Supplementary material for:

The risks of adverse events with venlafaxine for adults with major depressive disorder: a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis

CB Kamp, JJ Petersen, P Faltermeier, S Juul, F Siddiqui, J Moncrieff, MA Horowitz, MP Hengartner, I Kirsch, C Gluud, JC Jakobsen

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Supplementary Figure 1: Risk of Bias 2 assessments

		Risk of bias domains										
	Γ	D1	D2	D3	D4	D5	Overall					
	0600B 1-384-US/EU/CA	?	?	?	?	?	?					
	600-B-367-EU	-	X	X	X	-	X					
	Alvarez 2012	+	X	X	X	-	X					
	Claghorn 1990	+	X	X	X	-	X					
	Cunningham 1994	+	X	X	X	-	X					
	Cunningham 1997	-	X	X	X	-	X					
	EudraCT 2004-000562-13	-	X	X	X	-	X					
	EudraCT 2007-007025-51	-	X	X	X	-	X					
	Guelfi 1995	-	X	X	X	-	X					
	Hewett 2009	+	X	X	X	-	X					
	Hewett 2010	+	X	X	X	-	X					
	Higuchi 2016	-	X	X	X	-	X					
study	Khan 1998	-	X	X	X	-	X					
	Learned 2012	-	X	X	X	-	X					
	Lieberman 2008	-	X	X	X	-	X					
	Luthringer 1996	-	X	X	X	-	X					
	Mendels 1993	-	X	X	X	-	X					
	Nemeroff 2007	-	X	X	X	-	X					
	Rudolph 1998	-	X	X	X	-	X					
	Rudolph 1999	-	X	X	X	-	X					
	Schatzberg 2006	-	X	X	X	-	X					
	Schweizer 1994	+	X	X	X	-	X					
	Sheehan 2009	-	X	X	X	-	X					
	Silverstone 1999	+	X	X	X	-	X					
	Thase 1997	+	X	X	X	-	X					
	L.	Domains:	ining funges the			Judge	ment					
		D1: Bias ar D2: Bias du	ising from th ie to deviatio	e randomizati ns from inten	on process. ded interven	tion. 🗴 H	High					
		D3: Bias du D4: Bias in	le to missing measureme	outcome dat nt of the outco	a. ome.	- 9	Some concerns					
		D5: Bias in	selection of	the reported r	esult.	+ ι	_ow					
						1 🥎	No information					

Based on assessments of the primary outcomes.

Supplementary Figure 2: Subgroup analysis of placebo washout on suicides or suicide attempts

	Ven	lafaxine	PI	acebo				Odds ra	tio	Weight
Study	Events	No events	Events	No events				with 95%	o CI	(%)
No										
Higuchi 2016	1	353	1	182		-		0.52 [0.03,	8.29]	13.29
Sheehan 2009	0	95	0	95				1.00 [0.02,	50.92]	5.03
Heterogeneity: I ² = 0.00%,	$H^2 = 1.00$)			-			0.65 [0.07,	6.27]	
Test of $\theta_i = \theta_j$: Q(1) = 0.07	p = 0.79									
Test of θ = 0: z = -0.37, p =	= 0.71									
Yes										
0600B 1-384-US/EU/CA	2	178	3	65			_	0.24 [0.04,	1.49]	43.54
600-B-367-EU	1	165	1	82				0.50 [0.03,	8.05]	13.40
Cunningham 1994	0	72	1	75		-		0.33 [0.01,	8.60]	14.79
Hewett 2009	1	186	0	197				3.07 [0.13,	73.81]	5.01
Schweizer 1994	1	72	0	78			-	3.11 [0.13,	74.99]	4.95
Heterogeneity: I ² = 0.00%,	$H^2 = 1.00$)				-		0.65 [0.22,	1.90]	
Test of $\theta_i = \theta_j$: Q(4) = 3.17	p = 0.53									
Test of θ = 0: z = -0.79, p =	= 0.43									
Overall								0.65 [0.25,	1.71]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.00$)								
Test of $\theta_i = \theta_j$: Q(6) = 3.24	p = 0.78									
Test of θ = 0: z = -0.87, p =	= 0.38									
Test of group differences:	$Q_{b}(1) = 0.$	00, p = 1.00								
	-				1/64	1/4	4 6	- 4		

Fixed-effects Mantel-Haenszel model



Supplementary Figure 3: Trial Sequential Analysis of venlafaxine versus placebo on serious adverse events



Supplementary Figure 4: Subgroup analysis of placebo washout on serious adverse events

	\/		D			Diele vetie	14/-:
Study	Ven Events	No events	Fvents	No events		with 95% CI	(%)
No	Evento		Evento	No evenia			(/0)
Alvarez 2012	14	00	2	103		6 50 [1 51 27 9/]	4 72
FudraCT 2004-000562-13	6	121	2	118		2.83[0.58 13.77]	4.37
EudraCT 2007-007025-51	0	7	0	7		1.00[0.02 44.50]	1 20
Hewett 2009	6	181	9	188		0.70[0.25 1.93]	6.19
Hewett 2005	0	190	2	195		4.25[0.02 10.41]	4.54
Higuobi 2016	3	247	2	100		4.25 [0.95, 19.41]	2 10
Learned 2012 (study 1)	2	120	5	102		0.57[0.14]	1 96
Liebormon 2008 (225 mg)	10	00	1	121		19.02 [2.57 120.50]	4.00
Checker 2000 (225 mg)	10	99	1	122		2 00 [1 00 8 07]	5.37
Sneenan 2009	12	83	4	91		3.00[1.00, 8.97]	5.90
Heterogeneity: $T = 0.75$, $F = 0.75$, F	- 0.04	H ⁻ = 2.28				2.54 [1.16, 5.57]	
1000 f = 0; $Q(8) = 10.51$,	p = 0.04						
lest of $\theta = 0$: $z = 2.33$, $p = 0$.	.02						
Yes							
0600B 1-384-US/EU/CA	1	179	3	65		0.13[0.01. 1.19]	2.90
600-B-367-EU	10	155	4	79		1.26 [0.41. 3.89]	5.78
Claghorn 1990	2	77	0	80		5.06 [0.25, 103.80]	1.88
Cunningham 1994	4	68	4	72		1.06[0.27, 4.06]	5.06
Cunningham 1997 (IR)	6	90	2	48		1.56 [0.33. 7.46]	4.42
Cunningham 1997 (XR)	10	87	2	48		2.58 [0.59. 11.31]	4.66
Guelfi 1995	4	42	0	47		- 9.19[0.51, 166.04]	2.01
Mendels 1993	13	221	1	77		4.33 [0.58. 32.59]	3.33
Nemeroff 2007	10	90	1	101		10.20 [1.33. 78.21]	3.29
Rudolph 1998	40	226	2	90		6.92 [1.71. 28.06]	4.90
Rudolph 1999	9	91	4	94	4	2.21 [0.70. 6.92]	5.73
Schatzberg 2006	9	93	1	95		8.47 [1.09. 65.61]	3.27
Schweizer 1994	3	70	1	77		3.21 [0.34. 30.13]	2.91
Silverstone 1999	13	115	3	116		4.03 [1.18, 13.79]	5.44
Thase 1997	15	80	4	98		4.03 [1.39. 11.70]	6.00
Heterogeneity: $T^2 = 0.64$, $I^2 =$	50.47%	$H^2 = 2.02$	-			2.75 [1.52. 4.98]	
Test of $\theta_{1} = \theta_{1}$: Q(14) = 17.97	. p = 0.21				· · · · · · · · · · · · · · · · · · ·	,	
Test of $\theta = 0$; $z = 3.34$, $p = 0$.	.00						
····, p							
Overall					•	2.66 [1.67, 4.25]	
Heterogeneity: T ² = 0.65, I ² =	52.00%,	H ² = 2.08					
Test of $\theta_1 = \theta_1$: Q(23) = 34.88	, p = 0.05	5					
Test of $\theta = 0$: $z = 4.10$, $p = 0$.	.00						
Test of group differences: Q _b	(1) = 0.03	3, p = 0.87					
					1/64 1/4 4 64	-	

Supplementary Figure 5: Meta-analysis of venlafaxine versus placebo on sexual dysfunction

	Ven	lafaxine	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No events		1			with 95%	5 CI	(%)
600-B-367-EU	2	52	0	26					2.45 [0.12,	49.36]	6.41
Alvarez 2012	14	99	2	103			<u> </u>		6.50 [1.51,	27.94]	26.20
Cunningham 1997 (IR)	2	29	0	20				-	3.28 [0.17,	64.99]	6.48
Cunningham 1997 (XR)	10	27	0	21	-				- 12.16 [0.75,	197.55]	7.42
EudraCT 2004-000562-13	2	33	0	40					5.69 [0.28,	114.74]	6.40
Lieberman 2008 (225 mg)	4	32	1	44	_				5.00 [0.58,	42.80]	12.39
Mendels 1993	11	223	0	78					7.73 [0.46,	129.71]	7.25
Schatzberg 2006	9	93	1	95				-	8.47 [1.09,	65.61]	13.60
Thase 1997	8	27	1	40				_	9.37 [1.23,	71.31]	13.84
Overall									6.49 [3.02,	13.93]	
Heterogeneity: $\tau^2 = 0.03$, I^2 :	= 1.94%, I	H ² = 1.02									
Test of $\theta_i = \theta_i$: Q(8) = 1.07, p	o = 1.00										
Test of $\theta = 0$: $z = 4.79$, $p = 0$	0.00										
				1	/8	1 8	8 0	64	-		

Random-effects Sidik-Jonkman model

stata

Supplementary Figure 6: Meta-analysis of venlafaxine versus placebo on anorexia

	Ven	lafaxine	PI	acebo		Risk ra	tio	Weight
Study	Events	No events	Events	No events		with 95%	o CI	(%)
600-B-367-EU	2	163	2	81	_	0.50 [0.07,	3.51]	6.95
Cunningham 1997 (IR)	6	90	2	48		1.56 [0.33,	7.46]	9.21
Cunningham 1997 (XR)	10	87	2	48		2.58 [0.59,	11.31]	9.83
EudraCT 2004-000562-13	6	121	2	118		2.83 [0.58,	13.77]	9.09
Hewett 2010	9	189	2	185		4.25 [0.93,	19.41]	9.53
Lieberman 2008 (225 mg)	18	99	1	122		- 18.92 [2.57,	139.50]	6.68
Rudolph 1998	40	226	2	90		6.92 [1.71,	28.06]	10.45
Rudolph 1999	9	91	4	94		2.21 [0.70,	6.92]	12.76
Silverstone 1999	13	115	3	116		4.03 [1.18,	13.79]	11.94
Thase 1997	15	80	4	98		4.03 [1.39,	11.70]	13.55
Overall					•	3.23 [1.75,	5.97]	
Heterogeneity: $\tau^2 = 0.43$, $I^2 =$	44.71%,	H ² = 1.81						
Test of $\theta_i = \theta_i$: Q(9) = 9.45, p	= 0.40							
Test of $\theta = 0$: z = 3.75, p = 0.	.00							
					1/8 1 8 64			



Supplementary Figure 7: Meta-analysis of venlafaxine versus placebo on anxiety

	Ven	lafaxine	Pla	acebo			Risk ra	tio	Weight
Study	Events	No events	Events	No events	•		with 95%	6 CI	(%)
600-B-367-EU	2	163	2	81			0.50 [0.07,	3.51]	10.42
EudraCT 2004-000562-13	0	127	1	119		<u> </u>	0.32 [0.01,	7.66]	5.72
Hewett 2009	6	181	9	188		-	0.70 [0.25,	1.93]	16.08
Learned 2012	3	130	5	121		-	0.57 [0.14,	2.33]	13.51
Mendels 1993	13	221	1	77	-		4.33 [0.58,	32.59]	10.04
Nemeroff 2007	10	90	1	101		_	10.20 [1.33,	78.21]	9.94
Rudolph 1998	10	57	0	26			- 8.34 [0.51,	137.36]	6.85
Schatzberg 2006	2	100	4	92		-	0.47 [0.09,	2.51]	11.90
Sheehan 2009	12	83	4	91			3.00 [1.00,	8.97]	15.55
Overall					•		1.40 [0.57,	3.44]	
Heterogeneity: τ ² = 1.05, l ² =	60.44%,	H ² = 2.53							
Test of $\theta_i = \theta_i$: Q(8) = 15.05,	p = 0.06								
Test of θ = 0: z = 0.72, p = 0.	.47								
					1/64 1/4	4 64	-		



Supplementary Figure 8: Meta-analysis of venlafaxine versus placebo on worsening of depression

	Ven	lafaxine	PI	acebo				Risk ratio Weight
Study	Events	No events	Events	No events				with 95% CI (%)
600-B-367-EU	4	161	0	83				4.55 [0.25, 83.60] 18.97
Cunningham 1994	0	72	1	75		_		0.35[0.01, 8.49] 16.42
Hewett 2009	0	187	3	194				0.15[0.01, 2.89] 18.50
Hewett 2010	1	197	1	186	-			0.94 [0.06, 14.99] 20.54
Sheehan 2009	1	94	2	93	-			0.50 [0.05, 5.42] 25.58
Overall								0.65 [0.16, 2.73]
Heterogeneity: $\tau^2 = 0$	0.60, l ² =	22.54%, H ²	= 1.29					
Test of $\theta_i = \theta_j$: Q(4) =	= 2.92, p	= 0.57						
Test of $\theta = 0$: $z = -0$.	58, p = 0	.56						
					1/64	1/4	4	64
Random-effects Sidik	–Jonkma	n model						



Supplementary Figure 9: Meta-analysis of venlafaxine versus placebo on hypertension





Supplementary Figure 10: Meta-analysis of venlafaxine versus placebo on hypotension





Supplementary Figure 11: Meta-analysis of venlafaxine versus placebo on discontinuation symptoms





Supplementary Figure 12: Meta-analysis of venlafaxine versus placebo on fall

Study	Ven Events	lafaxine No events	Pl Events	acebo No events				Risk ratio with 95% CI	Weight (%)
600-B-367-EU Guelfi 1995	1 1	164 45	0 0	83 47				1.52 [0.06, 36.87] - 3.06 [0.13, 73.33]	49.77 50.23
Overall Heterogeneity: 1	r ² = 0.01,	l ² = 0.42%, l	H² = 1.00				-	2.16 [0.23, 20.60]	
Test of $\theta_i = \theta_i$: Q	(1) = 0.09	9, p = 0.76							
Test of $\theta = 0$: z =	= 0.67, p	= 0.50			1/8	1 8	6	-	

Random-effects Sidik-Jonkman model



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Supplementary Figure 13: Meta-analysis of venlafaxine versus placebo on intentional overdose



Fixed-effects Mantel-Haenszel model



Supplementary Figure 14: Meta-analysis of venlafaxine versus placebo on QTc

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No event	s			with 95% CI	(%)
Cunningham 1994	0	72	1	75				0.35 [0.01, 8.49]	50.12
Hewett 2010	1	197	0	187				2.83 [0.12, 69.14]	49.88
Overall								1.00 [0.08, 12.26]	
Heterogeneity: $\tau^2 = 0$	0.63, I ² =	19.33%, H ² :	= 1.24						
Test of $\theta_i = \theta_i$: Q(1) =	= 0.82, p =	= 0.36							
Test of $\theta = 0$: $z = -0.0$	00, p = 1.	00							
					1/64	1/4	4	64	



Supplementary Figure 15: Meta-analysis of venlafaxine versus placebo on syncope



Fixed-effects Mantel-Haenszel model



Supplementary Figure 16: Trial Sequential Analysis of venlafaxine versus

placebo on non-serious adverse events



Supplementary Figure 17: Subgroup analysis of placebo washout on non-serious adverse events

	Ven	Ilafaxine	PI	acebo		Risk ratio		Weight
Study	Events	No events	Events	No events		with 95% C	I	(%)
No								
Alvarez 2012	85	28	64	41		1.23 [1.02, 1	.49]	3.85
EudraCT 2004-000562-13	92	35	77	43	•	1.13 [0.95, 1	.34]	3.88
EudraCT 2007-007025-51	4	3	4	3		1.00 [0.40, 2	.48]	1.84
Hewett 2009	93	94	95	102		1.03 [0.84, 1	.26]	3.81
Hewett 2010	133	65	112	75		1.12 [0.96, 1	.31]	3.91
Higuchi 2016 (fixed dose)	131	43	61	30		1.12 [0.95, 1	.33]	3.88
Higuchi 2016 (flexible dose)	147	33	62	30		1.21 [1.03, 1	.42]	3.90
Learned 2012 (study 1)	94	39	77	49	-	1.16[0.97, 1	.38]	3.87
Lieberman 2008 (225 mg)	27	90	16	109		1.80 [1.03, 3	.17]	2.76
Sheehan 2009	87	8	85	10		1.02 [0.93, 1	.12]	3.99
Heterogeneity: τ^2 = 0.01, I^2 = 52.13%, H^2	= 2.09				•	1.13 [1.04, 1	.23]	
Test of $\theta_i = \theta_j$: Q(9) = 9.07, p = 0.43								
Test of $\theta = 0$: z = 2.86, p = 0.00								
Yes								
600-B-367-EU (75 mg)	56	27	25	16	-	1.11 [0.83, 1	.47]	3.61
600-B-367-EU (150 mg)	53	29	25	17	-	1.09[0.81, 1	.46]	3.59
Claghorn 1990	72	7	59	21		1.24 [1.07, 1	.43]	3.92
Cunningham 1994	71	1	56	20		1.34 [1.17, 1	.53]	3.93
Cunningham 1997 (IR)	43	53	5	45		4.48 [1.89, 10	.59]	1.95
Cunningham 1997 (XR)	44	53	5	45		4.54 [1.92, 10	.72]	1.95
Guelfi 1995	36	10	22	25		1.67 [1.19, 2	.35]	3.46
Khan 1991 (75 mg)	23	0	5	3		1.60 [0.95, 2	.71]	2.89
Khan 1991 (225 mg)	22	0	6	3	⊢∎	1.51 [0.95, 2	.38]	3.10
Khan 1991 (375 mg)	21	1	6	3	+	1.43 [0.89, 2	.29]	3.06
Khan 1998 (75 mg)	24	72	2	31		4.12 [1.03, 16	.52]	1.07
Khan 1998 (150 mg)	19	77	2	31		3.27 [0.80, 13	.27]	1.05
Khan 1998 (200 mg)	26	68	2	30	_	4.43 [1.11, 17	.61]	1.07
Luthringer 1996	5	7	6	6	-	0.83 [0.35, 2	.00]	1.91
Mendels 1993 (25 mg)	20	59	7	19		0.94 [0.45, 1	.97]	2.26
Mendels 1993 (50 - 75 mg)	19	57	7	19		0.93 [0.44, 1	.95]	2.24
Mendels 1993 (150 - 200 mg)	17	52	7	19		0.92 [0.43, 1	.95]	2.21
Nemeroff 2007	40	60	8	94		5.10 [2.51, 10	.34]	2.34
Rudolph 1999	36	64	14	84		2.52 [1.45, 4	.37]	2.81
Schatzberg 2006	94	8	83	13		1.07 [0.97, 1	.17]	3.99
Schweizer 1991 (75, 225 and 375 mg)	24	20	4	12		2.18 [0.90, 5	.32]	1.88
Schweizer 1994	63	10	64	14		1.05 [0.92, 1	.21]	3.93
Silverstone 1999	49	79	20	99		2.28 [1.44, 3	.59]	3.11
Thase 1997	34	61	18	84		2.03 [1.23, 3	.34]	2.97
Heterogeneity: τ^2 = 0.23, I^2 = 91.19%, H^2	= 11.36				•	1.63 [1.30, 2	.05]	
Test of $\theta_i = \theta_i$: Q(23) = 83.61, p = 0.00								
Test of $\theta = 0$: z = 4.18, p = 0.00								
Overall					•	1.43 [1.21, 1	.69]	
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 92.92\%$, H^2	= 14.13							
Test of $\theta_i = \theta_i$: Q(33) = 99.10, p = 0.00								
Test of $\theta = 0$: $z = 4.21$, $p = 0.00$								
Test of aroun differences: $O(1) = 9.59$	- 0.00							
$a_{b}(1) = 0.30, p$	- 0.00				1/2 1 2 4 8 1	т 6		

Supplementary Figure 18: Meta-analysis of venlafaxine versus placebo on nausea

Graph

17/03/2024, 18.33

Study	Ven Events	lafaxine No events	PI Events	acebo No events			Hisk ra with 95%	tio 5 CI	We (9
600-B-367-EU (75 mg)	15	68	3	38	-		2.47 [0.76,	8.05]	1.0
600-B-367-EU (150 mg)	22	60	2	40			5.63 [1.39,	22.82]	1.4
Alvarez 2012	38	75	10	95			3.53 [1.85,	6.72]	4.0
Claghorn 1990	35	44	7	73			5.06 [2.39,	10.71]	3.4
Cunningham 1994	32	40	4	72			8.44 [3.14,	22.68]	2.
Cunningham 1997 (IR)	43	53	5	45			4.48 [1.89,	10.59]	2.1
Cunningham 1997 (XR)	44	53	5	45			4.54 [1.92,	10.72]	2.
EudraCT 2004-000562-13	27	100	14	106		-	1.82 [1.00,	3.30]	4.
EudraCT 2007-007025-51	0	7	0	7			1.00 [0.02,	44.50]	0.
Guelfi 1995	8	38	1	46			8.17 [1.06,	62.78]	0.
Hewett 2009	36	151	21	176		-	1.81 [1.10,	2.98]	5.
Hewett 2010	53	145	16	171		-	3.13 [1.86,	5.27]	4.
Higuchi 2016 (fixed dose)	39	135	12	80		-	1.72 [0.95,	3.12]	4.
Higuchi 2016 (flexible dose)	53	127	12	79			2.23 [1.26,	3.96]	4.
Khan 1998 (75 mg)	8	88	1	32	-		2.75 [0.36,	21.17]	0.
Khan 1998 (150 mg)	7	89	0	33		-	5.26 [0.31,	89.63]	0.
Khan 1998 (200 mg)	16	78	0	32	-	-	11.46 [0.71,	185.79]	0.
Learned 2012	29	104	14	112			1.96 [1.09,	3.54]	4.
Lieberman 2008 (225 mg)	34	83	16	109		-	2.27 [1.33,	3.89]	4.
Mendels 1993 (25 mg)	22	57	з	23			2.41 [0.79,	7.41]	2.
Mendels 1993 (50 - 75 mg)	19	57	2	24			3.25 [0.81,	13.01]	1.
Mendels 1993 (150 - 200 mg)	23	56	2	24			3.78 [0.96,	14.97]	1.
Nemeroff 2007	40	60	8	94			5.10 [2.51,	10.34]	3.
Rudolph 1998 (75 mg)	29	60	4	27		_	2.53 [0.96,	6.61]	2.
Rudolph 1998 (225 mg)	34	55	4	27			2.96 [1.14,	7.67]	2.
Rudolph 1998 (375 mg)	51	37	5	25			3.48 [1.53,	7.89]	З.
Rudolph 1999	36	64	14	84			2.52 [1.45,	4.37]	4.
Schatzberg 2006	46	56	13	83			3.33 [1.92,	5.77]	4.
Schweizer 1994	20	53	11	67			1.94 [1.00,	3.77]	З.
Sheehan 2009	36	59	15	80		-	2.40 [1.41,	4.08]	4.
Silverstone 1999	52	76	33	86			1.46 [1.02,	2.10]	6.
Thase 1997	34	61	18	84		-	2.03 [1.23,	3.34]	5.
Overall						•	2.72 [2.26,	3.28]	
Heterogeneity: $\tau^2 = 0.11$, $l^2 = 46$	5.43%, H ²	= 1.87							
Test of θ _i = θ _i : Q(31) = 40.06, p	= 0.13								
Test of θ = 0: z = 10.54, p = 0.0	10								
				1	/22 1/2	8 1	28		

stata

Supplementary Figure 19: Meta-analysis of venlafaxine versus placebo on dry mouth

Graph

17/03/2024, 17.53

Study	Ven Events	lafaxine No events	PI Events	acebo No events		Risk ratio with 95% Cl	Weight (%)
600-B-367-EU (75 mg)	5	78	0	41		5.50 [0.31, 97.13]	0.63
600-B-367-EU (150 mg)	8	74	0	42		8.81 [0.52, 148.99]	0.65
Alvarez 2012	19	94	7	98		2.52 [1.11, 5.75]	4.46
Claghorn 1990	19	60	12	68		1.60 [0.84, 3.08]	5.62
Cunningham 1994	21	51	5	71		4.43 [1.77, 11.13]	3.93
Cunningham 1997 (IR)	21	75	4	46		2.73 [0.99, 7.53]	3.49
Cunningham 1997 (XR)	16	81	4	46		2.06 [0.73, 5.84]	3.37
EudraCT 2004-000562-13	17	110	1	119	_	16.06 [2.17, 118.84]	1.21
EudraCT 2007-007025-51	1	6	0	7		3.00 [0.14, 63.15]	0.56
Guelfi 1995	3	43	3	44		1.02 [0.22, 4.80]	1.87
Hewett 2009	13	174	11	186		1.25 [0.57, 2.71]	4.75
Hewett 2010	35	163	13	174		2.54 [1.39, 4.65]	5.99
Higuchi 2016 (fixed dose)	5	169	1	90		2.61 [0.31, 22.05]	1.08
Higuchi 2016 (flexible dose)	7	173	0	92		7.71 [0.45, 133.48]	0.64
Learned 2012	12	121	5	121		2.27 [0.82, 6.27]	3.48
Lieberman 2008 (225 mg)	30	87	9	116		3.56 [1.77, 7.18]	5.27
Mendels 1993 (25 mg)	14	65	4	22		1.15 [0.42, 3.19]	3.46
Mendels 1993 (50 - 75 mg)	16	60	3	23		1.82 [0.58, 5.76]	2.94
Mendels 1993 (150 - 200 mg)	23	56	3	23		2.52 [0.82, 7.72]	3.06
Nemeroff 2007	24	76	15	87		1.63 [0.91, 2.92]	6.15
Rudolph 1998 (75 mg)	16	73	4	27		1.39 [0.50, 3.85]	3.47
Rudolph 1998 (225 mg)	19	70	4	27		1.65 [0.61, 4.49]	3.56
Rudolph 1998 (375 mg)	17	71	4	26		1.45 [0.53, 3.97]	3.52
Schatzberg 2006	23	79	14	82	-	1.55 [0.85, 2.83]	6.00
Schweizer 1994	14	59	7	71		2.14 [0.91, 5.00]	4.32
Sheehan 2009	36	59	9	86		4.00 [2.04, 7.84]	5.47
Silverstone 1999	30	98	14	105		1.99 [1.11, 3.57]	6.15
Thase 1997	17	78	9	93		2.03 [0.95, 4.33]	4.88
Overall					•	2.16 [1.71, 2.74]	
Heterogeneity: $\tau^2 = 0.15$, $I^2 = 40$	0.74%, H ²	= 1.69					
Test of $\theta_i = \theta_j$: Q(27) = 23.19, p	= 0.67						
Test of θ = 0: z = 6.43, p = 0.00							
					1/4 2 16 1	28	
Random-effects Sidik-Jonkman	model						

stata

Supplementary Figure 20: Meta-analysis of venlafaxine versus placebo on dizziness

