) = 103.69	, p = 0.00	0					
Duloxetine dose > 60 mg/day							
Detke 2004 A	49	46	17	29		1.40 [0.91, 2.13]	1.34
Detke 2004 B	47	46	18	29		1.32 [0.87, 2.00]	1.40
Goldstein 2004 B	76	15	31	14		1.21 [0.98, 1.51]	2.42
Perahia 2006 A	39	54	14	35		1.47 [0.89, 2.43]	1.07
Perahia 2006 B	34	69	15	35		1.10 [0.66, 1.82]	1.18
F1J-MC-HMAT a (B)	75	9	33	12		1.22 [1.01, 1.47]	2.51
Heterogeneity; I ² = 0.00%, H ²	= 1.00					1.27 [1.11, 1.45]	
Test of $\theta_i = \theta_i$: Q(5) = 1.20, p =	= 0.95				•		
variable duloxetine dose dose		6	50	40		4.071.0.00 4.000	0.00
Goldstein 2002	62 73	8	58	12	T.	1.07 [0.93, 1.22]	3.39
F1J-MC-HMAQ (B)		9	55	20		1.21 [1.04, 1.42]	3.36
Heterogeneity: I ² = 32.98%, H						1.14 [1.03, 1.27]	
Test of $\theta_i = \theta_j$: Q(1) = 1.49, p =	= 0.22						
Overall					•	1.27 [1.22, 1.32]	
Heterogeneity: I ² = 73.04%, H	² = 3.71						
Test of $\theta_i = \theta_j$: Q(29) = 107.57	, p = 0.00	0					
Test of group differences: Q _b (2) = 4.16	6, p =	0.13				
					1 2 4		
ixed-effects Mantel-Haenszel	model						

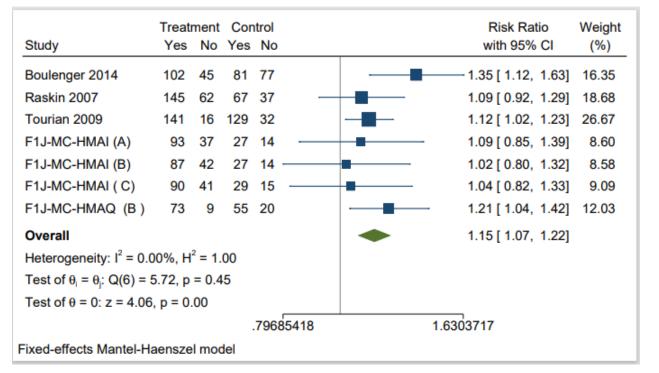
Supplementary Fig S27: Subgroup analysis of duloxetine dose on non-serious adverse events.

	Trea	tment	Co	ntrol		Risk Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
chronic or treatment resistant depression excluded							
Baldwin 2012	93	62	64	84		1.39 [1.11, 1.74]	3.82
Cutler 2009	54	95	15	142		3.79 [2.24, 6.42]	0.85
Detke 2002 A	118	5	92	30	-	1.27 [1.14, 1.42]	5.40
Detke 2002 B	111	17	108	31	.	1.12 [1.00, 1.25]	6.05
Detke 2004 A	49	46	17	29		1.40 [0.91, 2.13]	1.34
Detke 2004 B	47	46	18	29		1.32 [0.87, 2.00]	1.40
Goldstein 2004 A	73	13	30	14		1.24 [1.00, 1.55]	2.32
Goldstein 2004 B	76	15	31	14		1.21 [0.98, 1.51]	2.42
Goldstein 2002	62	8	58	12		1.07 [0.93, 1.22]	3.39
Katona 2012	118	33	89	56		1.27 [1.09, 1.49]	5.30
Mahableshwarkar 2015 A	119	31	94	65		1.34 [1.15, 1.56]	5.33
Mahableshwarkar 2013	120	30	81	70	-	1.49 [1.26, 1.77]	4.72
Mahableshwarkar 2015 B	84	123	41	150		1.89 [1.38, 2.60]	2.49
Nierenberg 2007	234	39	107	30		1.10 [0.99, 1.21]	8.32
Oakes 2012 A	44	213	7	120		- 3.11 [1.44, 6.70]	0.55
Oakes 2012 B	63	198	13	118		2.43 [1.39, 4.25]	1.01
Perahia 2006 A	39	54	14	35		1.47 [0.89, 2.43]	1.07
Perahia 2006 B	34	69	15	35		1.10 [0.66, 1.82]	1.18
11918A	97	36	80	56		1.24 [1.04, 1.48]	4.62
F1J-MC-HMAT a (A)	78	13	30	15		1.29 [1.03, 1.61]	2.35
F1J-MC-HMAT a (B)	75	9	33	12		1.22 [1.01, 1.47]	2.51
F1J-MC-HMAH	76	12	81	8		0.95 [0.85, 1.05]	4.70
NCT 01145755	30	17	16	28		1.76 [1.12, 2.74]	0.97
Heterogeneity: I ² = 79.00%, H ² = 4.76					•	1.32 [1.26, 1.38]	
Test of $\theta_i = \theta_j$: Q(22) = 104.78, p = 0.00							
chronic or treatment resistant depression not excluded							
Boulenger 2014	102	45	81	77		1.35 [1.12, 1.63]	4.56
Raskin 2007	145	62	67	37	-	1.09 [0.92, 1.29]	5.21
Tourian 2009	141	16	129	32		1.12 [1.02, 1.23]	7.44
F1J-MC-HMAI (A)	93	37	27	14		1.09 [0.85, 1.39]	2.40
F1J-MC-HMAI (B)	87	42	27	14		1.02 [0.80, 1.32]	2.39
F1J-MC-HMAI (C)	90	41	29	15		1.04 [0.82, 1.33]	2.54
F1J-MC-HMAQ (B)	73	9	55	20	-8-	1.21 [1.04, 1.42]	3.36
Heterogeneity: $I^2 = 0.00\%$, $H^2 = 1.00$					•	1.15 [1.07, 1.22]	
Test of $\theta_i = \theta_j$: Q(6) = 5.72, p = 0.45							
Overall					•	1.27 [1.22, 1.32]	
Heterogeneity: I ² = 73.04%, H ² = 3.71							
Test of $\theta_i = \theta_j$: Q(29) = 107.57, p = 0.00							
Test of group differences: $Q_{\scriptscriptstyle b}(1)$ = 12.24, p = 0.00						-	
					1 2 4		
Fixed-effects Mantel-Haenszel model							

Supplementary Fig S28: Subgroup analysis of chronic treatment-resistant depression on non-serious adverse events.

Study		Treatment		ntrol	Risk Ratio	Weight
olddy	Yes	No	Yes	No	with 95% CI	(%)
Baldwin 2012	93	62	64	84	1.39 [1.11, 1.74	5.30
Cutler 2009	54	95	15	142		1.18
Detke 2002 A	118	5	92	30	1.27 [1.14, 1.42	7.48
Detke 2002 B	111	17	108	31	1.12 [1.00, 1.25	8.39
Detke 2004 A	49	46	17	29	1.40 [0.91, 2.13	1.86
Detke 2004 B	47	46	18	29	1.32 [0.87, 2.00	1.94
Goldstein 2004 A	73	13	30	14	1.24 [1.00, 1.55	3.22
Goldstein 2004 B	76	15	31	14	1.21 [0.98, 1.51	3.36
Goldstein 2002	62	8	58	12	1.07 [0.93, 1.22	4.70
Katona 2012	118	33	89	56	1.27 [1.09, 1.49	7.36
Mahableshwarkar 2015 A	119	31	94	65	1.34 [1.15, 1.56	7.39
Mahableshwarkar 2013	120	30	81	70	1.49 [1.26, 1.77	6.54
Mahableshwarkar 2015 B	84	123	41	150	- 1.89 [1.38, 2.60	3.45
Nierenberg 2007	234	39	107	30	1.10 [0.99, 1.21	11.54
Oakes 2012 A	44	213	7	120	3.11 [1 <mark>.4</mark> 4, 6.70	0.76
Oakes 2012 B	63	198	13	118	2.43 [1.39, 4.25	1.40
Perahia 2006 A	39	54	14	35	- 1.47 [0.89, 2.43	1.49
Perahia 2006 B	34	69	15	35	1.10 [0.66, 1.82	1.64
11918A	97	36	80	56	1.24 [1.04, 1.48	6.41
F1J-MC-HMAT a (A)	78	13	30	15	1.29 [1.03, 1.61	3.25
F1J-MC-HMAT a (B)	75	9	33	12	1.22 [1.01, 1.47	3.48
F1J-MC-HMAH	76	12	81	8	0.95 [0.85, 1.05	6.52
NCT 01145755	30	17	16	28	- 1.76 [1.12, 2.74	1.34
Overall					1.32 [1.26, 1.38	l
Heterogeneity: I ² = 79.00%	$H^2 = 4$.76				
Test of $\theta_i = \theta_j$: Q(22) = 104.	78, p =	0.00				
Test of θ = 0: z = 12.31, p =	= 0.00					
					4	