Graph

17/03/2024, 18.34

	Ven	lafaxine	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
600-B-367-EU (75 mg)	15	68	2	39		3.70 [0.89, 15.44]	2.65
600-B-367-EU (150 mg)	8	74	2	40		2.05 [0.46, 9.22]	2.45
Alvarez 2012	14	99	8	97		1.63 [0.71, 3.72]	5.25
Claghorn 1990	15	64	5	75		3.04 [1.16, 7.96]	4.46
Cunningham 1994	12	60	4	72		3.17 [1.07, 9.37]	3.87
Cunningham 1997 (IR)	34	62	3	47		5.90 [1.91, 18.27]	3.67
Cunningham 1997 (XR)	28	69	3	47		4.81 [1.54, 15.05]	3.63
EudraCT 2004-000562-13	6	121	7	113		0.81 [0.28, 2.34]	3.97
Guelfi 1995	4	42	1	46		4.09 [0.47, 35.20]	1.36
Hewett 2009	9	178	14	183		0.68 [0.30, 1.53]	5.34
Hewett 2010	27	171	11	176		2.32 [1.18, 4.54]	6.31
Higuchi 2016 (fixed dose)	10	164	2	90		2.64 [0.59, 11.81]	2.47
Higuchi 2016 (flexible dose)	18	162	3	88		3.03 [0.92, 10.03]	3.41
Khan 1998 (75 mg)	5	91	1	32		1.72[0.21, 14.18]	1.41
Khan 1998 (150 mg)	2	94	0	33		1.75 [0.09, 35.60]	0.74
Khan 1998 (200 mg)	6	88	0	32		4.52 [0.26, 77.99]	0.82
Learned 2012	15	118	11	115	-	1.29 [0.62, 2.70]	5.83
Mendels 1993 (25 mg)	7	72	3	23		0.77 [0.21, 2.76]	3.11
Mendels 1993 (50 - 75 mg)	17	59	2	24		2.91 [0.72, 11.74]	2.74
Mendels 1993 (150 - 200 mg)	12	67	2	24		1.97 [0.47, 8.25]	2.64
Nemeroff 2007	13	87	3	99		4.42 [1.30, 15.04]	3.30
Rudolph 1998 (75 mg)	17	72	1	30		5.92 [0.82, 42.67]	1.58
Rudolph 1998 (225 mg)	20	69	1	30	_	6.97 [0.98, 49.77]	1.59
Rudolph 1998 (375 mg)	21	67	2	28		3.58 [0.89, 14.37]	2.76
Rudolph 1999	26	74	7	91		3.64 [1.66, 7.99]	5.51
Schatzberg 2006	17	85	5	91		3.20 [1.23, 8.34]	4.49
Schweizer 1994	12	61	3	75		4.27 [1.26, 14.54]	3.30
Sheehan 2009	15	80	3	92		5.00 [1.50, 16.71]	3.37
Silverstone 1999	49	79	20	99		2.28 [1.44, 3.59]	8.01
Overall					•	2.49 [1.90, 3.26]	
Heterogeneity: $\tau^2 = 0.18$, $l^2 = 37$	7.85%, H ²	= 1.61					
Test of $\theta_i = \theta_j$: Q(28) = 32.48, p	= 0.26						
Test of θ = 0: z = 6.64, p = 0.00						_	
					1/8 1 8 6	4	
Random-effects Sidik-Jonkman	model						



Supplementary Figure 21: Meta-analysis of venlafaxine versus placebo on sweating

	Ven	lafaxine	PI	acebo			Risk ra	tio	Weigh
Study	Events	No events	Events	No events			with 95%	6 CI	(%)
600-B-367-EU (75 mg)	8	75	1	40	-		3.95 [0.51,	30.54]	2.30
600-B-367-EU (150 mg)	12	70	0	42			12.95 [0.79,	213.54]	1.29
Alvarez 2012	17	96	2	103		_	7.90 [1.87,	33.37]	4.18
Claghorn 1990	8	71	1	79			8.10 [1.04,	63.28]	2.28
Cunningham 1994	9	63	1	75			9.50 [1.23,	73.11]	2.31
Cunningham 1997 (IR)	13	83	1	49			6.77 [0.91,	50.28]	2.38
Cunningham 1997 (XR)	18	79	2	48		—	4.64 [1.12,	19.20]	4.28
EudraCT 2004-000562-13	12	115	4	116			2.83 [0.94,	8.55]	6.29
Guelfi 1995	7	39	1	46			7.15 [0.92,	55.86]	2.28
Hewett 2009	15	172	7	190			2.26 [0.94,	5.41]	8.56
Hewett 2010	16	182	7	180			2.16[0.91,	5.13]	8.67
Higuchi 2016 (fixed dose)	3	171	1	91			1.59 [0.17,	15.03]	1.94
Higuchi 2016 (flexible dose)	15	165	1	90		—	7.58 [1.02,	56.51]	2.37
Learned 2012	15	118	3	123			4.74 [1.40,	15.97]	5.46
Lieberman 2008 (225 mg)	21	96	6	119			3.74 [1.56,	8.94]	8.59
Mendels 1993 (25 mg)	2	77	0	26		+ -	1.69 [0.08,	34.06]	1.13
Mendels 1993 (50 - 75 mg)	4	72	0	26			3.16 [0.18,	56.71]	1.22
Mendels 1993 (150 - 200 mg)	17	62	0	26			11.81 [0.73,	189.85]	1.31
Nemeroff 2007	14	86	2	100			7.14 [1.67,	30.61]	4.12
Rudolph 1999	10	90	3	95			3.27 [0.93,	11.51]	5.17
Schatzberg 2006	11	91	1	95			10.35 [1.36,	78.67]	2.33
Schweizer 1994	7	66	0	78			— 16.01 [0.93,	275.48]	1.25
Silverstone 1999	36	92	12	107			2.79 [1.52,	5.10]	12.56
Thase 1997	13	82	4	98			3.49 [1.18,	10.33]	6.44
Schweizer 1991	11	33	0	16	-		8.69 [0.54,	139.48]	1.31
Overall						•	3.99 [2.88,	5.54]	
Heterogeneity: $\tau^2 = 0.13$, $l^2 = 20$	0.46%, H ²	= 1.26							
Test of $\theta_i = \theta_j$: Q(24) = 13.18, p	= 0.96								
Test of $\theta = 0$: z = 8.28, p = 0.00)								
					1/8	1 8 64	_		



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Supplementary Figure 22: Meta-analysis of venlafaxine versus placebo on somnolence

00-B-367-EU (75 mg) 10-B-367-EU (150 mg) laghorn 1990 unningham 1994 unningham 1997 (IR) unningham 1997 (XR) udraCT 2004-000562-13	6 7 28 31 23 20 12	77 75 51 41 73 77	1 1 11 9 4	40 41 69 67		2.96 [0.37, 23.81] 3.59 [0.46, 28.19] 2.58 [1.38, 4.81]	1.07 1.10 8.17
00-B-367-EU (150 mg) laghorn 1990 unningham 1994 unningham 1997 (IR) unningham 1997 (XR) udraCT 2004-000562-13	7 28 31 23 20 12	75 51 41 73 77	1 11 9 4	41 69 67		3.59 [0.46, 28.19] 2.58 [1.38, 4.81]	1.10 8.17
laghorn 1990 unningham 1994 unningham 1997 (IR) unningham 1997 (XR) udraCT 2004-000562-13	28 31 23 20 12	51 41 73 77	11 9 4	69 67		2.58 [1.38, 4.81]	8.17
unningham 1994 unningham 1997 (IR) unningham 1997 (XR) udraCT 2004-000562-13	31 23 20 12	41 73 77	9 4	67			
unningham 1997 (IR) unningham 1997 (XR) udraCT 2004-000562-13	23 20 12	73 77	4			3.64 [1.86, 7.09]	7.46
unningham 1997 (XR) udraCT 2004-000562-13	20 12	77		46	-	2.99 [1.10, 8.18]	4.01
udraCT 2004-000562-13	12		5	45		2.06 [0.82, 5.17]	4.64
		115	3	117	_	3.78 [1.09, 13.06]	2.80
uelfi 1995	1	45	0	47		- 3.06 [0.13, 73.33]	0.47
ewett 2010	9	189	9	178		0.94 [0.38, 2.33]	4.78
iguchi 2016 (fixed dose)	21	153	7	85		1.59 [0.70, 3.59]	5.58
iguchi 2016 (flexible dose)	31	149	8	83		1.96 [0.94, 4.09]	6.52
han 1998 (75 mg)	7	89	0	33		- 5.26 [0.31, 89.63]	0.59
han 1998 (150 mg)	4	92	0	33		3.15 [0.17, 57.08]	0.57
han 1998 (200 mg)	4	90	0	32		3.13 [0.17, 56.52]	0.57
earned 2012	7	126	3	123		2.21 [0.58, 8.36]	2.47
eberman 2008 (225 mg)	22	95	13	112	- - -	1.81 [0.96, 3.42]	7.95
endels 1993 (25 mg)	15	64	3	23		1.65 [0.52, 5.24]	3.16
endels 1993 (50 - 75 mg)	13	63	3	23		1.48 [0.46, 4.79]	3.08
endels 1993 (150 - 200 mg)	22	57	3	23		2.41 [0.79, 7.41]	3.33
udolph 1998 (75 mg)	15	74	1	30		5.22 [0.72, 37.94]	1.18
udolph 1998 (225 mg)	16	73	1	30		5.57 [0.77, 40.30]	1.19
udolph 1998 (375 mg)	23	65	2	28		3.92 [0.98, 15.65]	2.30
udolph 1999	8	92	6	92		1.31 [0.47, 3.63]	3.91
chatzberg 2006	8	94	3	93		2.51 [0.69, 9.18]	2.58
chweizer 1994	19	54	11	67		1.85 [0.94, 3.61]	7.43
ilverstone 1999	17	111	7	112		2.26 [0.97, 5.25]	5.31
hase 1997	26	69	11	91		2.54 [1.33, 4.85]	7.79
verall					•	2.23 [1.78, 2.78]	
eterogeneity: $\tau^2 = 0.05$, $I^2 = 16$.92%, H ²	= 1.20					
est of $\theta_i = \theta_i$: Q(26) = 13.23, p =	= 0.98						
est of $\theta = 0$: $z = 7.09$, $p = 0.00$							
					1/4 1 4 16 6	, _ 64	

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Supplementary Figure 23: Meta-analysis of venlafaxine versus placebo on constipation

	Ven	lafaxine	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
600-B-367-EU (75 mg)	1	82	1	40		0.49 [0.03, 7.70]	1.13
600-B-367-EU (150 mg)	5	77	1	41		2.56 [0.31, 21.22]	1.79
Alvarez 2012	11	102	1	104		— 10.22 [1.34, 77.81]	1.91
Claghorn 1990	11	68	1	79	· · · · · · · · · · · · · · · · · · ·	— 11.14 [1.47, 84.25]	1.92
Cunningham 1994	16	56	3	73		5.63 [1.71, 18.51]	4.22
Cunningham 1997 (IR)	14	82	2	48		3.65 [0.86, 15.41]	3.26
Cunningham 1997 (XR)	16	81	2	48	_	4.12 [0.99, 17.23]	3.30
EudraCT 2004-000562-13	6	121	5	115		1.13 [0.36, 3.62]	4.36
Guelfi 1995	2	44	1	46		2.04 [0.19, 21.77]	1.47
Hewett 2010	12	186	3	184		3.78 [1.08, 13.18]	3.97
Higuchi 2016 (fixed dose)	17	157	4	88	- -	2.25 [0.78, 6.48]	4.86
Higuchi 2016 (flexible dose)	17	163	4	87		2.15 [0.74, 6.20]	4.86
Learned 2012	12	121	9	117		1.26 [0.55, 2.89]	6.26
Lieberman 2008 (225 mg)	9	108	2	123		4.81 [1.06, 21.79]	3.04
Mendels 1993 (25 mg)	6	73	2	24	_	0.99 [0.21, 4.60]	2.97
Mendels 1993 (50 - 75 mg)	9	67	2	24	_	1.54 [0.36, 6.67]	3.18
Mendels 1993 (150 - 200 mg)	15	64	2	24		2.47 [0.60, 10.08]	3.37
Nemeroff 2007	10	90	5	97		2.04 [0.72, 5.76]	4.98
Rudolph 1998 (75 mg)	17	72	3	28		1.97 [0.62, 6.28]	4.37
Rudolph 1998 (225 mg)	10	79	3	28		1.16 [0.34, 3.95]	4.08
Rudolph 1998 (375 mg)	17	71	4	26		1.45 [0.53, 3.97]	5.15
Schatzberg 2006	22	80	4	92		5.18 [1.85, 14.47]	5.03
Schweizer 1994	9	64	6	72		1.60 [0.60, 4.28]	5.29
Sheehan 2009	24	71	11	84		2.18 [1.13, 4.20]	7.55
Silverstone 1999	22	106	13	106		1.57 [0.83, 2.98]	7.68
Overall					•	2.24 [1.64, 3.04]	
Heterogeneity: τ ² = 0.21, l ² = 38	3.26%, H ²	= 1.62					
Test of $\theta_i = \theta_i$: Q(24) = 21.26, p	= 0.62						
Test of θ = 0: z = 5.13, p = 0.00							
					1/16 1/2 4 32		



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Supplementary Figure 24: Meta-analysis of venlafaxine versus placebo on nervousness

	Ven	lafaxine	PI	acebo			Risk ra	atio	Weight
Study	Events	No events	Events	No events			with 959	% CI	(%)
600-B-367-EU (75 mg)	1	82	1	40			0.49 [0.03,	7.70]	2.23
600-B-367-EU (150 mg)	2	80	1	41			1.02 [0.10,	10.97]	2.89
Claghorn 1990	7	72	6	74		—	1.18 [0.42,	3.36]	9.48
Cunningham 1994	15	57	9	67	-	-	1.76 [0.82,	3.77]	12.78
Guelfi 1995	3	43	0	47			7.15 [0.38,	134.66]	1.98
Mendels 1993 (25 mg)	4	75	2	24			0.66 [0.13,	3.39]	5.26
Mendels 1993 (50 - 75 mg)	7	69	1	25			2.39 [0.31,	18.55]	3.70
Mendels 1993 (150 - 200 mg)	13	66	1	25	-		4.28 [0.59,	31.15]	3.90
Rudolph 1998 (75 mg)	19	70	1	30	-		6.62 [0.92,	47.40]	3.95
Rudolph 1998 (225 mg)	12	77	1	30	_		4.18 [0.57,	30.84]	3.85
Rudolph 1998 (375 mg)	11	77	2	28			1.88 [0.44,	7.98]	6.30
Rudolph 1999	12	88	5	93	-		2.35 [0.86,	6.43]	9.89
Schatzberg 2006	2	100	2	94			0.94 [0.14,	6.55]	4.04
Schweizer 1994	10	63	3	75			3.56 [1.02,	12.43]	7.67
Silverstone 1999	23	105	8	111			2.67 [1.24,	5.74]	12.73
Thase 1997	16	79	4	98			4.29 [1.49,	12.39]	9.34
Overall						•	2.20 [1.43,	3.40]	
Heterogeneity: $\tau^2 = 0.23$, $I^2 = 33$.36%, H ²	= 1.50							
Test of $\theta_i = \theta_j$: Q(15) = 11.11, p =	= 0.74								
Test of θ = 0: z = 3.56, p = 0.00									
					1/16 1/2	4 32			



Supplementary Figure 25: Meta-analysis of venlafaxine versus placebo on insomnia

Study	Ven	lafaxine	Pl	acebo		Risk ratio	Weigh
	LVento	NO EVENIS	Lventa	140 6761113	_	with 35% Of	(70)
600-B-367-EU (75 mg)	2	81	2	39		0.49[0.07, 3.38]	1.36
600-B-367-EU (150 mg)	3	79	1	41		1.54 [0.16, 14.32]	1.04
Alvarez 2012	14	99	5	100		2.60 [0.97, 6.97]	4.15
Claghorn 1990	13	66	6	74		2.19 [0.88, 5.48]	4.60
Cunningham 1994	7	65	3	73		2.46 [0.66, 9.16]	2.65
EudraCT 2004-000562-13	14	113	8	112		1.65 [0.72, 3.80]	5.24
Guelfi 1995	3	43	3	44		1.02 [0.22, 4.80]	2.01
Hewett 2009	7	180	4	193		1.84 [0.55, 6.20]	3.02
Hewett 2010	13	185	8	179		1.53 [0.65, 3.62]	5.04
Higuchi 2016 (fixed dose)	4	170	3	89		0.70 [0.16, 3.08]	2.18
Higuchi 2016 (flexible dose)	8	172	3	88		1.35 [0.37, 4.96]	2.69
Khan 1998 (75 mg)	5	91	0	33		3.86 [0.22, 67.91]	0.65
Khan 1998 (150 mg)	3	93	0	33		2.45 [0.13, 46.29]	0.62
Khan 1998 (200 mg)	5	89	0	32		3.82 [0.22, 67.25]	0.65
Learned 2012	7	126	11	115		0.60 [0.24, 1.51]	4.61
Mendels 1993 (25 mg)	14	65	4	22		1.15 [0.42, 3.19]	3.95
Mendels 1993 (50 - 75 mg)	10	66	4	22		0.86 [0.29, 2.49]	3.67
Mendels 1993 (150 - 200 mg)	19	60	3	23	- -	2.08 [0.67, 6.48]	3.36
Nemeroff 2007	22	78	14	88		1.60 [0.87, 2.95]	7.51
Rudolph 1998 (75 mg)	20	69	3	28		2.32 [0.74, 7.28]	3.32
Rudolph 1998 (225 mg)	18	71	3	28		2.09 [0.66, 6.61]	3.28
Rudolph 1998 (375 mg)	12	76	3	27	—— — ——	1.36 [0.41, 4.51]	3.09
Schatzberg 2006	10	92	4	92		2.35 [0.76, 7.25]	3.40
Schweizer 1994	15	58	10	68		1.60 [0.77, 3.34]	6.13
Sheehan 2009	18	77	8	87		2.25 [1.03, 4.92]	5.67
Silverstone 1999	41	87	12	107		3.18 [1.76, 5.75]	7.73
Thase 1997	33	62	15	87		2.36 [1.37, 4.06]	8.40
Overall					•	1.73 [1.37, 2.19]	
Heterogeneity: $\tau^2 = 0.10$, $I^2 = 26$	6.87%, H ²	= 1.37					
Test of θ _i = θ _i : Q(26) = 19.55, p	= 0.81						
Test of θ = 0: z = 4.57, p = 0.00							
					1/8 1 8	64	



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Supplementary Figure 26: Meta-analysis of venlafaxine versus placebo on asthenia

	Ven	lafaxine	PI	acebo		Risk ra	tio	Weight
Study	Events	No events	Events	No events		with 95%	% CI	(%)
600-B-367-EU (75 mg)	5	78	1	40		2.47 [0.30,	20.46]	2.03
600-B-367-EU (150 mg)	3	79	1	41		1.54 [0.16,	14.32]	1.84
Alvarez 2012	11	102	6	99		1.70 [0.65,	4.44]	7.57
Claghorn 1990	5	74	2	78		2.53 [0.51,	12.67]	3.31
Cunningham 1994	7	65	3	73		2.46 [0.66,	9.16]	4.67
EudraCT 2004-000562-13	10	117	2	118		4.72 [1.06,	21.12]	3.75
Guelfi 1995	2	44	0	47		- 5.11 [0.25,	103.55]	1.04
Hewett 2009	9	178	4	193		2.37 [0.74,	7.57]	5.69
Hewett 2010	16	182	13	174		1.16 [0.57,	2.35]	11.20
Khan 1998 (75 mg)	5	91	0	33		3.86 [0.22,	67.91]	1.14
Khan 1998 (150 mg)	5	91	0	33		3.86 [0.22,	67.91]	1.14
Khan 1998 (200 mg)	3	91	0	32		2.43 [0.13,	45.84]	1.09
Learned 2012	13	120	5	121		2.46 [0.90,	6.71]	7.10
Lieberman 2008 (225 mg)	7	110	8	117		0.93 [0.35,	2.50]	7.30
Mendels 1993 (25 mg)	10	69	3	23		1.10 [0.33,	3.69]	5.32
Mendels 1993 (50 - 75 mg)	8	68	3	23		0.91 [0.26,	3.18]	5.06
Mendels 1993 (150 - 200 mg)	13	66	2	24		2.14 [0.52,	8.86]	4.10
Nemeroff 2007	10	90	5	97		2.04 [0.72,	5.76]	6.75
Rudolph 1999	10	90	2	96		4.90 [1.10,	21.79]	3.78
Schatzberg 2006	12	90	5	91		2.26 [0.83,	6.17]	7.07
Schweizer 1994	9	64	10	68		0.96 [0.41,	2.23]	9.02
Overall					•	1.78 [1.30,	2.43]	
Heterogeneity: $\tau^2 = 0.10$, $I^2 = 19$	9.72%, H ²	= 1.25						
Test of $\theta_i = \theta_i$: Q(20) = 12.71, p	= 0.89							
Test of $\theta = 0$: z = 3.58, p = 0.00								
					1/4 1 4 16 6	4		
Random-effects Sidik-Jonkman	model							



Supplementary Figure 27: Meta-analysis of venlafaxine versus placebo on tremor

	Ven	lafaxine	Placebo						Risk ra	tio	Weight
Study	Events	No events	Events	No events					with 95%	6 CI	(%)
600-B-367-EU (75 mg)	3	80	2	39		_			0.74 [0.13,	4.26]	8.49
600-B-367-EU (150 mg)	2	80	1	41		•	_		1.02 [0.10,	10.97]	5.50
Alvarez 2012	6	107	3	102			-		1.86 [0.48,	7.24]	11.42
Claghorn 1990	2	77	0	80					5.06 [0.25,	103.80]	3.71
EudraCT 2004-000562-13	4	123	3	117					1.26 [0.29,	5.51]	10.44
Guelfi 1995	2	45	2	45		•	-		1.00 [0.15,	6.81]	7.50
Hewett 2010	10	188	2	185			<u> </u>		4.72 [1.05,	21.27]	10.21
Learned 2012	7	126	5	121					1.33 [0.43,	4.07]	13.75
Rudolph 1999	9	91	1	97					8.82 [1.14,	68.32]	6.85
Schatzberg 2006	6	96	0	96	-		-		- 12.24 [0.70,	214.43]	4.06
Sheehan 2009	5	90	0	95	-		-		- 11.00 [0.62,	196.19]	4.02
Silverstone 1999	13	115	4	115			_		3.02 [1.01,	9.01]	14.06
Overall									2.30 [1.22,	4.32]	
Heterogeneity: τ ² = 0.43, l ² =	= 37.02%,	H ² = 1.59									
Test of $\theta_i = \theta_i$: Q(11) = 9.88,	p = 0.54										
Test of $\theta = 0$: $z = 2.57$, $p = 0$.01										
					1/8	1	8	64	-		



Supplementary Figure 28: Meta-analysis of venlafaxine versus placebo on decreased appetite

Study	Ven Events	lafaxine No events	PI Events	acebo No events	:					Risk ratio with 95% Cl		Weight (%)
Higuchi 2016 (fixed dose)	4	170	0	91						4.73 [0.26,	86.93]	9.13
Higuchi 2016 (flexible dose)	4	176	1	91				_		2.04 [0.23,	18.03]	16.27
Learned 2012	2	131	1	125		┼╺				1.89 [0.17,	20.64]	13.54
Schatzberg 2006	11	91	4	92						2.59 [0.85,	7.85]	61.06
Overall										2.52 [1.04,	6.09]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = -$	1.04%, H ²	= 1.01										
Test of $\theta_i = \theta_i$: Q(3) = 0.27, p =	= 0.97											
Test of θ = 0: z = 2.06, p = 0.0	4											
					1/4	1	4	16	64			



Supplementary Figure 29: Meta-analysis of venlafaxine versus placebo on abdominal pain

	Ven	lafaxine	Placebo						Risk rat	io	Weight
Study	Events	No events	Events	No event	S				with 95%	o CI	(%)
600-B-367-EU (75 mg)	0	83	2	39					0.10 [0.00,	2.04]	8.14
600-B-367-EU (150 mg)	2	80	1	41					-1.02 [0.10,	10.97]	11.43
EudraCT 2004-000562-13	8	119	11	109					0.69 [0.29,	1.65]	26.35
Hewett 2010	9	189	8	179				-	1.06 [0.42,	2.70]	25.66
Higuchi 2016 (fixed dose)	5	169	3	88				—	0.87 [0.21,	3.57]	19.85
Higuchi 2016 (flexible dose)	0	180	4	88				-	0.06 [0.00,	1.05]	8.58
Overall							-	-	0.58 [0.22,	1.57]	
Heterogeneity: $\tau^2 = 0.77$, $I^2 = 5$											
Test of $\theta_i = \theta_j$: Q(5) = 5.40, p =	= 0.37										
Test of $\theta = 0$: $z = -1.07$, $p = 0.2$	28										
					1/256	1/32	1/4	2	_		

Random-effects Sidik-Jonkman model

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Supplementary Figure 30: Meta-analysis of venlafaxine versus placebo on abnormal dreams

	Ven	lafaxine	Placebo						Risk ra	tio	Weight
Study	Events	No events	Events	No events	6				with 95%	6 CI	(%)
600-B-367-EU (75 mg)	2	81	1	40					0.99 [0.09,	10.58]	32.19
600-B-367-EU (150 mg)	0	82	0	42					0.52 [0.01,	25.66]	16.10
Cunningham 1997 (IR)	7	89	0	50		-			7.89 [0.46,	135.33]	25.63
Cunningham 1997 (XR)	12	85	0	50		+	_		- 13.01 [0.79,	215.32]	26.08
Overall						-			2.97 [0.51,	17.25]	
Heterogeneity: $\tau^2 = 1.04$, l ⁴	² = 32.26 ⁴	%, H ² = 1.48									
Test of $\theta_i = \theta_j$: Q(3) = 3.11,	p = 0.37										
Test of θ = 0: z = 1.21, p =	0.23										
					1/64	1/4	4	64	-		


Supplementary Figure 31: Meta-analysis of venlafaxine versus placebo on abnormal vision

	Ven	lafaxine	PI	acebo				Risk ra	atio	Weight
Study	Events	No events	Events	No event	s			with 95%	% CI	(%)
600-B-367-EU (75 mg)	0	83	1	40		-		0.17[0.01,	4.00]	5.77
600-B-367-EU (150 mg)	0	82	0	42				0.52[0.01,	25.66]	4.03
Alvarez 2012	6	107	2	103		-		2.79 [0.58,	13.51]	16.06
EudraCT 2004-000562-13	3	124	0	120				-6.62 [0.35,	126.78]	6.54
Guelfi 1995	1	45	0	47				3.06 [0.13,	73.33]	5.78
Lieberman 2008 (225 mg)	5	112	3	122				1.78 [0.44,	7.29]	18.21
Schatzberg 2006	8	94	5	91			_	1.51 [0.51,	4.44]	23.23
Sheehan 2009	10	85	3	92				3.33 [0.95,	11.73]	20.38
Overall							•	1.95 [0.85,	4.47]	
Heterogeneity: $\tau^2 = 0.46$, $I^2 =$	35.92%,	H ² = 1.56								
Test of $\theta_i = \theta_j$: Q(7) = 4.60, p	= 0.71									
Test of $\theta = 0$: $z = 1.58$, $p = 0$.11									
					1/128	1/8	2 32	-		



Supplementary Figure 32: Meta-analysis of venlafaxine versus placebo on agitation

	Ven	lafaxine	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No event	s				with 95%	6 CI	(%)
600-B-367-EU (75 mg)	2	81	0	41				_	2.50 [0.12,	50.91]	15.32
600-B-367-EU (150 mg)	2	80	0	42				_	2.59 [0.13,	52.76]	15.32
Cunningham 1994	7	65	0	76		ł			- 15.82 [0.92,	272.09]	16.62
Guelfi 1995	1	45	0	47			-		3.06 [0.13,	73.33]	14.21
Learned 2012	1	132	4	122			_		0.24 [0.03,	2.09]	23.28
Schatzberg 2006	2	100	0	96			-		4.71 [0.23,	96.84]	15.25
Overall									2.24 [0.55,	9.03]	
Heterogeneity: $\tau^2 = 0.94$, I	² = 31.15	%, H ² = 1.45									
Test of $\theta_i = \theta_j$: Q(5) = 6.14	, p = 0.29	1									
Test of θ = 0: z = 1.13, p =	0.26										
					1/32	1/2	8	128	-		

Random-effects Sidik-Jonkman model

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Supplementary Figure 33: Meta-analysis of venlafaxine versus placebo on back pain

	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No events	s				with 95% CI	(%)
600-B-367-EU (75 mg)	0	83	1	40					0.17 [0.01, 4.00]	7.81
600-B-367-EU (150 mg)	1	81	1	41					0.51 [0.03, 7.99]	10.42
EudraCT 2004-000562-13	3	124	6	114		-			0.47 [0.12, 1.85]	40.72
Schatzberg 2006	3	99	6	90		-			0.47 [0.12, 1.83]	41.05
Overall									0.44 [0.18, 1.07]	
Heterogeneity: $\tau^2 = 0.03$, $I^2 =$	= 2.67%, I	H ² = 1.03								
Test of $\theta_i = \theta_i$: Q(3) = 0.39, p	= 0.94									
Test of $\theta = 0$: $z = -1.81$, $p = 0$	0.07									
					1/128	1/16	1/2	4		



Supplementary Figure 34: Meta-analysis of venlafaxine versus placebo on increased blood pressure

	Ven	lafaxine	PI	acebo			Risk rat	io	Weight
Study	Events	No events	Events	No events	3		with 95%	CI	(%)
Higuchi 2016 (fixed dose)	4	170	1	91			2.11 [0.24,	18.65]	20.08
Higuchi 2016 (flexible dose)	5	175	1	90			2.53 [0.30,	21.32]	20.89
Schatzberg 2006	5	97	5	91			0.94 [0.28,	3.15]	59.03
Overall							1.36 [0.50,	3.70]	
Heterogeneity: $\tau^2 = 0.06$, $I^2 = 6$	6.64%, H ²	= 1.07							
Test of $\theta_i = \theta_j$: Q(2) = 0.84, p =	0.66								
Test of θ = 0: z = 0.60, p = 0.5	5								
					1/4	4 1	16		



Supplementary Figure 35: Meta-analysis of venlafaxine versus placebo on coughing

	Ven	lafaxine	Pla	acebo				Risk ra	tio	Weight
Study	Events	No events	Events	No events				with 95%	6 CI	(%)
600-B-367-EU (75 mg)	1	82	0	41			-	— 1.50 [0.06,	36.04]	17.33
600-B-367-EU (150 mg)	1	81	1	41				0.51 [0.03,	7.99]	23.07
Schatzberg 2006	2	100	4	92				0.47 [0.09,	2.51]	59.60
Overall					-			0.59 [0.15,	2.23]	
Heterogeneity: $\tau^2 = 0.05$, I^2	² = 3.02%	o, H ² = 1.03								
Test of $\theta_i = \theta_i$: Q(2) = 0.41,	p = 0.81									
Test of θ = 0: z = -0.78, p =	= 0.43									
					1/16	1/2	4	32		

Random-effects Sidik-Jonkman model

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Supplementary Figure 36: Meta-analysis of venlafaxine versus placebo on diarrhoea

	Ven	lafaxine	PI	acebo				Risk ratio Weig
Study	Events	No events	Events	No events				with 95% CI (%
600-B-367-EU (75 mg)	3	80	3	38				0.49 [0.10, 2.34] 3.5
600-B-367-EU (150 mg)	1	81	3	39		-		0.17 [0.02, 1.59] 3.4
Alvarez 2012	5	108	5	100		-		0.93 [0.28, 3.12] 4.5
Cunningham 1994	7	65	5	71				- 1.48 [0.49, 4.45] 4.2
Cunningham 1997 (IR)	5	91	3	47		-		0.87 [0.22, 3.48] 3.4
Cunningham 1997 (XR)	13	84	3	47				2.23 [0.67, 7.48] 3.4
EudraCT 2004-000562-13	3	124	6	114				0.47 [0.12, 1.85] 5.4
EudraCT 2007-007025-51	0	7	2	5		-		- 0.20 [0.01, 3.54] 2.2
Guelfi 1995	0	46	1	46				0.34 [0.01, 8.15] 1.3
Hewett 2010	10	188	9	178				1.05 [0.44, 2.53] 8.1
Higuchi 2016 (fixed dose)	6	168	3	88		-		- 1.05 [0.27, 4.09] 3.4
Higuchi 2016 (flexible dose)	8	172	4	88				1.02 [0.32, 3.31] 4.6
Learned 2012	8	125	8	118				0.95 [0.37, 2.45] 7.2
Nemeroff 2007	9	91	9	93				1.02 [0.42, 2.46] 7.8
Rudolph 1999	14	86	9	89				1.52 [0.69, 3.36] 7.9
Schatzberg 2006	12	90	13	83				0.87 [0.42, 1.81] 11.7
Silverstone 1999	22	106	19	100				1.08 [0.61, 1.89] 17.2
Overall							•	1.00 [0.78, 1.28]
Heterogeneity: I ² = 0.00%, H ²	= 1.00							
Test of $\theta_i = \theta_i$: Q(16) = 9.58, p	0 = 0.89							
Test of $\theta = 0$: $z = -0.02$, $p = 0$.99							
					1/64	1/8	1	8



Supplementary Figure 37: Meta-analysis of venlafaxine versus placebo on dyspepsia

	Ven	lafaxine	Pl	acebo					Risk ratio	Weight
Study	Events	No events	Events	No events	3				with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	2	39	-		-		0.49 [0.07, 3.38]	5.78
600-B-367-EU (150 mg)	1	81	2	40		-			0.26 [0.02, 2.74]	3.91
Cunningham 1994	2	70	5	71	-				0.42 [0.08, 2.11]	8.01
Learned 2012	2	131	2	124					0.95 [0.14, 6.62]	5.67
Nemeroff 2007	9	91	16	86		-			0.57 [0.27, 1.24]	25.56
Schatzberg 2006	11	91	8	88				-	1.29 [0.54, 3.08]	21.72
Silverstone 1999	13	115	16	103				-	0.76 [0.38, 1.50]	29.35
Overall									0.72 [0.44, 1.16]	
Heterogeneity: $\tau^2 = 0.08$, I^2	= 20.08	%, H ² = 1.25								
Test of $\theta_i = \theta_j$: Q(6) = 3.48,	p = 0.75									
Test of θ = 0: z = -1.36, p =	0.17									
					1/32	1/8	1/2	2	-	



Supplementary Figure 38: Meta-analysis of venlafaxine versus placebo on flatulence

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No event	s			with 95% CI	(%)
600-B-367-EU (75 mg)	0	83	1	40		_		0.17 [0.01, 4.00]	41.93
600-B-367-EU (150 mg)	0	82	0	42				0.52 [0.01, 25.66]	28.25
EudraCT 2007-007025-51	0	7	0	7				1.00 [0.02, 44.50]	29.82
Overall								0.39 [0.05, 3.22]	
Heterogeneity: $\tau^2 = 0.12$, $I^2 =$	3.51%, I	$H^2 = 1.04$							
Test of $\theta_i = \theta_j$: Q(2) = 0.53, p	= 0.77								
Test of θ = 0: z = -0.87, p = 0	0.38								
					1/128	1/8	2	32	



Supplementary Figure 39: Meta-analysis of venlafaxine versus placebo on headache

Study	Ven Events	lafaxine No events	PI Events	acebo No events				Risk ratio with 95% Cl	Weight (%)
600-B-367-EU (75 mg)	11	72	5	36				1.09 [0.40, 2.92]	1.76
600-B-367-EU (150 mg)	7	75	6	36		-		0.60 [0.21, 1.67]	1.65
Alvarez 2012	32	81	26	79				1.14 [0.73, 1.78]	6.73
Claghorn 1990	21	58	17	63				1.25 [0.72, 2.19]	4.75
Cunningham 1994	22	50	25	51				0.93 [0.58, 1.49]	6.12
EudraCT 2004-000562-13	29	98	34	86				0.81 [0.53, 1.24]	7.09
EudraCT 2007-007025-51	0	7	1	6			-	0.33 [0.02, 7.02]	0.20
Guelfi 1995	2	44	4	43			-	0.51 [0.10, 2.65]	0.66
Hewett 2009	25	162	19	178				1.39 [0.79, 2.43]	4.71
Hewett 2010	28	170	31	156				0.85 [0.53, 1.37]	6.19
Higuchi 2016 (fixed dose)	16	158	7	85				1.21 [0.52, 2.83]	2.31
Higuchi 2016 (flexible dose)	18	162	7	84				1.30 [0.56, 3.00]	2.39
Learned 2012	28	105	24	102				1.11 [0.68, 1.80]	5.86
Mendels 1993 (25 mg)	20	59	7	19				0.94 [0.45, 1.97]	2.98
Mendels 1993 (50 - 75 mg)	19	57	7	19				0.93 [0.44, 1.95]	2.94
Mendels 1993 (150 - 200 mg)	17	62	7	19				0.80 [0.37, 1.71]	2.83
Nemeroff 2007	36	64	34	68			-	1.08 [0.74, 1.58]	8.34
Rudolph 1998 (75 mg)	23	66	7	24				1.14 [0.55, 2.40]	2.96
Rudolph 1998 (225 mg)	23	66	7	24				1.14 [0.55, 2.40]	2.96
Rudolph 1998 (375 mg)	22	66	8	22			_ _	0.94 [0.47, 1.88]	3.31
Schatzberg 2006	27	75	21	75				1.21 [0.74, 1.99]	5.69
Schweizer 1994	19	54	21	57				0.97 [0.57, 1.65]	5.13
Silverstone 1999	57	71	59	60			- -	0.90 [0.69, 1.17]	12.45
Overall							•	1.01 [0.88, 1.15]	
Heterogeneity: $\tau^2 = 0.02$, $l^2 = 19$	9.96%, H ²	= 1.25							
Test of $\theta_i = \theta_i$: Q(22) = 8.69, p =	- 0.99								
Test of $\theta = 0$: $z = 0.09$, $p = 0.93$									
					1/32	1/8	1/2 2		
Random-effects Sidik–Jonkman	model								



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Supplementary Figure 40: Meta-analysis of venlafaxine versus placebo on infection

	Ven	lafaxine	PI	acebo					Risk rat	io	Weight
Study	Events	No events	Events	No events	S				with 95%	CI	(%)
600-B-367-EU (75 mg)	3	80	2	39		_			0.74 [0.13,	4.26]	6.51
600-B-367-EU (150 mg)	0	82	1	41					0.17 [0.01,	4.15]	4.81
Cunningham 1994	8	64	7	69				<u> </u>	1.21 [0.46,	3.16]	16.57
EudraCT 2004-000562-13	2	125	10	110					0.19 [0.04,	0.84]	25.02
Mendels 1993 (25 mg)	10	69	2	24					1.65 [0.39,	7.03]	7.32
Mendels 1993 (50 - 75 mg)	3	73	2	24					0.51 [0.09,	2.90]	7.25
Mendels 1993 (150 - 200 mg)	7	72	1	25				-	-2.30 [0.30,	17.86]	3.66
Rudolph 1999	13	87	6	92			+		2.12 [0.84,	5.36]	14.74
Schweizer 1994	3	70	6	72		-		_	0.53 [0.14,	2.06]	14.11
Overall							-	•	0.93 [0.61,	1.43]	
Heterogeneity: I ² = 28.97%, H ² :	= 1.41										
Test of $\theta_i = \theta_i$: Q(8) = 11.26, p =	0.19										
Test of θ = 0: z = -0.31, p = 0.75	5										
				1	1/128	1/16	1/2	4	-		



Supplementary Figure 41: Meta-analysis of venlafaxine versus placebo on influenza

	Ven	lafaxine	PI	acebo					Risk ratio		Weight
Study	Events	No events	Events	No event	ts				with 95% C		(%)
600-B-367-EU (75 mg)	2	81	2	39			<u> </u>		0.49 [0.07, 3	3.38]	16.83
600-B-367-EU (150 mg)	0	82	1	41		_	<u> </u>		0.17[0.01, 4	4.15]	7.93
Guelfi 1995	1	45	1	46			•	_	1.02 [0.07, 15	5.85]	10.09
Hewett 2010	4	194	9	178			+		0.42 [0.13, 1	1.34]	28.62
Rudolph 1999	7	93	4	94		-			1.72 [0.52, 5	5.67]	27.92
Schatzberg 2006	2	100	0	96					-4.71 [0.23, 96	6.84]	8.62
Overall									0.80 [0.30, 2	2.14]	
Heterogeneity: τ ² = 0.52, I	² = 37.51	%, H ² = 1.60)								
Test of $\theta_i = \theta_i$: Q(5) = 5.23	, p = 0.39)									
Test of θ = 0: z = -0.44, p	= 0.66										
					1/128	1/8	2	32	-		
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Supplementary Figure 42: Meta-analysis of venlafaxine versus placebo on malaise

	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No event	ts				with 95% CI	(%)
600-B-367-EU (75 mg)	0	83	1	40		_			0.17 [0.01, 4.00]	13.08
600-B-367-EU (150 mg)	0	82	0	42			-		-0.52 [0.01, 25.66]	9.25
Higuchi 2016 (fixed dose)	9	165	2	90			-		2.38 [0.52, 10.78]	35.52
Higuchi 2016 (flexible dose)	11	169	3	88			-		1.85 [0.53, 6.48]	42.15
Overall									1.31 [0.37, 4.69]	
Heterogeneity: $\tau^2 = 0.59$, $I^2 = 3$	36.17%, H	l ² = 1.57								
Test of $\theta_i = \theta_i$: Q(3) = 2.58, p =	= 0.46									
Test of $\theta = 0$: $z = 0.42$, $p = 0.6$	7									
					1/128	1/16	1/2	4	-	



Supplementary Figure 43: Meta-analysis of venlafaxine versus placebo on nasopharyngitis

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events				with 95% CI	(%)
Alvarez 2012	4	109	9	96				0.41 [0.13, 1.30]	9.04
Hewett 2010	11	187	9	178				- 1.15 [0.49, 2.72]	14.83
Higuchi 2016 (fixed dose)	35	139	20	72			<u> </u>	0.93 [0.57, 1.51]	32.95
Higuchi 2016 (flexible dose)	32	148	21	70				0.77 [0.47, 1.26]	32.84
Learned 2012	6	127	7	119		-		0.81 [0.28, 2.35]	10.34
Overall						-	-	0.83 [0.57, 1.19]	
Heterogeneity: $\tau^2 = 0.04$, $I^2 = 2$	25.40%, H	l ² = 1.34							
Test of $\theta_i = \theta_i$: Q(4) = 2.27, p =	= 0.69								
Test of θ = 0: z = -1.02, p = 0.	31								
					1/4	1/2	2	_	



Supplementary Figure 44: Meta-analysis of venlafaxine versus placebo on palpitations

	Ven	afaxine	PI.	acebo					Risk rat	io	Weight
Study	Events	No events	Events	No events	3				with 95%	CI	(%)
600-B-367-EU (75 mg)	0	83	1	40		-			0.17 [0.01,	4.00]	6.53
600-B-367-EU (150 mg)	3	79	1	41					1.54 [0.16,	14.32]	12.13
Higuchi 2016 (fixed dose)	8	166	2	89					2.09 [0.45,	9.65]	21.78
Higuchi 2016 (flexible dose)	6	174	3	89			—		1.02 [0.26,	3.99]	25.44
Learned 2012	5	128	2	124					2.37 [0.47,	11.99]	20.01
Rudolph 1998 (75 mg)	1	22	0	13					1.75 [0.08,	40.11]	6.71
Rudolph 1998 (225 mg)	2	20	0	13					3.04 [0.16,	58.90]	7.41
Overall						•			1.48 [0.63,	3.47]	
Heterogeneity: $\tau^2 = 0.26$, $I^2 = 1$	9.73%, ⊦	l² = 1.25									
Test of $\theta_i = \theta_j$: Q(6) = 2.85, p =	0.83										
Test of $\theta = 0$: $z = 0.91$, $p = 0.3$	6										
				1	/128	1/8	2	32			



Supplementary Figure 45: Meta-analysis of venlafaxine versus placebo on rhinitis

	Ven	lafaxine	Pl	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No events					with 95%	5 CI	(%)
600-B-367-EU (75 mg)	2	81	1	40					0.99 [0.09,	10.58]	11.97
600-B-367-EU (150 mg)	1	81	0	42		-		-	1.55 [0.06,	37.35]	5.89
Cunningham 1994	5	67	0	76	-		-		- 11.60 [0.65,	206.14]	4.35
Schweizer 1994	4	69	9	69		┢			0.47 [0.15,	1.48]	77.79
Overall									1.08 [0.49,	2.40]	
Heterogeneity: I ² = 36.15%	6, H ² = 1.	57									
Test of $\theta_i = \theta_j$: Q(3) = 4.70	, p = 0.20)									
Test of θ = 0: z = 0.20, p =	0.84										
					1/8	1	8	64	-		



Supplementary Figure 46: Meta-analysis of venlafaxine versus placebo on tachycardia

	Ven	lafaxine	PI	acebo				Risk ra	atio	Weight
Study	Events	No events	Events	No events	6			with 95%	% CI	(%)
EudraCT 2004-000562-13	0	127	0	120				0.95 [0.02,	47.27]	6.85
Higuchi 2016 (fixed dose)	4	170	0	92			-	4.78 [0.26,	87.88]	11.78
Higuchi 2016 (flexible dose)	7	173	0	91		-+	-	7.62 [0.44,	132.03]	12.21
Learned 2012	4	129	4	122			<u> </u>	0.95 [0.24,	3.71]	38.60
Lieberman 2008 (225 mg)	5	112	2	123		-+	-	2.67 [0.53,	13.50]	30.56
Overall						-	•	2.03 [0.70,	5.85]	
Heterogeneity: $\tau^2 = 0.27$, $I^2 = 1$	7.99%, H	l ² = 1.22								
Test of $\theta_i = \theta_j$: Q(4) = 2.59, p =	0.63									
Test of $\theta = 0$: $z = 1.31$, $p = 0.19$	9									
					1/32	1/2	8	128		



Supplementary Figure 47: Meta-analysis of venlafaxine versus placebo on urinary frequency

	Ven	lafaxine	PI	acebo					Risk rat	io	Weight
Study	Events	No events	Events	No event	ts				with 95%	CI	(%)
600-B-367-EU (75 mg)	0	83	1	40		_			0.17 [0.01,	4.00]	21.25
600-B-367-EU (150 mg)	0	82	0	42					0.52 [0.01,	25.66]	15.04
Schatzberg 2006	6	96	3	93					1.88 [0.48,	7.32]	63.71
Overall									0.93 [0.18,	4.70]	
Heterogeneity: τ ² = 0.60, I	² = 23.70	%, H ² = 1.31									
Test of $\theta_i = \theta_i$: Q(2) = 2.08	, p = 0.35	;									
Test of θ = 0: z = -0.09, p =	= 0.93										
					1/128	1/16	1/2	4	_		
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Supplementary Figure 48: Meta-analysis of venlafaxine versus placebo on vertigo

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No event	S			with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	1	40				0.99 [0.09, 10.58]	11.39
600-B-367-EU (150 mg)	2	80	1	41			•	1.02 [0.10, 10.97]	11.38
EudraCT 2004-000562-13	9	118	5	115		-		1.70 [0.59, 4.93]	43.14
Guelfi 1995	0	46	1	46				0.34 [0.01, 8.15]	6.58
Higuchi 2016 (fixed dose)	4	170	1	90			-	- 2.09 [0.24, 18.44]	13.32
Higuchi 2016 (flexible dose)	6	174	1	91				3.07 [0.37, 25.09]	14.19
Overall							-	1.52 [0.66, 3.49]	
Heterogeneity: $\tau^2 = 0.12$, $I^2 = 100$	10.59%, H	H ² = 1.12							
Test of $\theta_i = \theta_j$: Q(5) = 1.64, p =	= 0.90								
Test of θ = 0: z = 0.98, p = 0.3	3								
					1/64	1/8	1 8		



Supplementary Figure 49: Meta-analysis of venlafaxine versus placebo on vomiting

	Ven	lafaxine	PI	acebo		Risk ra	atio	Weight
Study	Events	No events	Events	No events	s	with 959	% CI	(%)
600-B-367-EU (75 mg)	2	81	1	40	_	0.99 [0.09,	10.58]	6.32
600-B-367-EU (150 mg)	3	79	1	41		1.54 [0.16,	14.32]	6.90
Alvarez 2012	4	109	1	104		3.72 [0.42,	32.72]	7.15
EudraCT 2004-000562-13	3	124	2	118	—— — ——	1.42 [0.24,	8.34]	9.34
Guelfi 1995	0	46	2	45		0.20 [0.01,	4.14]	4.37
Higuchi 2016 (fixed dose)	5	169	3	89		0.88 [0.22,	3.61]	12.00
Higuchi 2016 (flexible dose)	4	176	4	87		0.51 [0.13,	1.98]	12.39
Lieberman 2008 (225 mg)	3	114	0	125		7.47 [0.39,	143.17]	4.51
Nemeroff 2007	11	89	2	100		5.61 [1.28,	24.67]	11.41
Schatzberg 2006	9	93	2	94		4.24 [0.94,	19.11]	11.21
Sheehan 2009	9	86	4	91	+=-	2.25 [0.72,	7.06]	14.41
Overall					•	1.74 [0.86,	3.49]	
Heterogeneity: $\tau^2 = 0.54$, $I^2 = -$	41.12%, ł	H ² = 1.70						
Test of $\theta_i = \theta_i$: Q(10) = 11.62,	p = 0.31							
Test of θ = 0: z = 1.55, p = 0.1	12							
					1/64 1/4 4 64	1		
Random-effects Sidik-Jonkma	n model							

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Supplementary Figure 50: Meta-analysis of venlafaxine versus placebo on weight loss

	Ven	lafaxine	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No events					with 95%	% CI	(%)
600-B-367-EU (75 mg)	2	81	0	41					2.50 [0.12,	50.91]	26.35
600-B-367-EU (150 mg)	1	81	0	42				_	1.55 [0.06,	37.35]	23.69
Guelfi 1995	2	44	0	47		_			5.11 [0.25,	103.55]	26.42
Schatzberg 2006	1	101	0	96					2.83 [0.12,	68.52]	23.55
Overall									2.78 [0.59,	13.11]	
Heterogeneity: $\tau^2 = 0.02$,	² = 0.64%	5, H ² = 1.01									
Test of $\theta_i = \theta_i$: Q(3) = 0.29	, p = 0.96	;									
Test of θ = 0: z = 1.29, p =	= 0.20										
					1/8	1	8	64	-		

Random-effects Sidik-Jonkman model

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Supplementary Figure 51: Meta-analysis of venlafaxine versus placebo on abnormality of accommodation

	Ven	lafaxine	PI	acebo				Risk ratio We
Study	Events	No events	Events	No events	3		1	with 95% CI (%
600-B-367-EU (75 mg)	0	83	0	41		_		- 0.50 [0.01, 24.76] 9.
600-B-367-EU (150 mg)	2	80	0	42				2.59 [0.13, 52.76] 14.
Cunningham 1994	7	65	3	73		-		2.46 [0.66, 9.16] 60.
Guelfi 1995	2	44	0	47				5.11 [0.25, 103.55] 14.
Overall								2.39 [0.72, 7.99]
Heterogeneity: $\tau^2 = 0.17$,	² = 8.94%	6, H ² = 1.10						
Test of $\theta_i = \theta_i$: Q(3) = 0.87	, p = 0.83	;						
Test of $\theta = 0$: $z = 1.42$, $p =$	= 0.16							
					1/64	1/4	4	64



Supplementary Figure 52: Meta-analysis of venlafaxine versus placebo on pruritis

	Ven	lafaxine	PI	acebo					Risk ra	atio	Weight
Study	Events	No events	Events	No events	S				with 95%	% CI	(%)
600-B-367-EU (75 mg)	2	81	0	41					2.50 [0.12,	50.91]	25.05
600-B-367-EU (150 mg)	1	81	0	42					1.55 [0.06,	37.35]	23.50
Guelfi 1995	2	44	0	47					- 5.11 [0.25,	103.55]	25.09
Schatzberg 2006	0	102	5	91			+		0.09 [0.00,	1.53]	26.37
Overall									1.10 [0.15,	7.89]	
Heterogeneity: $\tau^2 = 1.68$, I	² = 41.43	%, H ² = 1.71									
Test of $\theta_i = \theta_j$: Q(3) = 4.34	, p = 0.23	;									
Test of θ = 0: z = 0.09, p =	0.93										
					1/128	1/8	2	32	-		



Supplementary Figure 53: Meta-analysis of venlafaxine versus placebo on vasodilation





Supplementary Figure 54: Meta-analysis of venlafaxine versus placebo on neck pain

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events	;			with 95% Cl	(%)
600-B-367-EU (75 mg)	0	83	0	41	. <u> </u>	_		0.50 [0.01, 24.76]	26.84
600-B-367-EU (150 mg)	1	81	1	41				0.51 [0.03, 7.99]	53.24
Guelfi 1995	1	45	0	47					19.92
Overall								1.02 [0.19, 5.46]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.0$	0							
Test of $\theta_i = \theta_i$: Q(2) = 0.83	, p = 0.66	;							
Test of θ = 0: z = 0.02, p =	0.98								
					1/64	1/4	4	64	



Supplementary Figure 55: Meta-analysis of venlafaxine versus placebo on pain

	Ven	lafaxine	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No events					with 95%	6 CI	(%)
600-B-367-EU (75 mg)	1	82	1	40		-			0.49 [0.03,	7.70]	30.78
600-B-367-EU (150 mg)	3	79	1	41	-				1.54 [0.16,	14.32]	42.83
Guelfi 1995	2	44	0	47					- 5.11 [0.25,	103.55]	26.39
Overall						-			1.49 [0.28,	7.93]	
Heterogeneity: $\tau^2 = 0.40$, I	² = 18.16 ⁴	%, H ² = 1.22									
Test of $\theta_i = \theta_i$: Q(2) = 1.26	, p = 0.53										
Test of θ = 0: z = 0.47, p =	= 0.64										
					1/16	1/2	4	32	-		



Supplementary Figure 56: Meta-analysis of venlafaxine versus placebo on increased salivation

	Ven	lafaxine	Placebo					Risk ratio	Weight	
Study	Events	No events	Events	No events	3			with 95% CI	(%)	
600-B-367-EU (75 mg)	1	82	0	41	-			- 1.50 [0.06, 36.04]	37.38	
600-B-367-EU (150 mg)	0	82	0	42				0.52 [0.01, 25.66]	25.15	
Guelfi 1995	1	45	0	47				3.06 [0.13, 73.33]	37.47	
Overall								1.50 [0.21, 10.91]		
Heterogeneity: $\tau^2 = 0.11$, I^2	² = 3.53%	b, H ² = 1.04								
Test of $\theta_i = \theta_j$: Q(2) = 0.48,)									
Test of θ = 0: z = 0.40, p =	0.69									
					1/64	1/4	4	64		



Supplementary Figure 57: Meta-analysis of venlafaxine versus placebo on tongue discolouration





Supplementary Figure 58: Meta-analysis of venlafaxine versus placebo on hypochromic anaemia





Supplementary Figure 59: Meta-analysis of venlafaxine versus placebo on hypercholesterolemia

	Ven	lafaxine	Placebo						Risk ratio	Weight	
Study	Events	No events	Events	No events	3				with 95% CI	(%)	
600-B-367-EU (75 mg)	0	83	0	41					0.50 [0.01, 24.76]	21.18	
600-B-367-EU (150 mg)	0	82	0	42					-0.52 [0.01, 25.66]	21.18	
Guelfi 1995	1	45	2	45				_	0.51 [0.05, 5.44]	57.64	
Overall									0.51 [0.08, 3.07]		
Heterogeneity: $\tau^2 = 0.00$,	l ² = 0.00%	6, H ² = 1.00									
Test of $\theta_i = \theta_i$: Q(2) = 0.00, p = 1.00											
Test of $\theta = 0$: z = -0.73, p	= 0.46										
					1/64	1/8	1	8	-		



Supplementary Figure 60: Meta-analysis of venlafaxine versus placebo on bronchitis