Supplementary Fig S29: Subgroup analysis of for participants without chronic treatment resistant depression on non-serious adverse events.



Supplementary Fig S30: Subgroup analysis of participants with chronic treatment resistant depression on non-serious adverse events.

Study	Trea Yes	tment No	Co Yes	ntrol No	Risk Ratio with 95% Cl	Weigh (%)
No placebo washout period reported						(,,,)
Boulenger 2014	102	45	81	77	1.35 [1.12, 1.63]	4.61
Katona 2012	118	33	89	56	- 1.27 [1.09, 1.49]	5.36
Mahableshwarkar 2013	120	30	81	70		4.76
Mahableshwarkar 2015 B	84	123	41	150	1.89 [1.38, 2.60]	2.52
Oakes 2012 A	44	213	7	120	3.11 [1.44, 6.70]	0.55
Oakes 2012 B	63	198	13	118	2.43 [1.39, 4.25]	1.02
Tourian 2009	141	16	129	32	1.12 [1.02, 1.23]	7.51
11918A	97	36	80	56	1.24 [1.04, 1.48]	4.67
Heterogeneity: $I^2 = 80.99\%$, $H^2 = 5.26$					▲ 1.40 [1.30, 1.50]	
Test of $\theta_i = \theta_i$: Q(7) = 36.82, p = 0.00					•	
Placebo washout period reported						
Baldwin 2012	93	62	64	84		3.86
Cutler 2009	54	95	15	142	3.79 [2.24, 6.42]	0.86
Detke 2002 A	118	5	92	30	1.27 [1.14, 1.42]	5.45
Detke 2002 B	111	17	108	31	1.12 [1.00, 1.25]	6.11
Detke 2004 A	49	46	17	29	1.40 [0.91, 2.13]	1.35
Detke 2004 B	47	46	18	29	1.32 [0.87, 2.00]	1.41
Goldstein 2004 A	73	13	30	14	1.24 [1.00, 1.55]	2.34
Goldstein 2004 B	76	15	31	14	1.21 [0.98, 1.51]	2.45
Goldstein 2002	62	8	58	12	1.07 [0.93, 1.22]	3.42
Mahableshwarkar 2015 A	119	31	94	65	- 1.34 [1.15, 1.56]	5.38
Nierenberg 2007	234	39	107	30	1.10 [0.99, 1.21]	8.40
Perahia 2006 A	39	54	14	35	1.47 [0.89, 2.43]	1.08
Perahia 2006 B	34	69	15	35	1.10 [0.66, 1.82]	1.19
Raskin 2007	145	62	67	37	- 1.09 [0.92, 1.29]	5.26
F1J-MC-HMAI (A)	93	37	27	14	1.09 [0.85, 1.39]	2.42
F1J-MC-HMAI (B)	87	42	27	14	1.02 [0.80, 1.32]	2.42
F1J-MC-HMAI (C)	90	41	29	15	1.04 [0.82, 1.33]	2.56
F1J-MC-HMAQ (B)	73	9	55	20		3.39
F1J-MC-HMAT a (A)	78	13	30	15	I .29 [1.03, 1.61]	2.37
F1J-MC-HMAT a (B)	75	9	33	12	- - 1.22 [1.01, 1.47]	2.53
F1J-MC-HMAH	76	12	81	8		4.75
Heterogeneity: $I^2 = 65.24\%$, $H^2 = 2.88$					♦ 1.21 [1.16, 1.26]	
Test of $\theta_i = \theta_j$: Q(20) = 57.54, p = 0.00						
Overall					1.27 [1.22, 1.31]	
Heterogeneity: $I^2 = 72.97\%$, $H^2 = 3.70$						
Test of $\theta_i = \theta_j$: Q(28) = 103.59, p = 0.00)					
Test of group differences: $Q_b(1) = 12.1$	8, p =	0.00				
					1 2 4	
ixed-effects Mantel-Haenszel model						

Supplementary Fig S31: Subgroup analysis of placebo washout period on non-serious adverse events.