	Ven	lafaxine	Placebo					Risk ratio	Weight
Study	Events	No events	Events	No events	3			with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	0	41				2.50 [0.12, 50.91]	39.74
600-B-367-EU (150 mg)	0	82	0	42				0.52 [0.01, 25.66]	24.26
Guelfi 1995	1	45	0	47				3.06 [0.13, 73.33]	36.00
Overall								1.84 [0.26, 13.00]	
Heterogeneity: $\tau^2 = 0.15$, I	² = 4.77%	5, H ² = 1.05							
Test of $\theta_i = \theta_i$: Q(2) = 0.54	Test of $\theta_i = \theta_i$: Q(2) = 0.54, p = 0.76								
Test of θ = 0: z = 0.61, p =	0.54								
					1/64	1/4	4	64	



Supplementary Figure 61: Meta-analysis of venlafaxine versus placebo on pharyngitis

	Ven	lafaxine	Placebo					Risk ratio	Weight
Study	Events	No events	Events	No events				with 95% CI	(%)
600-B-367-EU (75 mg)	4	79	1	40				1.98 [0.23, 17.12]	41.68
600-B-367-EU (150 mg)	3	79	1	41				1.54 [0.16, 14.32]	39.00
Guelfi 1995	1	45	0	47				3.06 [0.13, 73.33]	19.31
Overall								1.95 [0.48, 7.88]	
Heterogeneity: τ ² = 0.00, l ² = 0.30%, H ² = 1.00									
Test of $\theta_i = \theta_i$: Q(2) = 0.12	ļ.								
Test of θ = 0: z = 0.94, p =	= 0.35								
					1/4 1	4	16	64	



Supplementary Figure 62: Meta-analysis of venlafaxine versus placebo on urinary tract infection





Supplementary Figure 63: Meta-analysis of venlafaxine versus placebo on urine abnormality





Supplementary Figure 64: Meta-analysis of venlafaxine versus placebo on taste alteration





Supplementary Figure 65: Meta-analysis of venlafaxine versus placebo on HDRS-17

	\	/enlafaxi	ne		Placeb	0		Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Higuchi 2016 (fixed dose)	174	-10.76	6.6	92	-9.25	6.51		-1.51 [-3.17, 0.15]	33.45
Higuchi 2016 (flexible dose)	177	-10.37	6.52	92	-9.25	6.51		-1.12 [-2.76, 0.52]	34.17
Learned 2012 (study 1)	133	-14.9	6.53	126	-13	7.32		-1.90 [-3.59, -0.21]	32.38
Overall								-1.50 [-2.48, -0.53]	
Heterogeneity: $\tau^2 = 0.02$, $I^2 = 2$	2.54%	, H ² = 1.	03						
Test of $\theta_i = \theta_i$: Q(2) = 0.42, p =	= 0.81								
Test of $\theta = 0$: $z = -3.03$, $p = 0$.	00								
						-	4 -2	0	



Supplementary Figure 66: Meta-analysis of venlafaxine versus placebo on suicidal ideation

	Ven	lafaxine	Placebo						Risk ratio	v	/eight
Study	Events	No events	Events	No events					with 95% CI		(%)
600-B-367-EU (150 mg)	1	81	0	42					-1.55 [0.06, 37.3	85]	1.76
600-B-367-EU (75 mg)	0	84	0	41			-		0.49 [0.01, 24.4	7]	1.17
Hewett 2010	0	198	1	186		-			0.31 [0.01, 7.6	68]	1.74
Higuchi 2016 (fixed dose)	41	132	19	72			.		1.14 [0.70, 1.8	84] 4	4.19
Higuchi 2016 (flexible dose)	47	133	20	72			-		1.20 [0.76, 1.9	90] 4	6.55
Sheehan 2009	2	93	2	93			+	_	1.00 [0.14, 6.9	95]	4.59
Overall							•		1.13 [0.74, 1.7	'3]	
Heterogeneity: $\tau^2 = 0.05$, $I^2 = 1$	I5.80%, H	l ² = 1.19									
Test of $\theta_i = \theta_i$: Q(5) = 0.90, p =	0.97										
Test of $\theta = 0$: $z = 0.56$, $p = 0.5$	8										
					1/64	1/8	1	8	_		