Study	Treat Yes	tment No		ntrol No	,	Risk Ratio with 95% Cl	Weight (%)
Boulenger 2014	102	45	81	77		5 [1.12, 1.63]	14.86
Katona 2012	118	33	89	56	- 1.2	7 [1.09, 1.49]	17.28
Mahableshwarkar 2013	120	30	81	70		9 [1.26, 1.77]	15.36
Mahableshwarkar 2015 B	84	123	41	150		9 [1.38, 2.60]	8.12
Oakes 2012 A	44	213	7	120		1 [1.44, 6.70]	1.78
Oakes 2012 B	63	198	13	118	2.4	3 [1.39, 4.25]	3.29
Tourian 2009	141	16	129	32	- 1.1	2 [1.02, 1.23]	24.24
11918A	97	36	80	56		4 [1.04, 1.48]	15.06
Overall					♦ 1.4	0 [1.30, 1.50]	
Heterogeneity: I ² = 80.99%	$H^2 = 5$	5.26					
Test of $\theta_i = \theta_j$: Q(7) = 36.82	, p = 0.	00					
Test of θ = 0: z = 9.25, p =	0.00						
					2 4		
Fixed-effects Mantel-Haensz	el mod	lel					

Supplementary Fig S32: Subgroup analysis of trials without placebo washout period on non-serious adverse events.

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	Treat	ment	Co	ntrol		Risk Ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Baldwin 2012	93	62	64	84		1.39 [1.11, 1.74]	5.60
Cutler 2009	54	95	15	142		-3.79 [2.24, 6.42]	1.25
Detke 2002 A	118	5	92	30	-	1.27 [1.14, 1.42]	7.89
Detke 2002 B	111	17	108	31	.	1.12 [1.00, 1.25]	8.85
Detke 2004 A	49	46	17	29		1.40 [0.91, 2.13]	1.96
Detke 2004 B	47	46	18	29		1.32 [0.87, 2.00]	2.04
Goldstein 2004 A	73	13	30	14		1.24 [1.00, 1.55]	3.39
Goldstein 2004 B	76	15	31	14		1.21 [0.98, 1.51]	3.55
Goldstein 2002	62	8	58	12		1.07 [0.93, 1.22]	4.96
Mahableshwarkar 2015 A	119	31	94	65		1.34 [1.15, 1.56]	7.80
Nierenberg 2007	234	39	107	30	-	1.10 [0.99, 1.21]	12.18
Perahia 2006 A	39	54	14	35		1.47 [0.89, 2.43]	1.57
Perahia 2006 B	34	69	15	35		1.10 [0.66, 1.82]	1.73
Raskin 2007	145	62	67	37		1.09 [0.92, 1.29]	7.62
F1J-MC-HMAI (A)	93	37	27	14		1.09 [0.85, 1.39]	3.51
F1J-MC-HMAI (B)	87	42	27	14		1.02 [0.80, 1.32]	3.50
F1J-MC-HMAI (C)	90	41	29	15		1.04 [0.82, 1.33]	3.71
F1J-MC-HMAQ (B)	73	9	55	20		1.21 [1.04, 1.42]	4.91
F1J-MC-HMAT a (A)	78	13	30	15		1.29 [1.03, 1.61]	3.43
F1J-MC-HMAT a (B)	75	9	33	12		1.22 [1.01, 1.47]	3.67
F1J-MC-HMAH	76	12	81	8	+	0.95 [0.85, 1.05]	6.88
Overall					•	1.21 [1.16, 1.26]	
Heterogeneity: I ² = 65.24%	, H ² = 2	2.88					
Test of $\theta_i = \theta_j$: Q(20) = 57.5	i4, p = (0.00					
Test of θ = 0: z = 8.65, p =	0.00						
					1 2 4	-	
ixed-effects Mantel-Haensz	zel mod	lel					

Supplementary Fig S33: Subgroup analysis of trials with placebo washout period on non-serious adverse events.