Supplementary Figure 67: Meta-analysis of venlafaxine versus placebo on MADRS

	```	/enlafax	ine		Placeb	0			Mean diff.	Weight
Study	N	Mean	SD	N	Mean	SD		-	with 95% CI	(%)
600-B-367-EU (75 mg)	53	8.2	9.5	27	9.4	7.3		<b> </b>	-1.20 [ -5.29, 2.89]	6.02
600-B-367-EU (150 mg)	48	7.6	9	26	9.4	7.3		+-	-1.80 [ -5.83, 2.23]	6.13
Alvarez 2012	95	-24.2	8.8	88	-16.6	9.4			-7.60 [ -10.24, -4.96]	9.44
Guelfi 1995	36	13.6	10.5	23	19.1	13.2		╞	-5.50 [ -11.58, 0.58]	3.45
Hewett 2010	193	-17	10.56	186	-13.2	10.64			-3.80 [ -5.93, -1.67]	10.96
Higuchi 2016 (fixed dose)	172	-15.3	10.1	91	-12.41	10.12		-	-2.89 [ -5.46, -0.32]	9.64
Higuchi 2016 (flexible dose)	176	-15.05	10.08	91	-12.41	10.12			-2.64 [ -5.19, -0.09]	9.68
Khan 1991 (75 mg)	23	21.3	9.7	9	25.3	11.7			-4.00 [ -11.92, 3.92]	2.23
Khan 1991 (225 mg)	22	18.4	11.5	8	25.3	11.7		-	-6.90 [ -16.25, 2.45]	1.67
Khan 1991 (375 mg)	22	16.4	9.2	9	25.3	11.7			-8.90 [ -16.62, -1.18]	2.33
Mendels 1993 (25 mg)	78	-11.53	9.82	25	-10.53	8.98		-	-1.00 [ -5.34, 3.34]	5.59
Mendels 1993 (50 - 75 mg)	72	-12.53	9.6	25	-10.53	8.98		+	-2.00 [ -6.30, 2.30]	5.66
Mendels 1993 (150 - 200 mg)	77	-14.8	9.64	25	-10.53	8.98		+	-4.27 [ -8.55, 0.01]	5.69
Sheehan 2009	53	13.53	10.31	55	18.98	11.78			-5.45 [ -9.63, -1.27]	5.86
Thase 1997	91	15.2	1.14	100	20.6	1.08			-5.40 [ -5.71, -5.09]	15.67
Overall							٠		-4.03 [ -5.30, -2.75]	
Heterogeneity: $\tau^2 = 2.68$ , $I^2 = 60$	.01%,	$H^2 = 2.5$	60							
Test of $\theta_i = \theta_j$ : Q(14) = 26.70, p	= 0.02									
Test of θ = 0: z = -6.19, p = 0.00	)									
							-15 -10 -5	0	5	

Random-effects Sidik-Jonkman model



# Supplementary Figure 68: Meta-analysis of venlafaxine versus placebo on suicides or suicide attempts (sensitivity analysis)

	Ven	lafaxine	Placebo			Risk ratio	Weight
Study	Events	No events	Events	No events	3	with 95% CI	(%)
0600B 1-384-US/EU/CA	2	178	3	65		0.25 [ 0.04, 1.47]	29.49
600-B-367-EU	1	165	1	82		0.50 [ 0.03, 7.89]	14.51
Cunningham 1994	0	72	1	75		0.35 [ 0.01, 8.49]	11.28
Hewett 2009	1	186	0	197			11.22
Higuchi 2016	1	353	1	182		0.52 [ 0.03, 8.22]	14.45
Schweizer 1994	1	72	0	78		3.20 [ 0.13, 77.39]	11.28
Sheehan 2009	0	95	0	95	·•	1.00 [ 0.02, 49.88]	7.77
Overall					-	0.63 [ 0.20, 1.96]	
Heterogeneity: $\tau^2 = 0.32$ , l	² = 13.47 ⁴	%, H ² = 1.16					
Test of $\theta_i = \theta_j$ : Q(6) = 3.23	p = 0.78						
Test of $\theta$ = 0: z = -0.80, p =	= 0.43						
					1/64 1/4 4	64	
Random-effects Sidik-Jonk	man mod	el					

# Supplementary Figure 69: Meta-analysis of venlafaxine versus placebo on serious adverse events (sensitivity analysis)

Objection	Ven	lafaxine	Pl	acebo			Risk ra	tio	Weight
Study	Events	No events	Events	No events	S		with 95%	6 CI	(%)
0600B 1-384-US/EU/CA	1	179	3	65		-	0.13 [ 0.01,	1.19]	6.68
600-B-367-EU	10	155	4	79			1.26 [ 0.41,	3.89]	8.17
Alvarez 2012	14	99	2	103			6.50 [ 1.51,	27.94]	3.18
Claghorn 1990	2	77	0	80			5.06 [ 0.25,	103.80]	0.76
Cunningham 1994	4	68	4	72		<b></b>	1.06 [ 0.27,	4.06]	5.97
Cunningham 1997 (IR)	6	90	2	48			1.56 [ 0.33,	7.46]	4.04
Cunningham 1997 (XR)	10	87	2	48			2.58 [ 0.59,	11.31]	4.05
EudraCT 2004-000562-13	6	121	2	118			2.83 [ 0.58,	13.77]	3.16
EudraCT 2007-007025-51	0	7	0	7		<b></b>	1.00 [ 0.02,	44.50]	0.77
Guelfi 1995	4	42	0	47			9.19 [ 0.51,	166.04]	0.76
Hewett 2009	6	181	9	188			0.70 [ 0.25,	1.93]	13.45
Hewett 2010	9	189	2	185			4.25 [ 0.93,	19.41]	3.16
Higuchi 2016	7	347	1	182			3.62 [ 0.45,	29.19]	2.02
Learned 2012 (study 1)	3	130	5	121			0.57 [ 0.14,	2.33]	7.88
Lieberman 2008 (225 mg)	18	99	1	122			18.92 [ 2.57,	139.50]	1.50
Mendels 1993	13	221	1	77			4.33 [ 0.58,	32.59]	2.30
Nemeroff 2007	10	90	1	101			10.20 [ 1.33,	78.21]	1.52
Rudolph 1998	40	226	2	90			6.92 [ 1.71,	28.06]	4.56
Rudolph 1999	9	91	4	94	-		2.21 [ 0.70,	6.92]	6.20
Schatzberg 2006	9	93	1	95			8.47 [ 1.09,	65.61]	1.58
Schweizer 1994	3	70	1	77			3.21 [ 0.34,	30.13]	1.48
Sheehan 2009	12	83	4	91			3.00 [ 1.00,	8.97]	6.14
Silverstone 1999	13	115	3	116			4.03 [ 1.18,	13.79]	4.77
Thase 1997	15	80	4	98			4.03 [ 1.39,	11.70]	5.92
Overall						٠	2.89 [ 2.17,	3.83]	
Heterogeneity: I ² = 35.91%, H	H ² = 1.56								
Test of $\theta_i = \theta_j$ : Q(23) = 35.89,	, p = 0.04	ļ							
Test of $\theta = 0$ : $z = 7.32$ , $p = 0$ .	.00						_		
					1/64 1/4	4 64			
Fixed-effects Mantel-Haensze	el model								

# Supplementary Figure 70: Meta-analysis of venlafaxine versus placebo on sexual dysfunction (sensitivity analysis)

	Ven	lafaxine	Pl	acebo				Risk ra	tio	Weight
Study	Events	No events	Events	No events	3			with 95%	5 CI	(%)
600-B-367-EU	2	52	0	26				2.45 [ 0.12,	49.36]	8.35
Alvarez 2012	14	99	2	103			-	6.50 [ 1.51,	27.94]	25.80
Cunningham 1997 (IR)	2	29	0	20				3.28 [ 0.17,	64.99]	7.51
Cunningham 1997 (XR)	10	27	0	21	-			12.16 [ 0.75,	197.55]	7.88
EudraCT 2004-000562-13	2	33	0	40				5.69 [ 0.28,	114.74]	5.82
Lieberman 2008 (225 mg)	4	32	1	44	_			5.00 [ 0.58,	42.80]	11.06
Mendels 1993	11	223	0	78				7.73 [ 0.46,	129.71]	9.31
Schatzberg 2006	9	93	1	95				8.47 [ 1.09,	65.61]	12.82
Thase 1997	8	27	1	40				9.37 [ 1.23,	71.31]	11.46
Overall						-		6.85 [ 3.22,	14.58]	
Heterogeneity: I ² = 0.00%, H	² = 1.00									
Test of $\theta_i = \theta_i$ : Q(8) = 1.09, p	= 1.00									
Test of $\theta = 0$ : $z = 5.00$ , $p = 0$ .	.00									
					1/8	1 8	64			



# Supplementary Figure 71: Meta-analysis of venlafaxine versus placebo on anorexia (sensitivity analysis)

	Ven	lafaxine	Placebo			Risk ra	Risk ratio	
Study	Events	No events	Events	No events		with 95%	6 CI	(%)
600-B-367-EU	2	163	2	81		0.50 [ 0.07,	3.51]	9.86
Cunningham 1997 (IR)	6	90	2	48		1.56 [ 0.33,	7.46]	9.74
Cunningham 1997 (XR)	10	87	2	48		2.58 [ 0.59,	11.31]	9.78
EudraCT 2004-000562-13	6	121	2	118		2.83 [ 0.58,	13.77]	7.62
Hewett 2010	9	189	2	185		4.25 [ 0.93,	19.41]	7.62
Lieberman 2008 (225 mg)	18	99	1	122	<b>_</b>	- 18.92 [ 2.57,	139.50]	3.61
Rudolph 1998	40	226	2	90		6.92 [ 1.71,	28.06]	11.01
Rudolph 1999	9	91	4	94	<b>⊢∎</b>	2.21 [ 0.70,	6.92]	14.96
Silverstone 1999	13	115	3	116		4.03 [ 1.18,	13.79]	11.52
Thase 1997	15	80	4	98		4.03 [ 1.39,	11.70]	14.29
Overall					•	3.81 [ 2.47,	5.86]	
Heterogeneity: I ² = 9.16%, H	$f^2 = 1.10$							
Test of $\theta_i = \theta_j$ : Q(9) = 9.91, p	o = 0.36							
Test of $\theta$ = 0: z = 6.07, p = 0	0.00							
					1/8 1 8 64	_		

Fixed-effects Mantel-Haenszel model

# Supplementary Figure 72: Meta-analysis of venlafaxine versus placebo on anxiety (sensitivity analysis)

	Ven	lafaxine	Placebo						Risk ratio		Weight
Study	Events	No events	Events	No events	6				with 95%	5 CI	(%)
600-B-367-EU	2	163	2	81	-	-			0.50 [ 0.07,	3.51]	9.04
EudraCT 2004-000562-13	0	127	1	119		-			0.32 [ 0.01,	7.66]	5.24
Hewett 2009	6	181	9	188		_	_		0.70 [ 0.25,	1.93]	29.78
Learned 2012	3	130	5	121					0.57 [ 0.14,	2.33]	17.45
Mendels 1993	13	221	1	77		-			4.33 [ 0.58,	32.59]	5.10
Nemeroff 2007	10	90	1	101					10.20 [ 1.33,	78.21]	3.36
Rudolph 1998	10	57	0	26		-			8.34 [ 0.51,	137.36]	2.43
Schatzberg 2006	2	100	4	92		-			0.47 [ 0.09,	2.51]	14.00
Sheehan 2009	12	83	4	91					3.00 [ 1.00,	8.97]	13.59
Overall							•		1.61 [ 1.01,	2.56]	
Heterogeneity: I ² = 49.27%,	H ² = 1.97										
Test of $\theta_i = \theta_j$ : Q(8) = 15.77,	p = 0.05										
Test of $\theta$ = 0: z = 2.01, p = 0	.04										
					1/64	1/4	4	64	-		



#### Supplementary Figure 73: Meta-analysis of venlafaxine versus placebo on worsening of depression (sensitivity analysis)

	Ven	lafaxine	Placebo					Risk ratio Weight
Study	Events	No events	Events No events					with 95% CI (%)
600-B-367-EU	4	161	0	83			_	4.55 [ 0.25, 83.60] 7.76
Cunningham 1994	0	72	1	75		_		0.35 [ 0.01, 8.49] 17.05
Hewett 2009	0	187	3	194				0.15[0.01, 2.89] 39.82
Hewett 2010	1	197	1	186	-		———	0.94 [ 0.06, 14.99] 12.01
Sheehan 2009	1	94	2	93	-			0.50 [ 0.05, 5.42] 23.36
Overall								0.70 [ 0.24, 2.05]
Heterogeneity: $I^2 = 0$	.00%, H ²	= 1.00						
Test of $\theta_i = \theta_j$ : Q(4) =	= 2.93, p =	= 0.57						
Test of $\theta = 0$ : $z = -0.0$	65, p = 0.	52						
					1/64	1/4	4	64



# Supplementary Figure 74: Meta-analysis of venlafaxine versus placebo on hypertension (sensitivity analysis)

	Ven	lafaxine	Placebo					Risk ra	atio	Weight
Study	Events	No events	Events	No events				with 95°	% CI	(%)
600-B-367-EU	6	159	3	80				1.01 [ 0.26,	3.92]	80.27
Cunningham 1994	3	69	0	76		-		7.38 [ 0.39,	140.48]	9.79
Guelfi 1995	1	45	0	47		-		- 3.06 [ 0.13,	73.33]	9.95
Overall					-			1.83 [ 0.63,	5.37]	
Heterogeneity: I ² = 0	.00%, H ²	= 1.00								
Test of $\theta_i = \theta_j$ : Q(2) =	= 1.71, p	= 0.43								
Test of $\theta = 0$ : $z = 1.1$	1, p = 0.2	27								
					1/4	2	16	128		



# Supplementary Figure 75: Meta-analysis of venlafaxine versus placebo on hypotension (sensitivity analysis)





#### Supplementary Figure 76: Meta-analysis of venlafaxine versus placebo on discontinuation symptoms (sensitivity analysis)





# Supplementary Figure 77: Meta-analysis of venlafaxine versus placebo on fall (sensitivity analysis)





#### Supplementary Figure 78: Meta-analysis of venlafaxine versus placebo on intentional overdose (sensitivity analysis)



Random-effects Sidik-Jonkman model



# Supplementary Figure 79: Meta-analysis of venlafaxine versus placebo on QTc (sensitivity analysis)





#### Supplementary Figure 80: Meta-analysis of venlafaxine versus placebo on syncope (sensitivity analysis)



Random-effects Sidik-Jonkman model



#### Supplementary Figure 81: Meta-analysis of venlafaxine versus placebo on nonserious adverse events (sensitivity analysis)

	Ven	lafaxine	Р	lacebo	Risk ratio	Weight
Study	Events	No events	Events	No events	with 95% CI	(%)
600-B-367-EU (75 mg)	56	27	25	16	1.11 [ 0.83, 1.47]	2.79
600-B-367-EU (150 mg)	53	29	25	17		2.76
Alvarez 2012	85	28	64	41	1.23 [ 1.02, 1.49]	5.54
Claghorn 1990	72	7	59	21	1.24 [ 1.07, 1.43]	4.89
Cunningham 1994	71	1	56	20	1.34 [ 1.17, 1.53]	4.55
Cunningham 1997 (IR)	43	53	5	45	4.48 [ 1.89, 10.59	0.55
Cunningham 1997 (XR)	44	53	5	45	4.54 [ 1.92, 10.72	0.55
EudraCT 2004-000562-13	92	35	77	43	1.13 [ 0.95, 1.34	6.61
EudraCT 2007-007025-51	4	3	4	3	1.00 [ 0.40, 2.48]	0.33
Guelfi 1995	36	10	22	25		1.82
Hewett 2009	93	94	95	102	1.03 [ 0.84, 1.26]	7.72
Hewett 2010	133	65	112	75	1.12 [ 0.96, 1.31]	9.61
Higuchi 2016 (fixed dose)	131	43	61	30	1.12 [ 0.95, 1.33]	6.68
Higuchi 2016 (flexible dose)	147	33	62	30	1.21 [ 1.03, 1.42]	6.85
Khan 1991 (75 mg)	23	0	5	3	1.60 [ 0.95, 2.71]	0.67
Khan 1991 (225 mg)	22	0	6	3	1.51 [ 0.95, 2.38]	0.76
Khan 1991 (375 mg)	21	1	6	3	1.43 [ 0.89, 2.29]	0.71
Khan 1998 (75 mg)	24	72	2	31	4.12 [ 1.03, 16.52]	0.25
Khan 1998 (150 mg)	19	77	2	31	3.27 [ 0.80, 13.27]	0.25
Khan 1998 (200 mg)	26	68	2	30	4.43 [ 1.11, 17.61]	0.25
Learned 2012 (study 1)	94	39	77	49	1.16 [ 0.97, 1.38]	6.60
Lieberman 2008 (225 mg)	27	90	16	109	1.80 [ 1.03, 3.17]	1.29
Luthringer 1996	5	7	6	6	0.83 [ 0.35, 2.00]	0.50
Mendels 1993 (25 mg)	20	59	7	19	0.94 [ 0.45, 1.97]	0.88
Mendels 1993 (50 - 75 mg)	19	57	7	19	0.93 [ 0.44, 1.95]	0.87
Mendels 1993 (150 - 200 mg)	17	52	7	19	0.92 [ 0.43, 1.95]	0.85
Nemeroff 2007	40	60	8	94	5.10 [ 2.51, 10.34	0.66
Rudolph 1999	36	64	14	84	2.52 [ 1.45, 4.37]	1.18
Schatzberg 2006	94	8	83	13	1.07 [ 0.97, 1.17]	7.13
Schweizer 1991 (75, 225 and 375 mg)	24	20	4	12	2.18 [ 0.90, 5.32]	0.49
Schweizer 1994	63	10	64	14	1.05 [ 0.92, 1.21]	5.16
Sheehan 2009	87	8	85	10	1.02 [ 0.93, 1.12]	7.09
Silverstone 1999	49	79	20	99	2.28 [ 1.44, 3.59	1.73
Thase 1997	34	61	18	84	2.03 [ 1.23, 3.34	1.45
Overall					1.29 [ 1.23, 1.35]	l
Heterogeneity: I ² = 74.17%, H ² = 3.87						
Test of $\theta_i = \theta_i$ : Q(33) = 127.76, p = 0.00						
Test of θ = 0: z = 10.63, p = 0.00						
					1/2 1 2 4 8 16	
The distance Manufal II. and a large dat						

# Supplementary Figure 82: Meta-analysis of venlafaxine versus placebo on nausea (sensitivity analysis)

Graph

17/03/2024, 18.33

Study	Ven Events	lafaxine No events	PI Events	acebo No events	3		Risk rat with 95%	io Cl	Weight (%)
600-B-367-EU (75 ma)	15	68	3	38			2.47 [ 0.76.	8.051	1.34
600-B-367-EU (150 mg)	22	60	2	40			5.63 [ 1.39.	22.821	0.88
Alvarez 2012	38	75	10	95		-	3.53 [ 1.85.	6.721	3.45
Claphorn 1990	35	44	7	73			5.06 [ 2.39.	10.711	2.31
Cunningham 1994	32	40	4	72			8.44 [ 3.14.	22.681	1.29
Cunningham 1997 (IR)	43	53	5	45			4.48 [ 1.89.	10.591	2.19
Cunningham 1997 (XR)	44	53	5	45			4.54 [ 1.92,	10.72]	2.19
EudraCT 2004-000562-13	27	100	14	106			1.82 [ 1.00,	3.30]	4.79
EudraCT 2007-007025-51	0	7	0	7			1.00 [ 0.02,	44.50]	0.17
Guelfi 1995	8	38	1	46			8.17 [ 1.06,	62.78]	0.33
Hewett 2009	36	151	21	176		-	1.81 [ 1.10,	2.98]	6.80
Hewett 2010	53	145	16	171			3.13 [ 1.86,	5.27]	5.47
Higuchi 2016 (fixed dose)	39	135	12	80		-	1.72 [ 0.95,	3.12]	5.22
Higuchi 2016 (flexible dose)	53	127	12	79			2.23 [ 1.26,	3.96]	5.30
Khan 1998 (75 mg)	8	88	1	32			2.75 [ 0.36,	21.17]	0.49
Khan 1998 (150 mg)	7	89	0	33		-	5.26 [ 0.31,	89.63]	0.25
Khan 1998 (200 mg)	16	78	0	32	-	-	11.46 [ 0.71,	185.79]	0.25
Learned 2012	29	104	14	112			1.96 [ 1.09,	3.54]	4.78
Lieberman 2008 (225 mg)	34	83	16	109			2.27 [ 1.33,	3.89]	5.14
Mendels 1993 (25 mg)	22	57	з	23	-		2.41 [ 0.79,	7.41]	1.50
Mendels 1993 (50 - 75 mg)	19	57	2	24	1.1		3.25 [ 0.81,	13.01]	0.99
Mendels 1993 (150 - 200 mg)	23	56	2	24			3.78 [ 0.96,	14.97]	1.00
Nemeroff 2007	40	60	8	94			5.10 [ 2.51,	10.34]	2.63
Rudolph 1998 (75 mg)	29	60	4	27			2.53 [ 0.96,	6.61]	1.97
Rudolph 1998 (225 mg)	34	55	4	27			2.96 [ 1.14,	7.67]	1.97
Rudolph 1998 (375 mg)	51	37	5	25			3.48 [ 1.53,	7.89]	2.48
Rudolph 1999	36	64	14	84			2.52 [ 1.45,	4.37]	4.70
Schatzberg 2006	46	56	13	83			3.33 [ 1.92,	5.77]	4.45
Schweizer 1994	20	53	11	67			1.94 [ 1.00,	3.77]	3.54
Sheehan 2009	36	59	15	80			2.40 [ 1.41,	4.08]	4.99
Silverstone 1999	52	76	33	86			1.46 [ 1.02,	2.10]	11.37
Thase 1997	34	61	18	84			2.03 [ 1.23,	3.34]	5.77
Overall							2.68 [ 2.37,	3.04]	
Heterogeneity: I ² = 25.23%, H ² =	= 1.34								
Test of $\theta_i = \theta_j$ : Q(31) = 41.46, p	= 0.10								
Test of $\theta = 0$ : $z = 15.54$ , $p = 0.00$	)						_		
					1/32 1/2	8 1	28		
Fixed-effects Mantel–Haenszel m	odel								

# Supplementary Figure 83: Meta-analysis of venlafaxine versus placebo on dry mouth (sensitivity analysis)

#### Graph

17/03/2024, 17.54

Study	Ven Events	lafaxine	PI	acebo		Risk ratio	Weight
	Eventa		Lvoina	140 6461113		with 35% Of	(/0)
600-B-367-EU (75 mg)	5	78	0	41		5.50 [ 0.31, 97.13]	0.37
600-B-367-EU (150 mg)	8	74	0	42	-	- 8.81 [ 0.52, 148.99]	0.36
Alvarez 2012	19	94	7	98		2.52 [ 1.11, 5.75]	4.00
Claghorn 1990	19	60	12	68		1.60 [ 0.84, 3.08]	6.57
Cunningham 1994	21	51	5	71		4.43 [ 1.77, 11.13]	2.68
Cunningham 1997 (IR)	21	75	4	46		2.73 [ 0.99, 7.53]	2.90
Cunningham 1997 (XR)	16	81	4	46		2.06 [ 0.73, 5.84]	2.91
EudraCT 2004-000562-13	17	110	1	119		16.06 [ 2.17, 118.84]	0.57
EudraCT 2007-007025-51	1	6	0	7		3.00 [ 0.14, 63.15]	0.28
Guelfi 1995	3	43	3	44		1.02 [ 0.22, 4.80]	1.64
Hewett 2009	13	174	11	186		1.25 [ 0.57, 2.71]	5.91
Hewett 2010	35	163	13	174		2.54 [ 1.39, 4.65]	7.37
Higuchi 2016 (fixed dose)	5	169	1	90		2.61 [ 0.31, 22.05]	0.72
Higuchi 2016 (flexible dose)	7	173	0	92	-	7.71 [ 0.45, 133.48]	0.36
Learned 2012	12	121	5	121		2.27 [ 0.82, 6.27]	2.83
Lieberman 2008 (225 mg)	30	87	9	116		3.56 [ 1.77, 7.18]	4.80
Mendels 1993 (25 mg)	14	65	4	22		1.15 [ 0.42, 3.19]	3.32
Mendels 1993 (50 - 75 mg)	16	60	3	23		1.82 [ 0.58, 5.76]	2.46
Mendels 1993 (150 - 200 mg)	23	56	3	23		2.52 [ 0.82, 7.72]	2.49
Nemeroff 2007	24	76	15	87		1.63 [ 0.91, 2.92]	8.19
Rudolph 1998 (75 mg)	16	73	4	27	<b>_</b>	1.39 [ 0.50, 3.85]	3.27
Rudolph 1998 (225 mg)	19	70	4	27		1.65 [ 0.61, 4.49]	3.27
Rudolph 1998 (375 mg)	17	71	4	26		1.45 [ 0.53, 3.97]	3.29
Schatzberg 2006	23	79	14	82		1.55 [ 0.85, 2.83]	7.95
Schweizer 1994	14	59	7	71		2.14 [ 0.91, 5.00]	3.73
Sheehan 2009	36	59	9	86		4.00 [ 2.04, 7.84]	4.96
Silverstone 1999	30	98	14	105		1.99 [ 1.11, 3.57]	8.00
Thase 1997	17	78	9	93		2.03 [ 0.95, 4.33]	4.79
Overall					•	2.26 [ 1.91, 2.67]	
Heterogeneity: I2 = 0.00%, H2 =	1.00						
Test of $\theta_i = \theta_i$ : Q(27) = 23.70, p	= 0.65						
Test of $\theta = 0$ : z = 9.60, p = 0.00							
					1/4 2 16 12	28	
Fixed-effects Mantel-Haenszel n	nodel						

# Supplementary Figure 84: Meta-analysis of venlafaxine versus placebo on dizziness (sensitivity analysis)

Graph

17/03/2024, 18.34

Study	Ven Events	lafaxine No events	PI Events	acebo No events		Risk ratio with 95% Cl	Weight (%)
600-B-367-EU (75 mg)	15	68	2	39		3.70 [ 0.89, 15.44]	1.88
600-B-367-EU (150 mg)	8	74	2	40		2.05 [ 0.46, 9.22]	1.85
Alvarez 2012	14	99	8	97		1.63 [ 0.71, 3.72]	5.81
Claghorn 1990	15	64	5	75		3.04 [ 1.16, 7.96]	3.48
Cunningham 1994	12	60	4	72		3.17 [ 1.07, 9.37]	2.73
Cunningham 1997 (IR)	34	62	3	47		5.90 [ 1.91, 18.27]	2.77
Cunningham 1997 (XR)	28	69	з	47		4.81 [ 1.54, 15.05]	2.78
EudraCT 2004-000562-13	6	121	7	113		0.81 [ 0.28, 2.34]	5.05
Guelfi 1995	4	42	1	46		4.09 [ 0.47, 35.20]	0.69
Hewett 2009	9	178	14	183		0.68 [ 0.30, 1.53]	9.56
Hewett 2010	27	171	11	176		2.32 [ 1.18, 4.54]	7.93
Higuchi 2016 (fixed dose)	10	164	2	90		2.64 [ 0.59, 11.81]	1.83
Higuchi 2016 (flexible dose)	18	162	3	88		3.03 [ 0.92, 10.03]	2.79
Khan 1998 (75 mg)	5	91	1	32		1.72 [ 0.21, 14.18]	1.04
Khan 1998 (150 mg)	2	94	0	33		1.75 [ 0.09, 35.60]	0.52
Khan 1998 (200 mg)	6	88	0	32		4.52 [ 0.26, 77.99]	0.52
Learned 2012	15	118	11	115	-	1.29 [ 0.62, 2.70]	7.92
Mendels 1993 (25 mg)	7	72	3	23		0.77 [ 0.21, 2.76]	3.16
Mendels 1993 (50 - 75 mg)	17	59	2	24		2.91 [ 0.72, 11.74]	2.09
Mendels 1993 (150 - 200 mg)	12	67	2	24		1.97 [ 0.47, 8.25]	2.11
Nemeroff 2007	13	87	3	99		4.42 [ 1.30, 15.04]	2.08
Rudolph 1998 (75 mg)	17	72	1	30		5.92 [ 0.82, 42.67]	1.04
Rudolph 1998 (225 mg)	20	69	1	30		6.97 [ 0.98, 49.77]	1.04
Rudolph 1998 (375 mg)	21	67	2	28		3.58 [ 0.89, 14.37]	2.09
Rudolph 1999	26	74	7	91		3.64 [ 1.66, 7.99]	4.96
Schatzberg 2006	17	85	5	91		3.20 [ 1.23, 8.34]	3.61
Schweizer 1994	12	61	3	75		4.27 [ 1.26, 14.54]	2.03
Sheehan 2009	15	80	3	92		5.00 [ 1.50, 16.71]	2.10
Silverstone 1999	49	79	20	99		2.28 [ 1.44, 3.59]	14.53
Overall					•	2.54 [ 2.10, 3.08]	
Heterogeneity: I2 = 15.23%, H2	= 1.18						
Test of $\theta_i = \theta_i$ : Q(28) = 33.03, p	= 0.23						
Test of $\theta$ = 0: z = 9.57, p = 0.00						_	
					1/8 1 8	64	
Fixed-effects Mantel-Haenszel n	nodel						



# Supplementary Figure 85: Meta-analysis of venlafaxine versus placebo on sweating (sensitivity analysis)

	Ven	lafaxine	P	acebo			Risk ratio	Weight
Study	Events	No events	Events	No events	i		with 95% CI	(%)
600-B-367-EU (75 mg)	8	75	1	40	-		3.95 [ 0.51, 30.54]	2.02
600-B-367-EU (150 mg)	12	70	0	42			12.95 [ 0.79, 213.54]	0.99
Alvarez 2012	17	96	2	103			7.90 [ 1.87, 33.37]	3.12
Claghorn 1990	8	71	1	79			8.10 [ 1.04, 63.28]	1.50
Cunningham 1994	9	63	1	75			9.50 [ 1.23, 73.11]	1.47
Cunningham 1997 (IR)	13	83	1	49			6.77 [ 0.91, 50.28]	1.98
Cunningham 1997 (XR)	18	79	2	48			4.64 [ 1.12, 19.20]	3.97
EudraCT 2004-000562-13	12	115	4	116			2.83 [ 0.94, 8.55	6.19
Guelfi 1995	7	39	1	46			7.15 [ 0.92, 55.86]	1.49
Hewett 2009	15	172	7	190			2.26 [ 0.94, 5.41]	10.27
Hewett 2010	16	182	7	180			2.16[0.91, 5.13]	10.84
Higuchi 2016 (fixed dose)	3	171	1	91		- <b> </b>	1.59 [ 0.17, 15.03]	1.97
Higuchi 2016 (flexible dose)	15	165	1	90		<b></b>	7.58 [ 1.02, 56.51]	2.00
Learned 2012	15	118	3	123			4.74 [ 1.40, 15.97	4.64
Lieberman 2008 (225 mg)	21	96	6	119			3.74 [ 1.56, 8.94	8.74
Mendels 1993 (25 mg)	2	77	0	26			1.69 [ 0.08, 34.06	1.13
Mendels 1993 (50 - 75 mg)	4	72	0	26			3.16 [ 0.18, 56.71]	1.11
Mendels 1993 (150 - 200 mg)	17	62	0	26			- 11.81 [ 0.73, 189.85]	1.13
Nemeroff 2007	14	86	2	100			7.14 [ 1.67, 30.61]	2.98
Rudolph 1999	10	90	3	95			3.27 [ 0.93, 11.51]	4.56
Schatzberg 2006	11	91	1	95			10.35 [ 1.36, 78.67]	1.55
Schweizer 1994	7	66	0	78			- 16.01 [ 0.93, 275.48]	0.73
Silverstone 1999	36	92	12	107			2.79 [ 1.52, 5.10]	18.73
Thase 1997	13	82	4	98			3.49 [ 1.18, 10.33]	5.81
Schweizer 1991	11	33	0	16	-		8.69 [ 0.54, 139.48]	1.09
Overall						•	4.16 [ 3.18, 5.44]	
Heterogeneity: I ² = 0.00%, H ² =	1.00							
Test of $\theta_i = \theta_i$ : Q(24) = 13.92, p	= 0.95							
Test of $\theta = 0$ : $z = 10.41$ , $p = 0.0$	0							
					1/8	1 8 64	_	
Fixed-effects Mantel–Haenszel r	nodel							

# Supplementary Figure 86: Meta-analysis of venlafaxine versus placebo on somnolence (sensitivity analysis)

	Ven	lafaxine	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
600-B-367-EU (75 mg)	6	77	1	40		2.96 [ 0.37, 23.81]	0.94
600-B-367-EU (150 mg)	7	75	1	41		3.59 [ 0.46, 28.19]	0.93
Claghorn 1990	28	51	11	69		2.58 [ 1.38, 4.81]	7.71
Cunningham 1994	31	41	9	67		3.64 [ 1.86, 7.09]	6.18
Cunningham 1997 (IR)	23	73	4	46	<b>—</b>	2.99 [ 1.10, 8.18]	3.71
Cunningham 1997 (XR)	20	77	5	45	- <b>-</b>	2.06 [ 0.82, 5.17]	4.65
EudraCT 2004-000562-13	12	115	3	117	<b>_</b>	3.78 [ 1.09, 13.06]	2.18
Guelfi 1995	1	45	0	47		- 3.06 [ 0.13, 73.33]	0.35
Hewett 2010	9	189	9	178		0.94 [ 0.38, 2.33]	6.53
Higuchi 2016 (fixed dose)	21	153	7	85		1.59 [ 0.70, 3.59]	6.46
Higuchi 2016 (flexible dose)	31	149	8	83		1.96 [ 0.94, 4.09]	7.49
Khan 1998 (75 mg)	7	89	0	33			0.52
Khan 1998 (150 mg)	4	92	0	33		- 3.15 [ 0.17, 57.08]	0.52
Khan 1998 (200 mg)	4	90	0	32		3.13 [ 0.17, 56.52]	0.52
Learned 2012	7	126	3	123		2.21 [ 0.58, 8.36]	2.17
Lieberman 2008 (225 mg)	22	95	13	112		1.81 [ 0.96, 3.42]	8.86
Mendels 1993 (25 mg)	15	64	3	23		1.65 [ 0.52, 5.24]	3.18
Mendels 1993 (50 - 75 mg)	13	63	3	23		1.48 [ 0.46, 4.79]	3.15
Mendels 1993 (150 - 200 mg)	22	57	3	23		2.41 [ 0.79, 7.41]	3.18
Rudolph 1998 (75 mg)	15	74	1	30		5.22 [ 0.72, 37.94]	1.05
Rudolph 1998 (225 mg)	16	73	1	30		5.57 [ 0.77, 40.30]	1.05
Rudolph 1998 (375 mg)	23	65	2	28		3.92 [ 0.98, 15.65]	2.10
Rudolph 1999	8	92	6	92	<b>_</b>	1.31 [ 0.47, 3.63]	4.27
Schatzberg 2006	8	94	3	93		2.51 [ 0.69, 9.18]	2.18
Schweizer 1994	19	54	11	67	- <b>-</b>	1.85 [ 0.94, 3.61]	7.50
Silverstone 1999	17	111	7	112		2.26 [ 0.97, 5.25]	5.12
Thase 1997	26	69	11	91		2.54 [ 1.33, 4.85]	7.48
Overall					•	2.29 [ 1.89, 2.77]	
Heterogeneity: I ² = 0.00%, H ² =	1.00						
Test of $\theta_i = \theta_i$ : Q(26) = 13.35, p	= 0.98						
Test of $\theta = 0$ : z = 8.47, p = 0.00							
					1/4 1 4 16	64	
Fixed-effects Mantel-Haenszel r	nodel						



# Supplementary Figure 87: Meta-analysis of venlafaxine versus placebo on constipation (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk rat	io	Weigh
Study	Events	No events	Events	No events					with 95%	CI	(%)
600-B-367-EU (75 mg)	1	82	1	40		-			0.49 [ 0.03,	7.70]	1.25
600-B-367-EU (150 mg)	5	77	1	41			-		2.56 [ 0.31,	21.22]	1.24
Alvarez 2012	11	102	1	104					10.22 [ 1.34,	77.81]	0.97
Claghorn 1990	11	68	1	79					- 11.14 [ 1.47,	84.25]	0.93
Cunningham 1994	16	56	3	73				_	5.63 [ 1.71,	18.51]	2.73
Cunningham 1997 (IR)	14	82	2	48		-	-		3.65 [ 0.86,	15.41]	2.46
Cunningham 1997 (XR)	16	81	2	48			-	_	4.12 [ 0.99,	17.23]	2.47
EudraCT 2004-000562-13	6	121	5	115		-			1.13 [ 0.36,	3.62]	4.80
Guelfi 1995	2	44	1	46			-		2.04 [ 0.19,	21.77]	0.92
Hewett 2010	12	186	3	184				_	3.78 [ 1.08,	13.18]	2.88
Higuchi 2016 (fixed dose)	17	157	4	88		-			2.25 [ 0.78,	6.48]	4.89
Higuchi 2016 (flexible dose)	17	163	4	87		-			2.15 [ 0.74,	6.20]	4.96
Learned 2012	12	121	9	117		-	_		1.26 [ 0.55,	2.89]	8.64
Lieberman 2008 (225 mg)	9	108	2	123					4.81 [ 1.06,	21.79]	1.8
Mendels 1993 (25 mg)	6	73	2	24			<u> </u>		0.99 [ 0.21,	4.60]	2.8
Mendels 1993 (50 - 75 mg)	9	67	2	24			-		1.54 [ 0.36,	6.67]	2.78
Mendels 1993 (150 - 200 mg)	15	64	2	24		-	-		2.47 [ 0.60,	10.08]	2.8
Nemeroff 2007	10	90	5	97		-			2.04 [ 0.72,	5.76]	4.63
Rudolph 1998 (75 mg)	17	72	3	28		-			1.97 [ 0.62,	6.28]	4.16
Rudolph 1998 (225 mg)	10	79	3	28		-			1.16 [ 0.34,	3.95]	4.16
Rudolph 1998 (375 mg)	17	71	4	26		_			1.45 [ 0.53,	3.97]	5.5
Schatzberg 2006	22	80	4	92				_	5.18 [ 1.85,	14.47]	3.8
Schweizer 1994	9	64	6	72		_			1.60 [ 0.60,	4.28]	5.42
Sheehan 2009	24	71	11	84					2.18 [ 1.13,	4.20]	10.28
Silverstone 1999	22	106	13	106		-	-		1.57 [ 0.83,	2.98]	12.59
Overall							•		2.33 [ 1.87,	2.91]	
Heterogeneity: I ² = 0.00%, H ² =	1.00										
Test of $\theta_i = \theta_i$ : Q(24) = 21.87, p	= 0.59										
Test of $\theta = 0$ : $z = 7.48$ , $p = 0.00$	1										
					1/16	1/2	4	32	-		

# Supplementary Figure 88: Meta-analysis of venlafaxine versus placebo on nervousness (sensitivity analysis)

Study	Ven Events	lafaxine No events	Pl Events	acebo No events					Risk ra with 95%	tio 6 CI	Weight (%)
600-B-367-EU (75 mg)	1	82	1	40		-			0.49 [ 0.03,	7.70]	2.57
600-B-367-EU (150 mg)	2	80	1	41					1.02 [ 0.10,	10.97]	2.54
Claghorn 1990	7	72	6	74		_			1.18 [ 0.42,	3.36]	11.47
Cunningham 1994	15	57	9	67		+	-		1.76 [ 0.82,	3.77]	16.84
Guelfi 1995	3	43	0	47					7.15 [ 0.38,	134.66]	0.95
Mendels 1993 (25 mg)	4	75	2	24	_	-			0.66 [ 0.13,	3.39]	5.79
Mendels 1993 (50 - 75 mg)	7	69	1	25			-	_	2.39 [ 0.31,	18.55]	2.87
Mendels 1993 (150 - 200 mg)	13	66	1	25		-	-		4.28 [ 0.59,	31.15]	2.89
Rudolph 1998 (75 mg)	19	70	1	30		+	-		6.62 [ 0.92,	47.40]	2.85
Rudolph 1998 (225 mg)	12	77	1	30		-	-		4.18 [ 0.57,	30.84]	2.85
Rudolph 1998 (375 mg)	11	77	2	28		-	-		1.88 [ 0.44,	7.98]	5.74
Rudolph 1999	12	88	5	93		-	-		2.35 [ 0.86,	6.43]	9.71
Schatzberg 2006	2	100	2	94	-		<u> </u>		0.94 [ 0.14,	6.55]	3.96
Schweizer 1994	10	63	3	75		-	-	-	3.56 [ 1.02,	12.43]	5.58
Silverstone 1999	23	105	8	111			-		2.67 [ 1.24,	5.74]	15.95
Thase 1997	16	79	4	98				-	4.29 [ 1.49,	12.39]	7.42
Overall							•		2.39 [ 1.74,	3.30]	
Heterogeneity: I ² = 0.00%, H ² =	1.00										
Test of $\theta_i = \theta_j$ : Q(15) = 11.35, p	= 0.73										
Test of θ = 0: z = 5.35, p = 0.00											
					1/16	1/2	4	32	-		



# Supplementary Figure 89: Meta-analysis of venlafaxine versus placebo on insomnia (sensitivity analysis)

Object	Ven	lafaxine	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	2	39		0.49 [ 0.07, 3.38]	1.72
600-B-367-EU (150 mg)	3	79	1	41		1.54 [ 0.16, 14.32]	0.85
Alvarez 2012	14	99	5	100		2.60 [ 0.97, 6.97]	3.34
Claghorn 1990	13	66	6	74		2.19 [ 0.88, 5.48]	3.84
Cunningham 1994	7	65	3	73		2.46 [ 0.66, 9.16]	1.88
EudraCT 2004-000562-13	14	113	8	112		1.65 [ 0.72, 3.80]	5.30
Guelfi 1995	3	43	3	44	<b>_</b>	1.02 [ 0.22, 4.80]	1.91
Hewett 2009	7	180	4	193		1.84 [ 0.55, 6.20]	2.51
Hewett 2010	13	185	8	179		1.53 [ 0.65, 3.62]	5.30
Higuchi 2016 (fixed dose)	4	170	3	89		0.70 [ 0.16, 3.08]	2.53
Higuchi 2016 (flexible dose)	8	172	3	88		1.35 [ 0.37, 4.96]	2.57
Khan 1998 (75 mg)	5	91	0	33			0.48
Khan 1998 (150 mg)	3	93	0	33		2.45 [ 0.13, 46.29]	0.48
Khan 1998 (200 mg)	5	89	0	32			0.48
Learned 2012	7	126	11	115		0.60 [ 0.24, 1.51]	7.28
Mendels 1993 (25 mg)	14	65	4	22	<b>_</b>	1.15 [ 0.42, 3.19]	3.88
Mendels 1993 (50 - 75 mg)	10	66	4	22	<b>_</b>	0.86 [ 0.29, 2.49]	3.84
Mendels 1993 (150 - 200 mg)	19	60	3	23		2.08 [ 0.67, 6.48]	2.91
Nemeroff 2007	22	78	14	88	+	1.60 [ 0.87, 2.95]	8.93
Rudolph 1998 (75 mg)	20	69	3	28		2.32 [ 0.74, 7.28]	2.87
Rudolph 1998 (225 mg)	18	71	3	28		2.09 [ 0.66, 6.61]	2.87
Rudolph 1998 (375 mg)	12	76	3	27		1.36 [ 0.41, 4.51]	2.88
Schatzberg 2006	10	92	4	92		2.35 [ 0.76, 7.25]	2.65
Schweizer 1994	15	58	10	68	- <b></b>	1.60 [ 0.77, 3.34]	6.23
Sheehan 2009	18	77	8	87	_ <b></b>	2.25 [ 1.03, 4.92]	5.15
Silverstone 1999	41	87	12	107		3.18 [ 1.76, 5.75]	8.01
Thase 1997	33	62	15	87		2.36 [ 1.37, 4.06]	9.32
Overall					•	1.82 [ 1.51, 2.19]	
Heterogeneity: I ² = 0.00%, H ² =	1.00						
Test of $\theta_i = \theta_j$ : Q(26) = 19.57, p	= 0.81						
Test of $\theta$ = 0: z = 6.29, p = 0.00							
					1/8 1 8	64	
Fixed-effects Mantel–Haenszel r	nodel						



# Supplementary Figure 90: Meta-analysis of venlafaxine versus placebo on asthenia (sensitivity analysis)

Study	Ven Events	lafaxine No events	PI Events	acebo No events		Risk ra with 95%	itio % Cl	Weight (%)
600-B-367-EU (75 mg)	5	78	1	40		2.47 [ 0.30,	20.46]	1.62
600-B-367-EU (150 mg)	3	79	1	41		1.54 [ 0.16,	14.32]	1.60
Alvarez 2012	11	102	6	99		1.70 [ 0.65,	4.44]	7.54
Claghorn 1990	5	74	2	78		2.53 [ 0.51,	12.67]	2.41
Cunningham 1994	7	65	3	73		2.46 [ 0.66,	9.16]	3.54
EudraCT 2004-000562-13	10	117	2	118		4.72 [ 1.06,	21.12]	2.49
Guelfi 1995	2	44	0	47			103.55]	0.60
Hewett 2009	9	178	4	193		2.37 [ 0.74,	7.57]	4.72
Hewett 2010	16	182	13	174		1.16 [ 0.57,	2.35]	16.21
Khan 1998 (75 mg)	5	91	0	33		3.86 [ 0.22,	67.91]	0.90
Khan 1998 (150 mg)	5	91	0	33		3.86 [ 0.22,	67.91]	0.90
Khan 1998 (200 mg)	3	91	0	32		2.43 [ 0.13,	45.84]	0.90
Learned 2012	13	120	5	121		2.46 [ 0.90,	6.71]	6.23
Lieberman 2008 (225 mg)	7	110	8	117	<b>_</b>	0.93 [ 0.35,	2.50]	9.38
Mendels 1993 (25 mg)	10	69	3	23	<b>_</b>	1.10 [ 0.33,	3.69]	5.47
Mendels 1993 (50 - 75 mg)	8	68	3	23	<b>_</b>	0.91 [ 0.26,	3.18]	5.42
Mendels 1993 (150 - 200 mg)	13	66	2	24		2.14 [ 0.52,	8.86]	3.65
Nemeroff 2007	10	90	5	97		2.04 [ 0.72,	5.76]	6.00
Rudolph 1999	10	90	2	96		4.90 [ 1.10,	21.79]	2.45
Schatzberg 2006	12	90	5	91		2.26 [ 0.83,	6.17]	6.25
Schweizer 1994	9	64	10	68		0.96 [ 0.41,	2.23]	11.72
Overall					•	1.81 [ 1.39,	2.35]	
Heterogeneity: I ² = 0.00%, H ² =	1.00							
Test of $\theta_i = \theta_i$ : Q(20) = 12.89, p	= 0.88							
Test of $\theta = 0$ : $z = 4.40$ , $p = 0.00$								
					1/4 1 4 16 6	54		
- ixed-effects Mantel-Haenszel n	nodel							

# Supplementary Figure 91: Meta-analysis of venlafaxine versus placebo on tremor (sensitivity analysis)

	Ven	lafaxine	PI	acebo				Risk ra	tio	Weight