Exploratory outcomes

Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale and Beck's Depression Inventory Twelve trials reported mean change/follow-up scores and SD for HDRS-17.¹⁻¹² Only one trial reported mean change scores and corresponding SD for MADRS (NCT

01145755). However, we specified in the protocol that we will not pool change scores and end scores for standardized mean difference.

Response

Thirteen trials reported response on HDRS-17 scale,¹⁻¹³ six trials on MADRS scale ¹⁴⁻¹⁹ and one trial on HDRS-24 scale.¹⁸ Meta-analysis showed beneficial effect of

duloxetine on response (RR 1.47, 95%CI, 1.37 to 1.57; P < 0.01; 21 trials) (Fig S34).

Study	Dulox Yes	etine No	Plac Yes	ebo No		Risk Ratio with 95% CI	Weigh (%)
Response rates on HDRS scal		NO	res	NO		witti 95% Ci	(70)
Detke 2002 A	55	68	27	95		2.02 [1.37, 2.97]	3.04
Detke 2002 R	62	61	48	88		1.43 [1.07, 1.90]	5.12
Detke 2002 B	60	33	20	26		1.48 [1.03, 2.13]	3.00
Detke 2004 B	66	27	20	26		1.59 [1.13, 2.24]	3.13
Goldstein 2004 A	37	47	13	31		1.49 [0.89, 2.50]	1.92
Goldstein 2004 R	44	42	14	30		1.61 [1.00, 2.60]	2.08
Goldstein 2002	33	35	24	42		1.33 [0.89, 2.00]	2.00
Nierenberg 2007	117	156	44	93		1.33 [1.01, 1.76]	6.58
Perahia 2006 A	60	33	26	23		1.22 [0.90, 1.65]	3.82
Perahia 2006 B	69	33	25	25		1.35 [0.99, 1.84]	3.77
Raskin 2007	75	126	19	83		2.00 [1.29, 3.12]	2.83
F1J-MC-HMAQ (B)	40	41	28	44		1.27 [0.88, 1.83]	3.33
F1J-MC-HMAT a (A)	24	66	10	35		1.20 [0.63, 2.29]	1.50
F1J-MC-HMAT a (B)	24	53	14	30		1.09 [0.64, 1.84]	2.04
F1J-MC-HMAG (A)	12	12	9	13		1.22 [0.64, 2.32]	1.05
F1J-MC-HMAG (B)	8	12	7	15		1.22 [0.04, 2.32]	0.75
F1J-MC-HMAG (b)	28	58	25	61		1.12 [0.71, 1.75]	2.81
Higuchi 2009 A	42	31	28	44		1.48 [1.04, 2.10]	3.16
Higuchi 2009 B	38	36	28	45		1.34 [0.93, 1.93]	3.16
Heterogeneity: I ² = 0.00%, H ² =			20			1.42 [1.30, 1.56]	0.10
Test of $\theta_i = \theta_j$: Q(18) = 10.82, p					•		
Response rates on MADRS							
Baldwin 2012	85	64	68	77		1.22 [0.97, 1.52]	7.74
Boulenger 2014	74	72	32	126		-2.50 [1.77, 3.55]	3.45
Cutler 2009	74	71	55	97		1.37 [1.05, 1.79]	5.94
Katona 2012	104	43	52	93		1.97 [1.55, 2.51]	5.88
Mahableshwarkar 2015 A	80	66	60	93		1.40 [1.09, 1.79]	6.58
Mahableshwarkar 2015 B	102	85	69	98		1.32 [1.06, 1.65]	8.18
NCT 01145755	9	11	9	10 -		0.95 [0.48, 1.87]	1.04
Heterogeneity: I ² = 70.79%, H ²	-		9	10		1.51 [1.37, 1.68]	1.04
Test of $\theta_i = \theta_i$: Q(6) = 20.54, p :					•	1.51 [1.57, 1.00]	
Response rates on HDRS-24					_		
Mahableshwarkar 2013	76	73	48	101		1.58 [1.20, 2.10]	5.39
Heterogeneity: I ² = 0.00%, H ² =						1.58 [1.20, 2.10]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p =	•						
Overall					•	1.47 [1.37, 1.57]	
Heterogeneity: I ² = 19.46%, H ²	= 1.24						
Test of $\theta_i = \theta_j$: Q(26) = 32.28, p	= 0.18						
Test of group differences: Q _b (2) = 1.10, p	= 0.5	8	-		-	
				1/	2 1 2		
ixed-effects Mantel-Haenszel r	nodel						

Supplementary Fig S34: Meta-analysis of duloxetine vs. placebo on the outcome response rates.

Remission

Fourteen trials reported remission on HDRS-17 scale¹⁻¹³ and six trials on MADRS scale.¹⁴⁻¹⁹ Meta-analysis of these 17 trials showed beneficial effect of duloxetine on

remission (RR 1.49, 95%CI, 1.36 to 1.63; p < 0.01; Fig S35).

	Duloxetine		Placebo				Risk Ratio		tio	Weight	
Study	Yes	No	Yes	No				with 95%	CI	(%)	
REmission on HDRS											
Detke 2002 A	38	85	17	105				2.22 [1.33,	3.71]	2.95	
Detke 2002 B	39	84	33	103				1.31 [0.88,	1.94]	5.41	
Detke 2004 A	43	50	14	32				1.52 [0.93,	2.48]	3.23	
Detke 2004 B	48	45	14	33				1.73 [1.07,	2.80]	3.21	
Goldstein 2004 A	29	55	13	31				1.17 [0.68,	2.01]	2.94	
Goldstein 2004 B	43	43	13	31	-			1.69 [1.02,	2.80]	2.97	
Goldstein 2002	29	39	18	48				1.56 [0.97,	2.53]	3.15	
Katona 2012	51	96	28	117				1.80 [1.20,	2.68]	4.86	
Nierenberg 2007	88	185	37	100	-			1.19 [0.86,	1.65]	8.50	
Perahia 2006 A	41	52	16	33				1.35 [0.85,	2.14]	3.62	
Perahia 2006 B	41	61	17	33	-			1.18 [0.75,	1.86]	3.94	
Raskin 2007	55	146	15	87				1.86 [1.11,	3.13]	3.43	
F1J-MC-HMAQ (B)	32	49	21	51				1.35 [0.86,	2.12]	3.84	
F1J-MC-HMAT a (A)	22	68	8	37	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1			1.38 [0.67,	2.84]	1.84	
F1J-MC-HMAT a (B)	23	58	10	34				1.25 [0.66,	2.38]	2.24	
F1J-MC-HMAG (A)	9	15	4	18	-	-		2.06 [0.74.	5.751	0.72	
F1J-MC-HMAG (B)	6	14	1	21	-			-6.60 [0.87.	50.181	0.16	
F1J-MC-HMAH	11	75	11	75	_			1.00 [0.46,		1.90	
Higuchi 2009 A	24	49	16	56	-			1.48 [0.86,	10.00	2.78	
Higuchi 2009 B	26	48	16	57	1.00			1.60 [0.94,	1999 C.	2.78	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.$	00	893744	1000				1.49 [1.33,			
Test of $\theta_i = \theta_i$: Q(19) = 12.6											
Remission on MADRS											
Baldwin 2012	52	97	49	96	-			1.03 [0.75,	1.42]	8.57	
Boulenger 2014	54	92	19	139				3.08 [1.92,	4.93]	3.15	
Cutler 2009	45	90	31	130				1.73 [1.16,	2.57]	4.88	
Mahableshwarkar 2015 A	38	108	41	112	-			0.97 [0.67,	1.42]	6.91	
Mahableshwarkar 2013	51	59	33	86				1.67 [1.17,	2.381	5.47	
Mahableshwarkar 2015 B	63	124	36	131				1.56 [1.10,	2.221	6.56	
Heterogeneity: I ² = 75.23%	$H^2 = 4$	1.04						1.49 [1.29,	1.73]		
Test of $\theta_i = \theta_j$: Q(5) = 20.18					•				5000 7 4		
Overall								1.49 [1.36,	1.63]		
Heterogeneity: I ² = 23.93%	$H^2 = 1$.31						-	-		
Test of $\theta_i = \theta_j$: Q(25) = 32.8											
Test of group differences:	Q _b (1) =	0.00,	p = 0.	96							
100 1			9 - 193		1/2 2	8	32				
ixed-effects Mantel-Haens	zel moc	lel									

Supplementary Fig S35: Meta-analysis of duloxetine vs. placebo on the outcome remission rates.

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