Study	Events	No events	Events	No events				with 95%	5 CI	(%)
600-B-367-EU (75 mg)	3	80	2	39				0.74 [ 0.13,	4.26]	10.28
600-B-367-EU (150 mg)	2	80	1	41				1.02 [ 0.10,	10.97]	5.08
Alvarez 2012	6	107	3	102	_			1.86 [ 0.48,	7.24]	11.94
Claghorn 1990	2	77	0	80				5.06 [ 0.25,	103.80]	1.91
EudraCT 2004-000562-13	4	123	3	117				1.26 [ 0.29,	5.51]	11.84
Guelfi 1995	2	45	2	45				1.00 [ 0.15,	6.81]	7.68
Hewett 2010	10	188	2	185		<b>_</b>		4.72 [ 1.05,	21.27]	7.90
Learned 2012	7	126	5	121				1.33 [ 0.43,	4.07]	19.71
Rudolph 1999	9	91	1	97		<b>-</b>		8.82 [ 1.14,	68.32]	3.88
Schatzberg 2006	6	96	0	96	-	-		12.24 [ 0.70,	214.43]	1.98
Sheehan 2009	5	90	0	95	-	-		11.00 [ 0.62,	196.19]	1.92
Silverstone 1999	13	115	4	115				3.02 [ 1.01,	9.01]	15.91
Overall						•		2.58 [ 1.65,	4.04]	
Heterogeneity: I ² = 0.00%, H	l ² = 1.00									
Test of $\theta_i = \theta_j$ : Q(11) = 10.35	, p = 0.50	1								
Test of $\theta = 0$ : $z = 4.16$ , $p = 0$	.00									
					1/8	1 8	64			
					170	. 0	04			



# Supplementary Figure 92: Meta-analysis of venlafaxine versus placebo on decreased appetite (sensitivity analysis)

	Ven	lafaxine	PI	acebo				Risk ratio Weight
Study	Events	No events	Events	No events				with 95% Cl (%)
Higuchi 2016 (fixed dose)	4	170	0	91		-		4.73 [ 0.26, 86.93] 9.20
Higuchi 2016 (flexible dose)	4	176	1	91				2.04 [ 0.23, 18.03] 18.57
Learned 2012	2	131	1	125				1.89 [ 0.17, 20.64] 14.41
Schatzberg 2006	11	91	4	92			-	2.59 [ 0.85, 7.85] 57.82
Overall								2.58 [ 1.08, 6.18]
Heterogeneity: I ² = 0.00%, H ²	= 1.00							
Test of $\theta_i = \theta_j$ : Q(3) = 0.28, p =	= 0.96							
Test of $\theta$ = 0: z = 2.14, p = 0.0	03							
					1/4	1 4	16	64



### Supplementary Figure 93: Meta-analysis of venlafaxine versus placebo on abdominal pain (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk rat	io	Weight
Study	Events	No events	Events	No event	S				with 95%	o Cl	(%)
600-B-367-EU (75 mg)	0	83	2	39		_			0.10 [ 0.00,	2.04]	9.78
600-B-367-EU (150 mg)	2	80	1	41					- 1.02 [ 0.10,	10.97]	3.88
EudraCT 2004-000562-13	8	119	11	109				-	0.69 [ 0.29,	1.65]	33.19
Hewett 2010	9	189	8	179			-	—	1.06 [ 0.42,	2.70]	24.14
Higuchi 2016 (fixed dose)	5	169	3	88				<u> </u>	0.87 [ 0.21,	3.57]	11.56
Higuchi 2016 (flexible dose)	0	180	4	88				-	0.06 [ 0.00,	1.05]	17.44
Overall							•		0.64 [ 0.39,	1.07]	
Heterogeneity: I ² = 10.41%, H ²	² = 1.12										
Test of $\theta_i = \theta_j$ : Q(5) = 5.58, p =	0.35										
Test of $\theta$ = 0: z = -1.69, p = 0.0	)9										
					1/256	1/32	1/4	2	_		

Fixed-effects Mantel-Haenszel model

# Supplementary Figure 94: Meta-analysis of venlafaxine versus placebo on abnormal dreams (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No events	6				with 95%	5 CI	(%)
600-B-367-EU (75 mg)	2	81	1	40					0.99 [ 0.09,	10.58]	40.44
600-B-367-EU (150 mg)	0	82	0	42					0.52 [ 0.01,	25.66]	19.90
Cunningham 1997 (IR)	7	89	0	50		_			7.89 [ 0.46,	135.33]	19.80
Cunningham 1997 (XR)	12	85	0	50		-			13.01 [ 0.79,	215.32]	19.87
Overall									4.65 [ 1.28,	16.93]	
Heterogeneity: I ² = 14.35%	5, H ² = 1.	17									
Test of $\theta_i = \theta_j$ : Q(3) = 3.50,	p = 0.32	!									
Test of θ = 0: z = 2.33, p =	0.02										
					1/64	1/4	4	64			



#### Supplementary Figure 95: Meta-analysis of venlafaxine versus placebo on abnormal vision (sensitivity analysis)

Study	Ven Events	lafaxine No events	PI Events	acebo No event	s				Risk ra with 95%	itio 6 CI	Weight (%)
600-B-367-EU (75 mg)	0	83	1	40		_			0.17 [ 0.01,	4.00]	11.91
600-B-367-EU (150 mg)	0	82	0	42				_	0.52 [ 0.01,	25.66]	3.92
Alvarez 2012	6	107	2	103		_			2.79 [ 0.58,	13.51]	12.35
EudraCT 2004-000562-13	3	124	0	120			-		6.62 [ 0.35,	126.78]	3.06
Guelfi 1995	1	45	0	47			-		3.06 [ 0.13,	73.33]	2.95
Lieberman 2008 (225 mg)	5	112	3	122					1.78 [ 0.44,	7.29]	17.27
Schatzberg 2006	8	94	5	91		_			1.51 [ 0.51,	4.44]	30.68
Sheehan 2009	10	85	3	92					3.33 [ 0.95,	11.73]	17.86
Overall							•		2.04 [ 1.16,	3.61]	
Heterogeneity: I ² = 0.00%, H	² = 1.00										
Test of $\theta_i = \theta_i$ : Q(7) = 4.61, p	= 0.71										
Test of $\theta = 0$ : z = 2.46, p = 0.	.01				1/128	1/8	2	32	-		



# Supplementary Figure 96: Meta-analysis of venlafaxine versus placebo on agitation (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No event	s				with 95%	5 CI	(%)
600-B-367-EU (75 mg)	2	81	0	41			-		2.50 [ 0.12,	50.91]	9.62
600-B-367-EU (150 mg)	2	80	0	42			-		2.59 [ 0.13,	52.76]	9.51
Cunningham 1994	7	65	0	76					15.82 [ 0.92,	272.09]	7.02
Guelfi 1995	1	45	0	47			-		3.06 [ 0.13,	73.33]	7.14
Learned 2012	1	132	4	122		-			0.24 [ 0.03,	2.09]	59.28
Schatzberg 2006	2	100	0	96			-		4.71 [ 0.23,	96.84]	7.43
Overall							-		2.31 [ 0.94,	5.64]	
Heterogeneity: I ² = 19.48%	6, H ² = 1.3	24									
Test of $\theta_i = \theta_i$ : Q(5) = 6.21	, p = 0.29	1									
Test of $\theta = 0$ : z = 1.83, p =	0.07										
					1/32	1/2	8	128	•		



# Supplementary Figure 97: Meta-analysis of venlafaxine versus placebo on back pain (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No event	ts				with 95% CI	(%)
600-B-367-EU (75 mg)	0	83	1	40					0.17 [ 0.01, 4.00]	12.76
600-B-367-EU (150 mg)	1	81	1	41			-		0.51 [ 0.03, 7.99]	8.44
EudraCT 2004-000562-13	3	124	6	114		-	_		0.47 [ 0.12, 1.85]	39.36
Schatzberg 2006	3	99	6	90		-	_		0.47 [ 0.12, 1.83]	39.44
Overall									0.44 [ 0.18, 1.04]	
Heterogeneity: I ² = 0.00%, H	² = 1.00									
Test of $\theta_i = \theta_i$ : Q(3) = 0.39, p	= 0.94									
Test of $\theta$ = 0: z = -1.88, p = 0	0.06									
					1/128	1/16	1/2	4	-	



### Supplementary Figure 98: Meta-analysis of venlafaxine versus placebo on increased blood pressure (sensitivity analysis)

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events	3			with 95% CI	(%)
Higuchi 2016 (fixed dose)	4	170	1	91				2.11 [ 0.24, 18.65]	16.80
Higuchi 2016 (flexible dose)	5	175	1	90				-2.53 [ 0.30, 21.32]	17.06
Schatzberg 2006	5	97	5	91		<b>—</b>		0.94 [ 0.28, 3.15]	66.15
Overall								1.41 [ 0.56, 3.57]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00								
Test of $\theta_i = \theta_j$ : Q(2) = 0.85, p =	0.65								
Test of $\theta$ = 0: z = 0.72, p = 0.4	7								
					1/4	1 4	1 16	-	



# Supplementary Figure 99: Meta-analysis of venlafaxine versus placebo on coughing (sensitivity analysis)

	Ven	lafaxine	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
600-B-367-EU (75 mg)	1	82	0	41		1.50 [ 0.06, 36.04]	10.91
600-B-367-EU (150 mg)	1	81	1	41		0.51 [ 0.03, 7.99]	21.64
Schatzberg 2006	2	100	4	92		0.47 [ 0.09, 2.51]	67.45
Overall						0.59 [ 0.17, 2.12]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.0$	0					
Test of $\theta_i = \theta_i$ : Q(2) = 0.41	, p = 0.81						
Test of $\theta = 0$ : z = -0.81, p =	= 0.42						
					1/16 1/2 4	32	



# Supplementary Figure 100: Meta-analysis of venlafaxine versus placebo on diarrhoea (sensitivity analysis)

	Ven	lafaxine	Pl	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events				with 95% CI	(%)
600-B-367-EU (75 mg)	3	80	3	38			•	0.49 [ 0.10, 2.34]	3.73
600-B-367-EU (150 mg)	1	81	3	39		-		0.17 [ 0.02, 1.59]	2.02
Alvarez 2012	5	108	5	100		-		0.93 [ 0.28, 3.12]	5.46
Cunningham 1994	7	65	5	71				1.48 [ 0.49, 4.45]	6.22
Cunningham 1997 (IR)	5	91	3	47		_		0.87 [ 0.22, 3.48]	4.45
Cunningham 1997 (XR)	13	84	3	47				- 2.23 [ 0.67, 7.48]	5.47
EudraCT 2004-000562-13	3	124	6	114				0.47 [ 0.12, 1.85]	4.59
EudraCT 2007-007025-51	0	7	2	5		-		0.20 [ 0.01, 3.54]	1.27
Guelfi 1995	0	46	1	46		-		-0.34 [ 0.01, 8.15]	1.05
Hewett 2010	10	188	9	178				1.05 [ 0.44, 2.53]	8.23
Higuchi 2016 (fixed dose)	6	168	3	88		-		1.05 [ 0.27, 4.09]	4.59
Higuchi 2016 (flexible dose)	8	172	4	88		-		1.02 [ 0.32, 3.31]	5.70
Learned 2012	8	125	8	118				0.95 [ 0.37, 2.45]	7.52
Nemeroff 2007	9	91	9	93				1.02 [ 0.42, 2.46]	8.19
Rudolph 1999	14	86	9	89				1.52 [ 0.69, 3.36]	9.23
Schatzberg 2006	12	90	13	83				0.87 [ 0.42, 1.81]	9.92
Silverstone 1999	22	106	19	100				1.08 [ 0.61, 1.89]	12.36
Overall							•	0.97 [ 0.69, 1.36]	
Heterogeneity: $\tau^2 = 0.16$ , $I^2 = 3$	34.54%, ⊦	H ² = 1.53							
Test of $\theta_i = \theta_j$ : Q(16) = 9.57, p	= 0.89								
Test of $\theta = 0$ : $z = -0.18$ , $p = 0$ .	85							_	
					1/64	1/8	1	8	

Random-effects Sidik-Jonkman model



#### Supplementary Figure 101: Meta-analysis of venlafaxine versus placebo on dyspepsia (sensitivity analysis)

Study	Ven Events	lafaxine No events	Pl Events	acebo No events	5				Risk ratio with 95% CI	Weight (%)
600-B-367-EU (75 mg)	2	81	2	39					0.49 [ 0.07, 3.38]	5.06
600-B-367-EU (150 mg)	1	81	2	40		-	-		0.26 [ 0.02, 2.74]	5.00
Cunningham 1994	2	70	5	71			-		0.42 [ 0.08, 2.11]	9.19
Learned 2012	2	131	2	124					-0.95 [ 0.14, 6.62]	3.88
Nemeroff 2007	9	91	16	86				_	0.57 [ 0.27, 1.24]	29.94
Schatzberg 2006	11	91	8	88					1.29 [ 0.54, 3.08]	15.58
Silverstone 1999	13	115	16	103				<u> </u>	0.76 [ 0.38, 1.50]	31.34
Overall									0.72 [ 0.49, 1.07]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.0$	0								
Test of $\theta_i = \theta_i$ : Q(6) = 3.49,	p = 0.75									
Test of $\theta = 0$ : z = -1.61, p =	= 0.11									
					1/32	1/8	1/2	2	-	



### Supplementary Figure 102: Meta-analysis of venlafaxine versus placebo on flatulence (sensitivity analysis)




### Supplementary Figure 103: Meta-analysis of venlafaxine versus placebo on headache (sensitivity analysis)

Objete	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No events					With 95% CI	(%)
600-B-367-EU (75 mg)	11	72	5	36					1.09 [ 0.40, 2.92]	1.60
600-B-367-EU (150 mg)	7	75	6	36		-	-		0.60 [ 0.21, 1.67]	1.90
Alvarez 2012	32	81	26	79			-	-	1.14 [ 0.73, 1.78]	6.45
Claghorn 1990	21	58	17	63			-		1.25 [ 0.72, 2.19]	4.04
Cunningham 1994	22	50	25	51			-	H	0.93 [ 0.58, 1.49]	5.82
EudraCT 2004-000562-13	29	98	34	86			-	-	0.81 [ 0.53, 1.24]	8.37
EudraCT 2007-007025-51	0	7	1	6			•			0.36
Guelfi 1995	2	44	4	43			-		0.51 [ 0.10, 2.65]	0.95
Hewett 2009	25	162	19	178			-	-	1.39 [ 0.79, 2.43]	4.43
Hewett 2010	28	170	31	156			-	F	0.85 [ 0.53, 1.37]	7.63
Higuchi 2016 (fixed dose)	16	158	7	85					1.21 [ 0.52, 2.83]	2.19
Higuchi 2016 (flexible dose)	18	162	7	84					1.30 [ 0.56, 3.00]	2.23
Learned 2012	28	105	24	102			-	-	1.11 [ 0.68, 1.80]	5.90
Mendels 1993 (25 mg)	20	59	7	19				<b>—</b>	0.94 [ 0.45, 1.97]	2.52
Mendels 1993 (50 - 75 mg)	19	57	7	19				<b>—</b>	0.93 [ 0.44, 1.95]	2.50
Mendels 1993 (150 - 200 mg)	17	62	7	19					0.80 [ 0.37, 1.71]	2.52
Nemeroff 2007	36	64	34	68				-	1.08 [ 0.74, 1.58]	8.06
Rudolph 1998 (75 mg)	23	66	7	24					1.14 [ 0.55, 2.40]	2.49
Rudolph 1998 (225 mg)	23	66	7	24					1.14 [ 0.55, 2.40]	2.49
Rudolph 1998 (375 mg)	22	66	8	22				<b>—</b>	0.94 [ 0.47, 1.88]	2.86
Schatzberg 2006	27	75	21	75			-	-	1.21 [ 0.74, 1.99]	5.18
Schweizer 1994	19	54	21	57				-	0.97 [ 0.57, 1.65]	4.86
Silverstone 1999	57	71	59	60					0.90 [ 0.69, 1.17]	14.64
Overall								•	1.01 [ 0.90, 1.13]	
Heterogeneity: I ² = 0.00%, H ² =	1.00									
Test of $\theta_{i} = \theta_{i}$ : Q(22) = 8.71, p =	0.99									
Test of $\theta = 0$ : $z = 0.12$ , $p = 0.91$										
					1/32	1/8	1/2	2	_	
ixed-effects Mantel-Haenszel n	nodel									



# Supplementary Figure 104: Meta-analysis of venlafaxine versus placebo on infection (sensitivity analysis)

	Ven	lafaxine	Pla	acebo					Risk rat	tio	Weight
Study	Events	No events	Events	No event	ts				with 95%	o Cl	(%)
600-B-367-EU (75 mg)	3	80	2	39		_			0.74 [ 0.13,	4.26]	9.38
600-B-367-EU (150 mg)	0	82	1	41					0.17 [ 0.01,	4.15]	3.81
Cunningham 1994	8	64	7	69					1.21 [ 0.46,	3.16]	16.84
EudraCT 2004-000562-13	2	125	10	110			<u> </u>		0.19 [ 0.04,	0.84]	11.30
Mendels 1993 (25 mg)	10	69	2	24					1.65 [ 0.39,	7.03]	11.69
Mendels 1993 (50 - 75 mg)	3	73	2	24			-		0.51 [ 0.09,	2.90]	9.49
Mendels 1993 (150 - 200 mg)	7	72	1	25				-	2.30 [ 0.30,	17.86]	7.59
Rudolph 1999	13	87	6	92			-		2.12 [ 0.84,	5.36]	17.27
Schweizer 1994	3	70	6	72		-	-		0.53 [ 0.14,	2.06]	12.63
Overall									0.87 [ 0.44,	1.70]	
Heterogeneity: $\tau^2 = 0.46$ , $I^2 = 46$ .	59%, H²	= 1.87									
Test of $\theta_i = \theta_i$ : Q(8) = 11.21, p =	0.19										
Test of $\theta = 0$ : z = -0.42, p = 0.68											
					1/128	1/16	1/2	4			



# Supplementary Figure 105: Meta-analysis of venlafaxine versus placebo on influenza (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No events	s				with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	2	39					0.49 [ 0.07, 3.38	] 13.76
600-B-367-EU (150 mg)	0	82	1	41		-			0.17[0.01, 4.15	] 10.16
Guelfi 1995	1	45	1	46					1.02 [ 0.07, 15.85	] 5.08
Hewett 2010	4	194	9	178			_		0.42 [ 0.13, 1.34	] 47.58
Rudolph 1999	7	93	4	94		-			1.72 [ 0.52, 5.67	] 20.77
Schatzberg 2006	2	100	0	96					4.71 [ 0.23, 96.84	] 2.65
Overall						-			0.82 [ 0.43, 1.55	]
Heterogeneity: I ² = 4.50%	, H ² = 1.0	5								
Test of $\theta_i = \theta_j$ : Q(5) = 5.24	, p = 0.39	1								
Test of $\theta$ = 0: z = -0.61, p	= 0.54									
				1	1/128	1/8	2	32	-	
Fixed-effects Mantel-Haen	szel mod	əl								



### Supplementary Figure 106: Meta-analysis of venlafaxine versus placebo on malaise (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No event	ts				with 95% CI	(%)
600-B-367-EU (75 mg)	0	83	1	40					0.17 [ 0.01, 4.00]	21.60
600-B-367-EU (150 mg)	0	82	0	42			-		-0.52 [ 0.01, 25.66]	7.11
Higuchi 2016 (fixed dose)	9	165	2	90				-	2.38 [ 0.52, 10.78]	28.25
Higuchi 2016 (flexible dose)	11	169	3	88					1.85 [ 0.53, 6.48]	43.03
Overall							-		1.54 [ 0.67, 3.58]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00									
Test of $\theta_i = \theta_j$ : Q(3) = 2.58, p =	= 0.46									
Test of $\theta$ = 0: z = 1.01, p = 0.3	1									
					1/128	1/16	1/2	4	_	



# Supplementary Figure 107: Meta-analysis of venlafaxine versus placebo on nasopharyngitis (sensitivity analysis)

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events				with 95% CI	(%)
Alvarez 2012	4	109	9	96		-	+	0.41 [ 0.13, 1.30]	11.69
Hewett 2010	11	187	9	178			┤■──	1.15 [ 0.49, 2.72]	11.59
Higuchi 2016 (fixed dose)	35	139	20	72			<b>—</b>	0.93 [ 0.57, 1.51]	32.77
Higuchi 2016 (flexible dose)	32	148	21	70			+-	0.77 [ 0.47, 1.26]	34.94
Learned 2012	6	127	7	119		_		0.81 [ 0.28, 2.35]	9.00
Overall						-		0.83 [ 0.62, 1.11]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00								
Test of $\theta_i = \theta_j$ : Q(4) = 2.27, p =	= 0.69								
Test of $\theta$ = 0: z = -1.25, p = 0.	21								
					1/4	1/2	1 2	 !	



## Supplementary Figure 108: Meta-analysis of venlafaxine versus placebo on palpitations (sensitivity analysis)

	Ven	lafaxine	PI	acebo				Risk ratio Weight
Study	Events	No events	Events	No events	3			with 95% CI (%)
600-B-367-EU (75 mg)	0	83	1	40			<u> </u>	0.17 [ 0.01, 4.00] 15.12
600-B-367-EU (150 mg)	3	79	1	41				1.54 [ 0.16, 14.32] 10.00
Higuchi 2016 (fixed dose)	8	166	2	89		_		2.09 [ 0.45, 9.65] 19.86
Higuchi 2016 (flexible dose)	6	174	3	89			<b>—</b>	1.02 [ 0.26, 3.99] 30.02
Learned 2012	5	128	2	124		_		2.37 [ 0.47, 11.99] 15.53
Rudolph 1998 (75 mg)	1	22	0	13			•	— 1.75 [ 0.08, 40.11] 4.77
Rudolph 1998 (225 mg)	2	20	0	13				3.04 [ 0.16, 58.90] 4.70
Overall							•	1.50 [ 0.74, 3.00]
Heterogeneity: I ² = 0.00%, H ²	= 1.00							
Test of $\theta_i = \theta_i$ : Q(6) = 2.85, p =	= 0.83							
Test of $\theta = 0$ : $z = 1.13$ , $p = 0.2$	26							
				1	/128	1/8	2	32
Fixed-effects Mantel-Haenszel	model							



#### Supplementary Figure 109: Meta-analysis of venlafaxine versus placebo on rhinitis (sensitivity analysis)





# Supplementary Figure 110: Meta-analysis of venlafaxine versus placebo on tachycardia (sensitivity analysis)

	Ven	lafaxine	Pl	acebo				Risk ra	atio	Weight
Study	Events	No events	Events	No events	6			with 95°	% CI	(%)
EudraCT 2004-000562-13	0	127	0	120		_		0.95 [ 0.02,	47.27]	6.53
Higuchi 2016 (fixed dose)	4	170	0	92				4.78 [ 0.26,	87.88]	8.29
Higuchi 2016 (flexible dose)	7	173	0	91				7.62 [ 0.44,	132.03]	8.42
Learned 2012	4	129	4	122			<b></b>	0.95 [ 0.24,	3.71]	52.19
Lieberman 2008 (225 mg)	5	112	2	123				2.67 [ 0.53,	13.50]	24.57
Overall							<b>•</b>	2.25 [ 0.95,	5.35]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00									
Test of $\theta_i = \theta_i$ : Q(4) = 2.74, p =	0.60									
Test of $\theta = 0$ : $z = 1.84$ , $p = 0.0$	7									
					1/32	1/2	8	128		



#### Supplementary Figure 111: Meta-analysis of venlafaxine versus placebo on urinary frequency (sensitivity analysis)

	Ven	lafaxine	Pla	acebo					Risk rat	tio	Weight
Study	Events	No events	Events	No event	ts				with 95%	CI	(%)
600-B-367-EU (75 mg)	0	83	1	40			-		0.17 [ 0.01,	4.00]	34.78
600-B-367-EU (150 mg)	0	82	0	42			-		-0.52 [ 0.01,	25.66]	11.46
Schatzberg 2006	6	96	3	93					1.88 [ 0.48,	7.32]	53.76
Overall									1.13 [ 0.38,	3.32]	
Heterogeneity: I ² = 4.25%,	$H^2 = 1.0$	4									
Test of $\theta_i = \theta_j$ : Q(2) = 2.09	, p = 0.35	i									
Test of θ = 0: z = 0.22, p =	0.82										
					1/128	1/16	1/2	4	-		



# Supplementary Figure 112: Meta-analysis of venlafaxine versus placebo on vertigo (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ratio	Weight
Study	Events	No events	Events	No event	s				with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	1	40					0.99 [ 0.09, 10.58]	11.23
600-B-367-EU (150 mg)	2	80	1	41					1.02 [ 0.10, 10.97]	11.09
EudraCT 2004-000562-13	9	118	5	115					1.70 [ 0.59, 4.93]	43.12
Guelfi 1995	0	46	1	46		_			0.34 [ 0.01, 8.15]	12.45
Higuchi 2016 (fixed dose)	4	170	1	90		-			2.09 [ 0.24, 18.44]	11.01
Higuchi 2016 (flexible dose)	6	174	1	91					-3.07 [ 0.37, 25.09]	11.10
Overall							-	•	1.57 [ 0.76, 3.26]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00									
Test of $\theta_i = \theta_i$ : Q(5) = 1.64, p =	= 0.90									
Test of θ = 0: z = 1.21, p = 0.2	23									
					1/64	1/8	1	8	_	
Fixed-effects Mantel-Haenszel	model									



## Supplementary Figure 113: Meta-analysis of venlafaxine versus placebo on vomiting (sensitivity analysis)

	Ven	lafaxine	Pl	acebo				Risk ra	atio	Weight
Study	Events	No events	Events	No events	;			with 959	% CI	(%)
600-B-367-EU (75 mg)	2	81	1	40			<u> </u>	0.99 [ 0.09,	10.58]	5.15
600-B-367-EU (150 mg)	3	79	1	41			•	1.54 [ 0.16,	14.32]	5.09
Alvarez 2012	4	109	1	104				3.72 [ 0.42,	32.72]	3.99
EudraCT 2004-000562-13	3	124	2	118			<b></b>	1.42 [ 0.24,	8.34]	7.91
Guelfi 1995	0	46	2	45		-		0.20 [ 0.01,	4.14]	9.52
Higuchi 2016 (fixed dose)	5	169	3	89			<b>—</b>	0.88 [ 0.22,	3.61]	15.10
Higuchi 2016 (flexible dose)	4	176	4	87			-	0.51 [ 0.13,	1.98]	20.44
Lieberman 2008 (225 mg)	3	114	0	125			-	7.47 [ 0.39,	143.17]	1.86
Nemeroff 2007	11	89	2	100				5.61 [ 1.28,	24.67]	7.62
Schatzberg 2006	9	93	2	94				4.24 [ 0.94,	19.11]	7.93
Sheehan 2009	9	86	4	91		-		2.25 [ 0.72,	7.06]	15.39
Overall							•	1.89 [ 1.19,	3.02]	
Heterogeneity: I ² = 14.66%, H ²	² = 1.17									
Test of $\theta_i = \theta_j$ : Q(10) = 11.72, p	0 = 0.30									
Test of $\theta = 0$ : $z = 2.69$ , $p = 0.0$	1									
					1/64	1/4	4 64	_		



# Supplementary Figure 114: Meta-analysis of venlafaxine versus placebo on weight loss (sensitivity analysis)

	Ven	lafaxine	Pl	acebo				Risk ra	tio	Weight
Study	Events	No events	Events	No events				with 95%	5 CI	(%)
600-B-367-EU (75 mg)	2	81	0	41				2.50 [ 0.12,	50.91]	28.55
600-B-367-EU (150 mg)	1	81	0	42				1.55 [ 0.06,	37.35]	28.21
Guelfi 1995	2	44	0	47				- 5.11 [ 0.25,	103.55]	21.19
Schatzberg 2006	1	101	0	96	·			2.83 [ 0.12,	68.52]	22.05
Overall					-		-	2.86 [ 0.63,	13.02]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.0$	D								
Test of $\theta_i = \theta_i$ : Q(3) = 0.29,	p = 0.96	i								
Test of $\theta$ = 0: z = 1.36, p =	0.17									
					1/8	1 8	64	-		



# Supplementary Figure 115: Meta-analysis of venlafaxine versus placebo on abnormality of accommodation (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk ra	atio	Weight
Study	Events	No events	Events	No events	3				with 959	% CI	(%)
600-B-367-EU (75 mg)	0	83	0	41		_		_	0.50 [ 0.01,	24.76]	14.07
600-B-367-EU (150 mg)	2	80	0	42					2.59 [ 0.13,	52.76]	13.90
Cunningham 1994	7	65	3	73		-			2.46 [ 0.66,	9.16]	61.59
Guelfi 1995	2	44	0	47					5.11 [ 0.25,	103.55]	10.44
Overall									2.48 [ 0.87,	7.07]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.0$	D									
Test of $\theta_i = \theta_i$ : Q(3) = 0.87,	p = 0.83										
Test of $\theta$ = 0: z = 1.70, p =	0.09										
					1/64	1/4	4	64			



#### Supplementary Figure 116: Meta-analysis of venlafaxine versus placebo on pruritis (sensitivity analysis)



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#### Supplementary Figure 117: Meta-analysis of venlafaxine versus placebo on vasodilation (sensitivity analysis)





#### Supplementary Figure 118: Meta-analysis of venlafaxine versus placebo on neck pain (sensitivity analysis)





# Supplementary Figure 119: Meta-analysis of venlafaxine versus placebo on pain (sensitivity analysis)





#### Supplementary Figure 120: Meta-analysis of venlafaxine versus placebo on increased salivation (sensitivity analysis)



Fixed-effects Mantel-Haenszel model

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# Supplementary Figure 121: Meta-analysis of venlafaxine versus placebo on tongue discolouration (sensitivity analysis)





# Supplementary Figure 122: Meta-analysis of venlafaxine versus placebo on hypochromic anaemia (sensitivity analysis)





# Supplementary Figure 123: Meta-analysis of venlafaxine versus placebo on hypercholesterolemia (sensitivity analysis)

	Ven	lafaxine	PI	acebo					Risk rat	io	Weight
Study	Events	No events	Events	No events	;				with 95%	CI	(%)
600-B-367-EU (75 mg)	0	83	0	41					0.50 [ 0.01,	24.76]	20.18
600-B-367-EU (150 mg)	0	82	0	42					0.52 [ 0.01,	25.66]	19.94
Guelfi 1995	1	45	2	45					0.51 [ 0.05,	5.44]	59.88
Overall									0.51 [ 0.08,	3.08]	
Heterogeneity: I ² = 0.00%	$H^2 = 1.0$	0									
Test of $\theta_i = \theta_i$ : Q(2) = 0.00	, p = 1.00	)									
Test of $\theta$ = 0: z = -0.73, p											
					1/64	1/8	1	8	-		



### Supplementary Figure 124: Meta-analysis of venlafaxine versus placebo on bronchitis (sensitivity analysis)

	Ven	lafaxine	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events	6			with 95% CI	(%)
600-B-367-EU (75 mg)	2	81	0	41				2.50 [ 0.12, 50.91]	36.63
600-B-367-EU (150 mg)	0	82	0	42				0.52 [ 0.01, 25.66]	36.19
Guelfi 1995	1	45	0	47			-	3.06 [ 0.13, 73.33]	27.18
Overall								1.94 [ 0.32, 11.86]	
Heterogeneity: I ² = 0.00%	, H ² = 1.0	0							
Test of $\theta_i = \theta_i$ : Q(2) = 0.55	i, p = 0.76	6							
Test of $\theta = 0$ : z = 0.71, p =	= 0.48								
					1/64	1/4	4	64	



# Supplementary Figure 125: Meta-analysis of venlafaxine versus placebo on pharyngitis (sensitivity analysis)

	Ven	lafaxine	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
600-B-367-EU (75 mg)	4	79	1	40		1.98 [ 0.23, 17.12]	42.42
600-B-367-EU (150 mg)	3	79	1	41		1.54 [ 0.16, 14.32]	41.91
Guelfi 1995	1	45	0	47		3.06 [ 0.13, 73.33]	15.68
Overall						1.96 [ 0.49, 7.83]	
Heterogeneity: I ² = 0.00%,	$H^2 = 1.0$	0					
Test of $\theta_i = \theta_i$ : Q(2) = 0.12	, p = 0.94						
Test of θ = 0: z = 0.95, p =	0.34						
					1/4 1 4 16	64	



#### Supplementary Figure 126: Meta-analysis of venlafaxine versus placebo on urinary tract infection (sensitivity analysis)





# Supplementary Figure 127: Meta-analysis of venlafaxine versus placebo on urine abnormality (sensitivity analysis)





#### Supplementary Figure 128: Meta-analysis of venlafaxine versus placebo on taste alteration (sensitivity analysis)





# Supplementary Figure 129: Meta-analysis of venlafaxine versus placebo on HDRS-17 (sensitivity analysis)

Venlafaxine			Placeb	0		Mean diff.	Weight
Mean	SD	Ν	Mean	SD		with 95% Cl	(%)
-10.76	6.6	92	-9.25	6.51		-1.51 [ -3.17, 0.15]	33.45
-10.37	6.52	92	-9.25	6.51		-1.12 [ -2.76, 0.52]	34.19
-14.9	6.53	126	-13	7.32	<b>_</b>	-1.90 [ -3.59, -0.21]	32.36
						-1.50 [ -2.46, -0.54]	
00							
1							
					4 -2	) D	
	Venlafaxi <u>Mean</u> 4 -10.76 7 -10.37 3 -14.9 00 1	Veniafaxine         Mean         SD           4         -10.76         6.6           7         -10.37         6.52           3         -14.9         6.53           00         1	Venlafaxine         N           Mean         SD         N           4         -10.76         6.6         92           7         -10.37         6.52         92           3         -14.9         6.53         126           00         1         1         1	Venlafaxine         Placeb           Mean         SD         N         Mean           4         -10.76         6.6         92         -9.25           7         -10.37         6.52         92         -9.25           3         -14.9         6.53         126         -13           00         1         1         1         1	Venlafaxine         Placebo           Mean         SD         N         Mean         SD           4         -10.76         6.6         92         -9.25         6.51           7         -10.37         6.52         92         -9.25         6.51           3         -14.9         6.53         126         -13         7.32           00         1	Venlafaxine Placebo Mean SD N Mean SD 4 -10.76 6.6 92 -9.25 6.51 7 -10.37 6.52 92 -9.25 6.51 3 -14.9 6.53 126 -13 7.32 00 1 -4 -2	Ventafaxine         Placebo         Mean diff.           Mean         SD         N         Mean         SD         With 95% Cl           4         -10.76         6.6         92         -9.25         6.51         -1.51 [-3.17, 0.15]           7         -10.37         6.52         92         -9.25         6.51         -1.12 [-2.76, 0.52]           3         -14.9         6.53         126         -13         7.32         -1.90 [-3.59, -0.21]           -100         -4         -2         0         -1.50 [-2.46, -0.54]

Fixed-effects inverse-variance model



## Supplementary Figure 130: Meta-analysis of venlafaxine versus placebo on suicidal ideation (sensitivity analysis)

	Ven	lafaxine	PI	acebo			Risk ratio	Weight
Study	Events	No events	Events	No events	3		with 95% CI	(%)
600-B-367-EU (150 mg)	1	81	0	42		•	- 1.55 [ 0.06, 37.35]	1.17
600-B-367-EU (75 mg)	0	84	0	41			0.49 [ 0.01, 24.47]	1.19
Hewett 2010	0	198	1	186			0.31 [ 0.01, 7.68]	2.74
Higuchi 2016 (fixed dose)	41	132	19	72		ŀ	1.14 [ 0.70, 1.84]	44.28
Higuchi 2016 (flexible dose)	47	133	20	72		-	1.20 [ 0.76, 1.90]	47.06
Sheehan 2009	2	93	2	93			1.00 [ 0.14, 6.95]	3.56
Overall					•	•	1.14 [ 0.82, 1.57]	
Heterogeneity: I ² = 0.00%, H ²	= 1.00							
Test of $\theta_i = \theta_j$ : Q(5) = 0.91, p =	= 0.97							
Test of θ = 0: z = 0.78, p = 0.4	14							
					1/64 1/8	1 8		
Fixed-effects Mantel-Haenszel	model							

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# Supplementary Figure 131: Meta-analysis of venlafaxine versus placebo on MADRS (sensitivity analysis)

	Venlafaxine				Placeb	0				Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD				with 95% CI	(%)
600-B-367-EU (75 mg)	53	8.2	9.5	27	9.4	7.3				-1.20 [ -5.29, 2.89]	0.54
600-B-367-EU (150 mg)	48	7.6	9	26	9.4	7.3				-1.80 [ -5.83, 2.23]	0.55
Alvarez 2012	95	-24.2	8.8	88	-16.6	9.4		-		-7.60 [ -10.24, -4.96]	1.29
Guelfi 1995	36	13.6	10.5	23	19.1	13.2			-	-5.50 [ -11.58, 0.58]	0.24
Hewett 2010	193	-17	10.56	186	-13.2	10.64				-3.80 [ -5.93, -1.67]	1.97
Higuchi 2016 (fixed dose)	172	-15.3	10.1	91	-12.41	10.12				-2.89 [ -5.46, -0.32]	1.36
Higuchi 2016 (flexible dose)	176	-15.05	10.08	91	-12.41	10.12				-2.64 [ -5.19, -0.09]	1.37
Khan 1991 (75 mg)	23	21.3	9.7	9	25.3	11.7				-4.00 [ -11.92, 3.92]	0.14
Khan 1991 (225 mg)	22	18.4	11.5	8	25.3	11.7				-6.90 [ -16.25, 2.45]	0.10
Khan 1991 (375 mg)	22	16.4	9.2	9	25.3	11.7				-8.90 [ -16.62, -1.18]	0.15
Mendels 1993 (25 mg)	78	-11.53	9.82	25	-10.53	8.98				-1.00 [ -5.34, 3.34]	0.48
Mendels 1993 (50 - 75 mg)	72	-12.53	9.6	25	-10.53	8.98			_	-2.00 [ -6.30, 2.30]	0.48
Mendels 1993 (150 - 200 mg)	77	-14.8	9.64	25	-10.53	8.98	-			-4.27 [ -8.55, 0.01]	0.49
Sheehan 2009	53	13.53	10.31	55	18.98	11.78	_			-5.45 [ -9.63, -1.27]	0.51
Thase 1997	91	15.2	1.14	100	20.6	1.08				-5.40 [ -5.71, -5.09]	90.33
Overall								•		-5.24 [ -5.54, -4.95]	
Heterogeneity: I ² = 47.57%, H ² =	= 1.91										
Test of $\theta_i = \theta_j$ : Q(14) = 26.70, p	= 0.02										
Test of θ = 0: z = -34.35, p = 0.00											
							-15 -10	-5 0	)	5	

Fixed-effects inverse-variance model

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Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Selection criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Search strategy & Supplementary
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Outcomes and Subgroup analysis
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Protocol
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Protocol
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Protocol
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Protocol
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Assessment of statistical and clinical significance



#### Supplementary Table 1: PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item	Location where item is reported			
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Assessment of statistical and clinical significance			
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Protocol			
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Protocol & Results			
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Protocol			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Protocol			
RESULTS	-					
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1			
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results			
Study characteristics	17	Cite each included study and present its characteristics.	Table 1			
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results			
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results			
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.				
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results			
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results			
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results & Supplementary			
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results			
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results			
DISCUSSION	r					
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion			
	23b	Discuss any limitations of the evidence included in the review.	Discussion			
	23c	Discuss any limitations of the review processes used.	Discussion			
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion			
OTHER INFORMA	TION					
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods			



#### Supplementary Table 1: PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item	Location where item is reported
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Differences between the protocol and the review
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Financial Support & Competing Interests
Competing interests	26	Declare any competing interests of review authors.	Competing Interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data used for all analyses are available in the results.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 For more information, visit: <u>http://www.prisma-statement.org/</u>

#### Supplementary Table 2: Search strategies

Search strategies for 'Venlafaxine or Mirtazapine for major depressive disorder' (C Kamp) Updated searches performed 7 March 2024									
Total number of records identified:10691 recordsNumber of duplicates excluded:2770 recordsNumber of records in final list:7921 recordsNumber of new records sent to authors:763 records									
Cochrane Central Register of Controlled Trials (2024, Issue 2) in the Cochrane Library (813 hits) #1 MeSH descriptor: [Venlafaxine Hydrochloride] explode all trees #2 MeSH descriptor: [Mirtazapine] explode all trees #3 (venlafaxin* or ef*exor* or mirtazapin* or org*3770 or remeron*) #4 #1 or #2 #3 #5 MeSH descriptor: [Depressive Disorder, Major] explode all trees #6 MeSH descriptor: [Depressive Disorder] this term only #7 MeSH descriptor: [Seasonal Affective Disorder] explode all trees #8 MeSH descriptor: [Dysthymic Disorder] explode all trees #9 MeSH descriptor: [Depression] explode all trees #10 MeSH descriptor: [Affective Symptoms] this term only #11 ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)) #12 #5 or #6 or #7 or #8 or #9 or #10 or #11 #13 #4 and #12									

#### MEDLINE Ovid (1946 to 7 March 2024) (2963 hits)

- 1. exp Venlafaxine Hydrochloride/
- 2. exp Mirtazapine/

3. (venlafaxin* or ef*exor* or mirtazapin* or org*3770 or remeron*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

- 4. 1 or 2 or 3
- 5. exp Depressive Disorder, Major/
- 6. Depressive Disorder/
- 7. exp Seasonal Affective Disorder/
- 8. exp Dysthymic Disorder/
- 9. exp Depression/
- 10. Affective Symptoms/

11. ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

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

15. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16. 13 and (14 or 15)

17. limit 16 to ("adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

#### Embase Ovid (1974 to 7 March 2024) (5650 hits)

- 1. exp venlafaxine/
- 2. exp mirtazapine/

3. (venlafaxin* or ef*exor* or mirtazapin* or org*3770 or remeron*).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]

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

10. ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)).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. 5 or 6 or 7 or 8 or 9 or 10
- 12. 4 and 11
- 13. Randomized controlled trial/ or Controlled clinical trial/ or trial.ti.

14. (random* or blind* or placebo* or meta-analys*).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)
- 16. limit 15 to (adult <18 to 64 years> or aged <65+ years>)

#### LILACS (Bireme; 1982 to 7 March 2024) (50 hits)

((mh:(venlafaxine hydrochloride OR d02.033.415.510.500.901 OR d02.092.471.683.948 OR

d02.455.426.392.368.367.318.750 OR d10.289.510.500.901 OR mirtazapine OR d03.633.300.240.588)) OR ((venlafaxin* OR ef*exor* OR mirtazapin* OR org*3770 OR remeron*))) AND ((mh:(depressive disorder, major OR f03.600.300.375 OR depressive disorder OR f03.600.300 OR seasonal affective disorder OR f03.600.300.775 OR dysthymic disorder OR f03.600.300.400 OR depression OR f01.145.126.350 OR f01.470.282 OR affective symptoms OR f01.145.126.100)) OR (((depress* OR affective OR dysthym*) AND (disorder* OR disease* OR symptom*)))) AND ( db:("LILACS"))

#### PsycINFO (EBSCO host; 1806 to 7 March 2024) (562 hits)

S17 S15 AND S16

S16 TI adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged OR AB adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged

S15 S13 AND S14

S14 TX ( (random* or blind* or placebo* or meta-analys*) ) OR TI trial*

S13 S4 AND S12

S12 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11

- S11 TX ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
- S10 MA Affective Symptoms
- S9 MA Depression

- S8 MA Dysthymic Disorder
- S7 MA Seasonal Affective Disorder
- S6 MA Depressive Disorder Expanders
- S5 MA Depressive Disorder, Major
- S4 S1 OR S2 OR S3
- S3 TX (venlafaxin* or effexor* or efexor* or mirtazapin* or "org 3770" or org3770 or org-3770 or remeron*)
- S2 MA mirtazapine
- S1 MA venlafaxine

Science Citation Index Expanded (Web of Science; 1900 to 7 March 2024); Conference Proceedings Citation Index – Science (Web of Science; 1990 to 7 March 2024); Social Sciences Citation Index (Web of Science; 1956 to 7 March 2024), and Conference Proceedings Citation Index- Social Science & Humanities (Web of Science; 1990 to 7 March 2024) (653 hits)

#7 #5 AND #6

#6 TS=(adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged)

#5 #3 AND #4

#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1

#2 TS=((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))

#1 TS=(venlafaxin* or ef*exor* or mirtazapin* or org*3770 or remeron*)

#### Supplementary Table 3: Characteristics of the included trials

Trial ID	Registry/ published	Risk of for- profit bias	Inclusion criteria	Exclusion criteria	Dose range (mg/day)	Control	Placebo washout	Length of intervention	No. randomised to Venlafaxine	No. randomised to control	Baseline HDRS Venlafaxine	Baseline HDRS	Co- interventions		
0600B 1-384-US/EU/CA	protocol No	Yes	NI	NI	150 - 375	Placebo	NI	period 6 weeks	180	83	NI	control NI	NI		
					mg/day										
600-8-367-EU (150 mg)	No	Yes	I. Were 18 years of age and of legal age of consent or older 2. Were outpatients 3. Met DSM-III-R criteria for major depression; had a minimum screening and	Had a decrease of more than 20% in the HAM-D total score between the screening and baseline visits.     Had a myocardial infarction within 6 months of the start of double-blind treatment.     Had a history or the presence of clinically significant hepatic or renal disease or other medical	Mean: 150 mg/day	Placebo	Yes	8 weeks	82	41	27.1	26.6	No		
			baseline score of 20 on the HAM-b total score 4. Had symptoms of depression for at least Imonth before entry into the study. 5. Signed informed consent form.	disease that may have compromised the study. A Mada history of presence of any psychotic disorder not associated with depression 5. Hada history or presence of blagat action of the study of the s											
				empoyee. 5 Was a lactating woman or a woman of childbearing potential with a positive beta-HCG test result cluring the prestudy evaluation. Used any investigational drug, antipsychotic drug, electroconvulsive therapy (ECT) within 30 days, fluxestine within 21 days; or used any MAD inhibitor, paroxetine, or sertraline within 14 days; or used any other antidepresant, analykict, seatibet-hyporotic drug (secord thola layhoted) or any other and orgenesant, analykict, seatibet-hyporotic drug (secord thola layhoted) or any other											
				psychotropic drug or substance within 7 days of the start of the double-bilding treatment period. Like day an onspychotpharmaclogic drug with psychotropic effective within 7 days of the start of the double-bilding treatment period unless a stable done of the drug has been maintained for at least Jarom before the treat of the double-bilding treatment period. Had a history of drug or alcohol dependence within 1 years as defined by DSM-IIB extires. Had dirically significant atomication the starbid period treatment period.											
600-B-367-EU (75 mg)	No	Yes	I. Were 18 years of age and of legal age of consent or older	arug screen.  1. Had a decrease of more than 20% in the HAM-D total score between the screening and baseline	Mean: 75	Placebo	Yes	8 weeks	83	42	26.5	4.7	No		
			<ol> <li>Were objective:</li> <li>McH 2DM-HR Criteria for major depression; had a minimum screening and bandlers score of 20 on the HAM-D total score</li> <li>A static symptoms of depression for at least 1 month before entry into the 4. Signed informed consent form.</li> </ol>	visits. 2. Had a microardial infraction within 6 months of the start of double blind treatment. 3. Had a history or the presence of clinically significant hepatics or real disease or and medical disease that may be accomposited the start within the start of the start of disease that may be accomposited the start within the start of the start of the start of the start of 4. Had a history or presence of blight discussed. 7. Had a history or presence of blight discussed. 7. Had a history or presence of blight discussed. 8. Was acceled validation to unit a discusse that the start of the start of the start of the Microardian start of the start of the start of the start of the start of the Microardian start of the start of the start of the start of the start of the Microardian start of the start of the start of the start of the start of the Microardian start of the start of the start of the start of the start of the Microardian start of the start of the Microardian start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the start of the sta	mg/day										
				in https:// indigitary.com/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/section/se											
Alvarez 2012	Yes	Yes	Patients with MDD presenting with a current major depressive episode according to DSM-10-178 criteria (APA, 1994) were included in the study if they were an outpassite of either sex, aged from 18 yr to 55 yr, with a Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) total score of 30 at the baseline visit.	Patients were serubdied if they had any current pupulation disorder other than MDD as defined in DSD VTI Bassesse during MDM. Serub Havin International Neurophysikalis (Interbus) (NNII: Shechan et al. 1998)). or if they had a current or past history of manic or hypomanic spisode, schizophrene and applicable. Gooder, hunding major depression with spirachise External retradiation, organic metal disorders, or metal disorders due to a general mediatic conductor, any sublance about disorder within they provide. Thesting and they applicable transcriptional metal disorders. The second disorder of the state of the spirate of the second disorder and the spirate of the second actional within they provide. The state of the spirate of the spirate of the social provides of the spirate of the social general disorder of the spirate of	75-225 mg/day	Placebo	No	6 weeks	114	105	29.4	29.7	No		
				compension the study. Healterist a stroke, risk of validels, based on the investigator's influed judgement, or who had a score of of 5 on ten 10 of the MADRS scale builded thoughts) were also excludes, as were those receiving that and basicour benergy or systemic targe/hostherap, or were preparation of breast-feeding, had a known hippersensitivity or were non-response to validation, or who's preparative anyothoms were considered by the investigator to have been ensistent to two addecate an adopterable and threatments of at least 6 wild scales, or had providualy been responded to Liu AL2000. A faintes were directly and the stroke of the directly stroke of the stroke of the directly stroke of the stroke of the directly stroke of the stroke of the directly stroke of the stroke of the directly stroke of the stroke of the directly stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the stroke of the											
Claphorn 1990	No	Yes	NI	Ni	75-225	Placebo	Yes	6 weeks	83	82	23.6	24.6	No		
Cunningham 1994	No	No	Patients whose HAM-D score dropped 20% or more between screen and	Patients included women or men 18 years of age or older. All women of child-bearing potential had to	mg/d 75-200	Placebo	Yes	6 weeks	Unclear	Unclear	25.02	24.41	No		
			were enduded from the double blind phase. Patients were also excluded if they had unsable medical conditions, ingritional bloorstory or KIG absommalies, history of sature disorder, any psycholic disorder medical structures and the sature of	have negative P human chronic granddoroph regramsrup test before receiving double-billed medication and agree to an effective contraction until the completion of the protocols. At patients med DSA HR a chama lar major depression, either single or recurrent episode, nearget that Hey must specification and agree and a must structure distance interview. At mission was polyhold to the the specification of the single or the single or the single Scale for Depression (HMAO) score of 20 was required at both the initial screening visit and at the baseline wish before randomization.	mg/day										
Cunningham 1997 (IR)	No	Yes	Outpatients aged 18 years or older who me to SM-III-R criteria for a major depressive episode; had a minimum baseline score of 20 on the 21-leem Hamilton Depression Rating Scale (HAM-D)(12), with not more than a 20% decrease in score between screening and baseline; and had symptoms of depression for at least one month before study entry were eligible.	Patients were excluded if they had previously been treated with veralization. Women who were lacating or of childening potential with a positive β-human chironic genadotropic (HCG) pregnancy test were not included. In addition, patients with a history of chirally significant medical deuses or chirality significant altonomiation on a screening physical examination, exteriorating patient (ECG), or biocetary tests: scate suicidal tendencies: a history of a secure disorder; presence of an organic metal disorder; biplard moderor, a history of an secure physical canonication, extension of the physical examination, extended in the physical examination, extension of the physical examination, extension of the physical examination of the physical examin	Max: 150 mg/day	Placebo	Yes	12 weeks	Unclear	Unclear	24.0	24.9	No		
Cunningham 1997 (X8)	No	Yes	Datastients aged 18 wast or older who met DOM-III-8 ritheris for a major.	operpraction were exoluted, unter relation for exolution fait and any mentiographical ang. Interpretation cargo, electroconsolute hereauxien histo i days, foreast entrol and any monoamine and are inhibitor, parametine, or serbraine within 13 days, for an editory and indicates and, another inhibitor, parametine, and any any participation of the and and any	Mar: 150	Placebo	Yest	12 weeks	Linclear	Linclear	24.5	24.9	No		
			depressive epilode; had a minimum baseline score of 20 on the 21-tem Hamilton Depression stating scale (UAM-D)(12), with not more than a 20% decrease in score between screening and baseline; and lad ymptoms of depression for at least one month before study entry were eligible.	Latation or of childbearing potential with a positive P- human choroine genadatoropin (PCG) argement extreme end included in additora, patiente with a history of chinally significant model disease of inclualy significant abromalities on a screening physical examination, electrocardiogram (ECG) or lobotaristy trist, such suicidal tetratives, a history of a server disorder, presence of an organic mental disorder, bipoker disorder, or a history of any psychotic disorder not associated with diversion were exiculated. Other reasons for exclusion were used any investigational diverge, antipsychotic disord, or electrocomovalue that pays within 30 days, fluoretine within 12 days, or managemic endusies in teatments, used any subtractive diverger and the server antidepresensat, annologic, tediaber hypotic diverger and the spectrative divertial exists of double-blackers), unites the double-black barry within 10 days and the start of double-blackers of the start of double-blackers of days in the start of double-blacker of days are trained within 12 days, or a disregate blackers), unites the double-blacker blacker blacker blacker blackers within 7 blackers and the traineting or a lattory or day are shared blackers within 7 blackers.	mg/day										
EudraCT 2004-000562-13	Yes	Yes	Men and women 18 to 75 years of age, inclusive; outpatients; subjects must have had a primary diagnosis of MDD based on the criteria in the	Subjects treated with DVS SR at any time in the past, treated with venlafaxine (immediate release [IR] or ER) within 90 days of study Day 1, and subjects with know hypersensitivity to venlafaxine (IR or ER)	Max: 150 mg/day	Placebo	No	8 weeks	128	123	25.8	26.0	No		
			Diagnostic and Statistical Manual of Mental Disorders, fourth editors, higher orrectancer galacode without approximate features. If other allowable performance of the state of the state of the state of the state of the performance appendix the fourth of the state of the state of the data, states of at least 22 on the heamilion Psychiatric failing Scale for persistion, 12-linear linked 5021, and as core of at least 30 data impression Scale develops of the state 10 and	were excluded from the study.											
EudraCT 2007-007025-51	Yes	Yes	In- and outpatients with a primary diagnosis of Major Depressive Episode (MDE) according to DSM-VI-YRIM criteria, who: had a MDE of 32 months duration at screening had a Montgomery-Asberg Depression Rating Scale (MADRS) total score 226 at screening and at baseline were 218 and 55 years of age		Max: 225 mg/day	Placebo	No	8 weeks	7	7	Unclear	Unclear	No		
Guelfi 1995	No	Yes	Inpatients with a primary diagnosis of depression, aged 18 or older, were enrolled if they met the DSM-III.R criteria for major depression and melanchola based on a structured inventory. The patient were required to have a minimum prestudy and initial study day score of 25 or more on the Montgomery-Abdres Depression Scale (MADRS) and symptoms of depression for at least 1 month before they could enter the study.	Patients were neighbe for enrolment if they bad significant physical or mental incress (sinth them operation), a mycareal induction within a control of the study, a bintro of storate disorder or any psycholic disorder not associated with depression, or a history of disord exploration. Indition, patients what a score of a for mean on the suicidal theory of any of activable dependence. In addition, patients what a score of a for mean on the suicidal theory is then of the MADNA were excluded from entry. Investigational days, antipopholes, before antidipersamits, molytics, and the study schedule score) were combined and and any ophodeneogy (defined as muchin's schedule sciencil) were combined.	150-375 mg/day	Placebo	Yes	4 weeks	46	47	28.2	28.6	No		
Hewett 2009	No	Yes	Patients aged 13–64 years with a DOM-M diagnosis of MOM for a minimum of 8 weak were eligible for inclusion. Eligible patients required an Interactive Veice Response Synthem (IVKS) Hamilton Depression Rating bable (IAMA) 12–64 mod las core of all a struct host recenting and baseline visits (IGAA), et al. (1995), which must not how decreased or increated interpression-Servery for lifesa (IGA) structure and a structure impression-Servery for lifesa (IGA) structure at both screening and askeline was also required. Patients with co-motivations were allowed to errol if their condition had been stable for at least 3 month.	Patients were excluded if they had been homicalial at any time or unical within the pair 4 months. Those with anorema homics are blank in which the pairs 12 months, paycholic disorders, may-cardal infraction within the pairs year, a statute disorder or blood persure 3120/p5 mmilly were also accluded. Nations were on eligible to participate if they had table buogenion or vanifabane within the pairs 6 months, or had experienced a significant adverse response to either antidopersuant in the eligible and the second significant adverse response to either antidopersus the statute of the second significant adverse response to either antidopersus of eliferent classes were also excluded. To be elifible, during the 2 week pairs to the study, patients, should on the used the following: any psychotherapy or psychotropic drugs; to them medications with potential pharmacefulnet interactions on a might be the size of the statute how the sistent behavior. Study participants were required to test regaritive in a unite days cereer, and to have above no endeemed eliabed to buokance aboved dependence within the pair 12 months.	75-150 mg/day	Placebo	No	8 weeks	Unclear	Unclear	Unclear	Unclear	No		
Trial ID	Registry/ Risk of for published profit bias		Registry/ Risk of for- published profit bias		Inclusion criteria	Exclusion criteria	Dose range (mg/day)	Control intervention	Placebo washout	Length of intervention	No. randomised to Venlafaxine	No. randomised to control	Baseline HDRS Venlafaxine	Baseline HDRS	Co- interventions
------------------------------------------------	------------------------------------------------	-----	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------	--------------------	------------------------	-------------------------	--------------------	---------------------------	----------------------------------	------------------------------	------------------------------	------------------	----------------------
Hewett 2010	No	Yes	Patients aged 18–64 years with a DSM-M diagnosis of MDD for a minimum of eight weeks duration were digible for indusion. Eligible industriant squared and interactive Vice Reproduce System (VIIS) lamittee Depression hang. Scale (IsAM) 1/1 hern total score of 2.1 at both the contract of interactive bioteneous systems (VIIS) is a total in the Clinical Global imprevalues the memory bioteneous contract of a score of 24 on the Clinical Global imprevalues-Severity of Times (CGI-S) scale at both screening and baseline was also required.	Patients were excluded if they had a history of manic episode, past or current psychotic disorder or a current Au is il diagnosis that suggested non-responsiveness or non-compliance with therapy. Also disolded were patients that had been founding at any time in the therapy exclusion within the past 6 months, thus within works more an advantage and a single main the therapy and a single single s	75-150 mg/day	Placebo	No	period 8 weeks	Unclear	Unclear	30.1	control 30.6	No		
Hguch 2016 (flord dose)	Yes	Yes	In the double-binned study, parameters aged a least 20 years with a minary diagonic of 1000 on the basic of 100 M/ or dirent, when we english for the study, in addition, patients should have enguinesed englishes for the study, in addition, patients should have enguinesed these 28 days in a recurrent episoide before the screening with and have obspace in the screening and baseline with sum a change in MADB to the study and parameters are should be the screening in MADB to the study of the screening and baseline with sum a change in MADB to the study of the screening and baseline with sum a change in MADB to the study of the screening and baseline with a screening and baseline with clubs the screening and a scree of at least or the Clubsal clubal impressions. Scale Screenity (Club 21 the screening and baseline withs harding end to the screening of the screening and baseline withs perioders aspects of the study and were wilking and dated the screening. All formals and marks patterns who were biologically capabed for schedule withs; the screening and baseline withs, and other study procedures. All formals and marks patterns who were biologically capabed of bins; control during the study period and for 28 days after the last dose of study metal control during the study period and for 28 days after the last dose of study metal control during the study period and for 28 days after the last dose of last screening the study period and for 28 days after the last dose of last screening the study period and for 28 days after the last dose of last screening the study period and for 28 days after the last dose of last screening the study period and for 28 days after the last dose of last screening the screening and baseline withs to study metal control screening the screening and baseline withs to study metal control screening the screening and baseline to the screening and baseline withs to study metal control screening the screening and the 28 days after the last dose dattaget metal screening th	Patients who had received treatment with verifiabative or deventifation in the part, a history of promoting disologies metal retradicious subscripts profits disorders, disensitive subscripts and the second seco	Mean: 75 mg/day	Placebo	No	8 weeks	Unclear	Unclear	22.6	22.4	No		
tiguchi 2016 (flexible doce)	Yes	Yes	In the double-blinked study, constantes aged a text 20 years with a primary dapsion of 4000 on the basis of the DAH V circlen, who experienced single or recurrent episodes without psycholic feature, were primary dapsion of the dadion, primaris subda have experienced epible for the tacky in address, primar subda have experienced these 23 days in a recurrent episode bridge the screening with a data for the screening and baseline visits with a dampe in MARDs total text as a days in a recurrent episode bridge the screening with a data data and the screening and baseline visits with a dampe in MARDs total text as a data data or begin data. The screening with a data data with the screening and the screening with a data data with the screening and the screening with a data the DAMDS total screen data screening the screening with a data impression. Scale Screenity (GIS) at the screening with a data and more data screen of text screening with a data and more data and the screening text and the screening with a data and the screening text and the screening with the data of the screening text and the screening with a data data and more down the screening text screening with a data and more data and make patients who were biologically capabe of the with data with the use of a reliable method d brink control during the study period and the Vid days after the last dose d taking more data and the screening with a data method d brink control during the study period and the Vid days after the last dose d taking more data screening the screening with the screening and taking more data with the screening with the screening with the screening with a screening with the screening with a data with the screening with a screening with the screening with a data with the screening with a data with with the s	Patients who had received trastmere with verdiations or descentification: In the gate, a history of proceeding disorder protest interactions there also provide indication, denomination, descrive compulsive disorder protest transmits classical works protocol indications, denomination and a straight and a straight and a straight and a straight and a straight and and a straight and a straight and a straight and the straight and and a straight and a straight and a straight and an environgencies to hear antidepressant trastments in the parat, had a history of chronic trastment and an environgencies to hear antidepressant trastments in the parat, had a history of chronic trastment and the bencification for longer than in mental disorder because of a general medical condition or a neurologic disorder were also excluded.	75-225 mg/day	Placebo	No	8 weeks	Unclear	Undear	22.4	22.4	No		
Hopkins 2013	Yes	Yes	The duration of the current episode must be at least 1 month but not longer than 12 months. Solgets must have a primary disposis of Major Depressive Diorder: Solgets must have and least one previous diagnosed episode of MDD MDD must be the condition that was chefly responsible for motivating the ubject to seek transment. Solget to is in general good health.	Solget is participating in, his participateri in, or plans to participater in any investigational drug study, Solget with his docubard blood within his lest 30 day or plans to barding and a blog- following any encipation. Solwer failure in composed (in the part 5 years) to two adequate (docu end duration) antibare and solwer failure in composed (in the part 5 years) to two adequate (docu end duration) antibare and solwer failure in composed (in the part 5 years) to two adequate (docu end duration) antibare and solwer the solwer and the solwer failure in the solwer failure in the solwer failure in the development failure in the solwer failure in the development failure in the solwer failure in the development failure in the solwer failure (in the solwer failure in the solwer failure in the solwer failure in the development with an iddependence or abuse (excluding notation with an iddependence or abuse (excluding notation with an iddependence or abuse (excluding notation with a bitter) of significant in the divation and adding of a solwer failure in the solwer failure in the solwer failure in the duration of the solwer failure in the duration of the solwer failure in the solwer failure in the duration of the solwer failure in the	Mean: 150 mg/day	Placebo	No	8 weeks	Unclear	Unclear	Unclear	Unclear	No		
Hunter 2010 (study 2) Hunter 2010 (study 3)	No	Yes	Salpets were encluded if they previously had failed to benefit from transmer with the autofersors and treps studied. If they had a biotory of suides attempt, or if they suffered from any medical liness or received medication because tailoftabarty affect from function. Salpets were recruited through outpatient clinics and community advertisement and met HOO diagnostic clinics using a structured demonstration of the HOO diagnostic clinics and community are excluded if they privately had failed to benefit from restances at the an addreps state (Isam-Dir) / Isamiton. JSG0) score 316. Salpets were excluded if they privately had failed to benefit from restances with the antidepressant being studied, if they had a history of suice attempt, or if they suffered from any medical liness or received any medication	Solpics were excluded if they previously had failed to benefit from treatment with the antidgressant being studied, if they ad a hatrop of suicide tempt, or if they sitefact from any medical lifes or received any medication known to significantly affect train function. Solpics were encluded if they previously had failed to benefit from treatment with the antidgressant being studied. If they all hatrop of suicide a barrel for the method from any medical lifes or received any medication known to significantly affect than function.	Mean: 150 mg/day Mean: 150 mg/day	Placebo	Yes	8 weeks 8 weeks	Unclear Unclear	Unclear Unclear	Unclear Unclear	Unclear Unclear	No		
Kahn 1998 (150 mg)	No	Yes	known to significantly affect brain function. To be included, patients had to have had demonstrated symptoms of depression for at least 1 month before study entry and to have minimum		Mean: 150 mg/day	Placebo	Yes	12 weeks	Unclear	Unclear	24.5	25.1	No		
Kahn 1998 (200 mg)	No	Yes	scores of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D) [15] both prestudy and on study day 1 (baseline). To be included, patients had to have had demonstrated symptoms of		Mean: 200	Placebo	Yes	12 weeks	Unclear	Unclear	24.8	25.1	No		
Kahn 1998 (75 mg)	No	Yes	scores of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D) [15] both prestudy and on study day 1 (baseline). To be included, patients had to have had demonstrated symptoms of		Mean: 75	Placebo	Yes	12 weeks	Unclear	Unclear	24.3	25.1	No		
			depression for at least 1 month before study entry and to have minimum scores of 20 on the 21-item Hamilton Rating Scale for Depression (HAMD) [15] both prestudy and on study day 1 (baseline).		mg/day										
Learned 2012 (study 1)	Yes	Yes	In both studies, male and female patients (12-64 years odd) were required to have a adjurosis (10-64 with MO) (singer or resur-net pecidods according to the Diagnostic and Statistical Manual of Mental Diorders, Holdston, Test Revision (2044): MT(3), wait and an extense topoded curston of at least to weeks but less than two years. Patients were required to have a Chical Global Intersion Serverth of Iller strates (CoS) (Sci Sci Sci Sci Sci Sci Sci Sci Sci Sci	Patients were excluded if the symptoms of a presenting lines were better accounted for by another diagnosis or if the patients that a current SDM-Tri diagnosis of any patient disorder, antioscia to other line personality disorder, biplant disorder, chickophersia, or other psychotic disorders. Patients were excluded if they hap disorders line that there mother of screening, or had arrower antidopressants, had started psycho-therapy within three mother of screening, or lisad exceeding. Patients considered by the investigator to be at risk for succide or who had any previous disorder started exceeding the hips the investigator to be at risk for succide or who had any previous disorder starters considered by the investigator to be at risk for succide or who had any previous disorder starters considered by the investigator to be at risk for succide or who had any previous disorder starters considered by had the starter motion of the starters with exceeding the block had at screening were excluded.	Max: 225 mg/day	Placebo	No	10 weeks	134	126	Unclear	Unclear	No		
uedeman 2006 (223 mg)	Tes		mind all outsides, a synchronic art y fees to all with all outsides of a synchronic ob- sense of the synchronic and the synchronic and the synchronic and Psynchronic Association, 1994 (inters, single or recorrect exclusion) (Phono Psynchronic Saturus, we eighbe for study and trigonation. All sociaties and sucrearing, patients were also required to have a minimum MAM-D17 zoor Appholic for the synchronic and the synchronic and the synchronic Mathematic and the synchronic and the synchronic and the synchronic and the synchronic of the synchronic and the synchronic and the synchronic and the synchronic synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and the synchronic and	reaction during of a solution of a solution is were excluded, numeric, judiens with Catolician permetalized analysis of advances, park (disorder, a cold analysis) policies were activated to permetalized analysis long as MGD was the primary diagnosis. Policients at high risk for suicidal behaviors were excluded.	mg/day	Piacebo		a weeks		127	23.1	Unclear	NU		
Luthringer 1996	No	Yes	18 years or older with DSM-III cirretio of clinical depression for a minimum of 4 weeks. They had to have a 21-time MAM-D score of at least 20 at both the initial screening and pre-treatment baseline.	Patients were excluded if their affective lines was lippior or primarily psycholic or 10 bey reported indexed suicial lackation, scenal studied or drug dependence or about any scitator or untable medical supported from of latin costol and were admitted to the tauly only of a beta human chronice quadratoria testa and any scenario sc	75–225 mg/day	Placebo	Yes	29 days	12	12	28.2	27.1	No		
Mendels 1993 - 150 - 200 mg	No	Yes	Outpatients aged 18 to 75 years with a diagnosis of major depression which or prycholic futures (ISOM-IIII-9) (tortes) were screened at 15 centers. Patients were required to have a total score of at least 20 on the 21-hem Namilno stating Sale for Depression (NAM-O), a score of at least 9 on the Raskin score, and a moderate or greater seventy of illines on the Canical Global mersion (ISG) rack	Exclusion or incrine included active suicidial letestion or suicide attempts in the last 12 month; dissipativensi, aggruine meak syndhenises, a strate disorders, failed in respond to an adequate strate and the strate of the strate syndhesis and the strate disorders (failed attempt and within 32 days of the study; moreovanime excitate inhibition or meurologics within 3.4 days of active drug treatment; and use of other antidepressants or annicipation within 3.4 days of baseline.	150- 200mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	25.57	25.39	No		
wendels 1993 - 25 mg	No	Yes	Lutpatients between the ages of 18 and 65 years were eligable to participate if they met DSM-III-R criteria for major depression (American Psychiatric Association 1987) and had a minimum score of 20 on the 21- item Hamilton Rating Scale of Decression (HAM-D: Hamilton 1960)	vations were ineligable for enrollment if they had significant physical illness or mental illnesses other than depression or a history of drug or alcohol dependence within 2 years of the study. Patients were not enrollen if they were suicidal to a degree that precautions against suicide had to be taken. Patients with a history of biplair disorder or psychosis were excluded from the study.	25mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	25.92	25.39	No		
Mendels 1993 - 50 - 75 mg	No	Yes	Outpatients between the ages of 18 and 65 years were eligable to participate if they met DSM-III-R criteria for major depression (American Psychiatric Association 1997) and had a minimum score of 20 on the 21- tem Hamilton Rating Scale of Depression (HAM-O)-Hamilton 1960).	Patients were ineligable for enrollment if they had significant physical liness or mental linesses other than depression or a history of drug or alcohol dependence within 2 years of the study. Patients were not enrollen if they were suicidal to a degree that precaution against suicide had to be taken. Patients with a history of bloght disorder or prochois were excluded from the study.	50- 75mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	25.43	25.39	No		
Nemenofi 2007	No	Yes	Perdicipants over advanteent 31 apera or defen eld me Dugonott and solutional Mexand Solut, and a solution Solution 2004 (V ontra for major depres - sixe discorte (M ontrains) Psychiatric Association, 1984). a garaients had aynamis on greant or at attach a month before advantation, and a corred at least 20 on the 21-tem Hamilton Rating Scale for Depression (HAM-021).	plantism seare standard in Hery had a history aprim-case of logical disorder can significant distantism with history of locad or automatory history history of logical distantism with history of locad or automatory and locad disorders or alternative distribu- tably, as were those who had any clinically significant mediad disorders or alternative distribu- tion of locad distribution of locad distribution consolitation of locad disorders or alternative distribution of locad distribution of locad distribution of locad distribution patients were excluded if they were acutely suicidal to the degree that precusions against suicide mere mediad. Automatic auto for exclusions history of moresponses to verification of holesce time. Further, any patient who had researched either study disu within 6 months prior to starting the double- ding arangement of the starting distribution of the double-study distribution of the double- ding distribution of the double-start distribution distribution of the double- ding distribution of the double-study distribution distribution of the double- rand distribution distribution parateristic on variation within 14 days, and their and dispersant, anavolatic, seative-hispontic dis greater charanter and the double-study distribution of the double-blind terminanter and the distribution of the distribution of the double-blind terminanter and the double-blind terminant anti- antia distribution distribution and the distribution of the double-study distribution of the double-blind terminanter and distribution of the double-blind terminanter and the double-study distribution and the double-study distribution of the double-blind terminanter and distribution of the double-blind terminanter and the double-study distribution of the double-blind terminanter and and the study distribution distribution of the double-study distribution of the double-blind terminanter and distribution distribution distribution of the double-study distribution distribution distribution distribution distribution distribution d	75-225 mg/day	Placebo	Yes	6 weeks	102	102	23.5	23.7	No		

Trial ID	Registry/ published protocol	Risk of for- profit bias	Inclusion criteria	Exclusion criteria	Dose range (mg/day)	Control intervention	Placebo washout	Length of intervention period	No. randomised to Venlafaxine	No. randomised to control	Baseline HDRS Venlafaxine	Baseline HDRS control	Co- interventions
Rudolph 1998 (225 mg) + Khan 1991, Schweizer 1991	No	Yes	The study oppulation consisted of psychiatric outpatients between the ages of 18 and 65 who met Diagnostic and Statistical Manual of Mental Diorders (DSM)-III criteria for major depression. In addition, symptoms of depression had to have been present for at least 1 month before study entry, and the patients had to have minimum and baseline (After wahoud scores of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D 21)	Women of childbaring age were not recruited, not were subjects with bipolar mood disorder (or bipolar II), schizofrenia, and other psychotic disorders.	Mean: 225 mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	25	25	No
Rudolph 1998 (375 mg) + Khan 1991, Schweizer 1991	No	Yes	The study appulation consisted of psychiatric outpatients between the ages of 18 and 65 who met Diagnostic and Statistical Manual of Mental Diorders (ICMA) efficienta for major devision. In addition, symptoms of depression had to have been present for at leas 1 month before study entry, and the patients had to have minimum and baseline (left weakhoul) scores of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D 2) 21)	Women of childbauring age were not recruined, not were subjects with bipolar mood disorder (or bipolar II), schizofrenia, and other psychotic disorders.	Mean: 375 mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	25	25	No
Rudolph 1998 (75 mg) + Khan 1991, Schweizer 1991	No	Yes	The study appulation consisted of psychiatric outpatients between the ages of 13 and 65 whom Re Diagonics and Satistical Manual of Mental Diordens (DSM)-III criteria for major depression. In addition, symptoms of depression had to have been present for at least 1 month before study entry, and the patients had to have minimum and baseline (later washoul) scores of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D 21)	Women of childbauring age were not recruinds, not were subjects with bipolar mood disorder (or bipolar II), schizofrenia, and other psychotic disorders.	Mean: 75 mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	26	25	No
Rudolph 1999	No	Yes	The study population consists of outpatients age 18 years and older how the Diagnostic and Sattistic - Jahnanal of Annet Diaoders (2004), yill criteria for major depressive disorder (Tak Force on 1504 hr (1594)). The outpatient of the patient and subsequence completion by the investigator of a worksheet containing the DSM V criteria. In add: - Han, patients hat on the semantism of a special containing the DSM V criteria. In add: - Han, patients, hat on the semantism of a diabate semantism of the semantism of the semantism of a semantism of the semantism of the semantism of a semantism of the semantism of the semantism of a semantism of the sem	Patients were excluded from study participa- tion if they had recent (within is month) treatment who is a lower hyperbandling to either of the active study days, carries specified medical con- ditions, basiner model disorder, approches disorder or associated with depression, or a history of the study of the study activity some were taken excluded. Patient whole NAMO 31 activity and the study from the prestudy evaluation to the baseline evaluation were excluded from randomization. Each properties study patient gave written informed consert.	75–225 mg/day	Placebo	Yes	8 weeks	100	98	25	25	No
Schatzberg 2006	No	Yes	Male or formal subjects aged 65 years or other and not fining in a residential storing wave eligible for this study. In addition, eligible par- ticipants met Diagnostic and Statistical Manual for Mental Disorders, fourth folliton orientics of possibility of possibility of particular nonpsycholicity, with a current giologic of at lasts frow weeks in duration; had 2 31 etem HMAD (MMAO 21) score 230 at the initial visit; and were willing and able to provide informed consent.	Subject with bipolar disorder, a projectic disorder on criteria to depression, current subdance data conclustance depresence with the pest syste (other than Ancienci, or were Matalian either pest access with the pest syste (other than Ancienci, or were tablance in the pest size moth, decisoroandwice berasy with the they for there monthe, or any inves- tigational ding or antipolycletic motical estimation of the size of the test of the size of the bace-science were subjects who used astematics, cise priorit, summarian testeration the study, networks, or any mosamine oxidase inhibitor within 14 days, used any other antidipresiant, analysis, or any mosamine oxidase inhibitor within 14 days, used any other antidipresiant, analysis, or any mosamine oxidase inhibitor within 14 days, used any other antidipresiant, analysis, or any mosamine oxidase inhibitor within 14 days, used any other antidipresiant, antidation of the size of the size of the double-biblitor testement period. The size were astrated endory, or migrations of housenits, use with the prior of born the study and and abarear double, or migrations within the prior for month, and patients with a server, acute, or unable model and the server call abarear to approximate the size of the double-biblitor within 14 days, and patients with a server, acute, or unablation estimations or molecular antipolicy the size size of the output size of the antidoxies, and patients with a server, acute, or unable model and the server call abarear to approximate the size of the output size of the output size of the output size of the size of the output	Max: 225 mg/day	Placebo	Yes	8 weeks	104	96	24	23	No
Schweizer 1994	No	Yes	Patients aged 18 years or older were recruited who met DSM-III-R criteria for major depression for a mini-mum of 4 weeks. The 21-item Hamilton Rating Scale for Depression (HAM-D) total score had to be at least 20 at both the initial screen evaluation and the pretreatment baseline. The score should not have decreased by more than 20% during the screening period.	Patients were excluded if their affective illness was bipolar, required hospitalization, or was pimarly apprichtic. Patients to were excluded if they reported marked availad leation recent (in the past 2 years) alsohol or drug dependence or abuse, any axite or unstable medical problem, or a history of actures. Women exable of becoming program twere required to use a medical approach form of birth control and were admitted to the study only if a -human chorionic gonadotropin test was negative.	Max 182 mg/day	Placebo	Yes	6 weeks	Unclear	Unclear	25.5	24.6	No
Sheehan 2009	No	Yes	Participants were selected from patients who were hopatizational before sciencing, inputation and get 24 spars, who fulfilled criteria of the Diagnostic and Statistical Manual of Mental Dioxrdens, fourth edition American Psychiatric Association, 1984) of the melanoholic study-get of MDD ad at least 1 month duration, were eligible for study enrolment if they science at least 2 in one H2.1 kern Hamilton Rating Scale for Depression (IVMA 021)(Hamilton, 1960).	Matical literace, honon hipersensitivity to effer study day, treatment with effer study day within a hondha, or mycaalia larkration within the match before the star of daube-linit dheapy, in addition, patients with clinically inplicant abnomalities on the physical examination, effectivacing days, holdowy tests, or wind example of the star of the second star of the star of	Max: 225 mg/day	Placebo	No	6 weeks	95	95	29.9	29.4	No
Silverstone 1999	No	Yes	Outpatients aged 18 years or offer who met DSM-V orients for major deproxive disorder were eligible if they had animum baseline score of 20 on the fort 17 term of the 21-term Hamilton Rating Scale for Depresion (HAM-O) who in other can bas 2005 decress in score between scorening and baseline. They also had a minimum score of 8 on the Covi scale and symptoms of depression for at least 1 month before study entry.	cobiol of drug dependence or abuse within 1 year before double- blind treatment were also excluded. Comen who were prepare, luctating, or of childbarring potentialized has positive beta-human. Micronic groadstroips (BCG) prepare, treat-treat-live ere on included. Also excluded were prepare the set of the s		Placebo	Yes	12 weeks	128	119	27.6	27.1	No
Thase 1997	No	Yes	Eligible patients (I) were outpatients, (2) aged 14 years or older, (3) satisfied DSM / vertia for mayed depresent disorder for at least 1 month, and (4) had a minimum baseline score of 20 on the 21-tem Hamilton Batting Scattor Depression (HVAD), with not more than a 20% decrease in score between screening and baseline.	Patients were excluded if if they had previously been trated with verifiations. Women who were licitating or preparely the, a positive 5-should on theman chonomic soudortopin test) were not included. Patients were also excluded they had a history of chically significant abnormalities on a conterin physical examismon, an electrocargogian (EG) or bioscopy tests. Addressed exclusion criterin included a sunte suicial interdences, a history of resize disorder, a history or preserve of a distributed and the suicial interdences, a history of resize disorder, a history or preserve of a depression. Patients could not have network an investigational drug, an anticyphotic drug, or depression. Patients could not have network an investigational drug, an anticyphotic, drug, or history or preserve of the star of a patient were with 20 days, an anticyphotic, or disor hypothorize, drug or a university of the star of double-disord transmitter. Use of nonpsychotropic drug as uninnum of 1 a moth before double divel distances. Use of nonpsychotropic drugs with hypothorize (Fisci) (e.g., & Jademsregic blockney) use parmitted if the danage vers stable for a naminum of 1 a moth before double distances.	Max: 225 mg/day	Placebo	Yes	8 weeks	102	95	25	24	No

### **Supplementary Table 4: Summary of Findings**

#### Venlafaxine compared to control for adults with major depressive disorder

Patient or population: adults with major depressive disorder

Setting:

Intervention: venlafaxine

Comparison: control

	Anticipated absolute effects* (95% CI)					
Outcomes	Risk with control	Risk with venlafaxine	Relative effect (95% Cl)	№ of participants (studies)	evidence (GRADE)	Comments
Suicides or suicide attempts follow-up: range 6 weeks to 8 weeks	8 per 1.000	<b>5 per 1.000</b> (2 to 13)	<b>OR 0.65</b> (0.25 to 1.71)	1907 (7 RCTs)	⊕⊖⊖⊖ Very low ^{a,b}	
Serious adverse events follow-up: range 4 weeks to 12 weeks	25 per 1.000	<b>65 per 1.000</b> (41 to 104)	<b>RR 2.66</b> (1.67 to 4.25)	5526 (22 RCTs)	⊕⊖⊖⊖ Very low ^{a,b,c}	
Non-serious adverse events follow-up: range 4 weeks to 13 weeks	472 per 1.000	<b>674 per 1.000</b> (571 to 797)	<b>RR 1.43</b> (1.21 to 1.69)	5483 (24 RCTs)	⊕⊖⊖⊖ Very lowa.b.c	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; RR: risk ratio

**GRADE Working Group grades of evidence** 

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

#### Explanations

a. Downgraded 2 levels for high risk of bias in included studies.

b. Downgraded 2 levels for imprecision due to Trial Sequential Analysis showing that there was not enough information to confirm or reject a relative risk reduction (RRR) of 20% and the accrued number of participants is below 50% of the diversity-adjusted required information size (DARIS).

c. Downgraded 1 level for indirectness due to differences in measurement of outcome.

## **Supplementary Table 5: RoB2 table with explanations**

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
0600B 1-384-US/EU/CA	No information	No information	No information	No information	No information
600-B-367-EU	No information on concealment.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not sufficiently detailed.
Alvarez 2012	Random sequence, concealed.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not sufficiently detailed.
Clarborn 1990	Random sequence,	Blinding unclear. Not	Unclear or more	Adequate description of outcome measurement. Blinding unclear. Unclear if lack of blinding can affect	Protocol/registration /statistical analysis
ставнони таал	concealed.	proper ITT.	missing.	the outcomes.	plan not available.
Cunningham 1994	Random sequence, concealed.	Blinding unclear. Not proper ITT.	Unclear or more than 5% missing.	Adequate description of outcome measurement. Blinding unclear. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Cunningham 1997	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
EudraCT 2004-000562-13	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes	Protocol/registration /statistical analysis plan not sufficiently detailed.

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
EudraCT 2007-007025-51	No information on sequence/concealment	Described as double- blind, but no further details. Analysis inadequately described.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Guelfi 1995	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Hewett 2009	Random sequence, concealed.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not sufficiently detailed.
Hewett 2010	Random sequence, concealed.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Higuchi 2016	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not sufficiently detailed.
Khan 1998	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
Learned 2012	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not sufficiently detailed.
Lieberman 2008	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not sufficiently detailed.
Luthringer 1996	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Mendels 1993	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Nemeroff 2007	No information on sequence/concealment	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Rudolph 1998	No information on concealment.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
Rudolph 1999	No information on concealment.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Schatzberg 2006	No information on concealment.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Schweizer 1994	Random sequence, concealed.	Blinding unclear. Not proper ITT.	Unclear or more than 5% missing.	Adequate description of outcome measurement. Blinding unclear. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Sheehan 2009	No information on concealment.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Silverstone 1999	Random sequence, concealed.	Blinded participants and caregivers. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Unclear binding of outcome assessors. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.
Thase 1997	Random sequence, concealed.	Described as double- blind, but no further details. Not proper ITT.	Unclear or more than 5% missing.	No/inadequate description of outcome measurement. Described as double- blind, but no further details. Unclear if lack of blinding can affect the outcomes.	Protocol/registration /statistical analysis plan not available.

## Supplementary Table 6: Individual serious adverse events

	Number of trials							Number
	reporting the	Venlafaxine	Venlafaxine	Control	Control	Relative risk		needed to
Events	event	events	analysed	events	analysed	(95% CI)	P-value	harm
Sexual dysfunction	8	62	677	5	472	6.49 (3.02,13.93)	< 0.01	12
Anorexia	9	128	1389	24	1024	3.23 (1.75,5.97)	< 0.01	14
Anxiety	9	58	1210	27	923	1.40 (0.57,3.44)	0.47	
Discontinuation symptoms	2	1	73	0	78	3.12 (0.33,29.66)	0.32	
Fall	2	2	211	0	130	2.16 (0.23,20.60)	0.50	
Hypertension	3	10	283	3	206	1.82 (0.44,7.48)	0.41	
Hypotension	2	8	519	1	266	2.78 (0.47,16.30)	0.26	
Intentional overdose	3	1	332	1	254	0.90 (0.16,5.09)	0.90	
QTc	2	1	270	1	263	1.00 (0.08,12.26)	1.00	
Syncope	2	2	352	2	280	0.74 (0.11,5.02)	0.75	
Worsening of depression	5	6	717	7	638	0.65 (0.16,2.73)	0.56	

### Supplementary Table 7: Serious adverse events in the included trials

Trial ID	Venlafaxine gro	up	Control group			
		Proportion of				
	Numbers and types of serious	participants with a	Numbers and types of serious	Proportion of participants with a		
	adverse events	serious adverse	adverse events	serious adverse event		
		event				
0600B 1-384-US/EU/CA	1 suicide attempt	1 out of 180	3 suicide attempts	3 out of 68		
600A-:302-US, CA/302	None mentioned	0 out of 72	1 suicide attempt	1 out of 76		
	6 hypertension, 2 anorexia, 2					
	anxiety, 2 abnormal					
	ejaculation (men), 2 worsening					
	of depression, 1 coma, 1					
	psychotic depression, 1					
	hospitalisation for depression,		3 hypertension, 2 anorexia, 2			
	1 libido decreased, 1		anxiety, 2 hospitalisation for			
	hypotension, 1 syncope, 1		anxiety, 1 hospitalisation for			
	tinnitus, 1 suicide, 1		depression, 1 syncope, 1			
	hospitalisation for anxiety, 1		arthritis, 1 amnesia, 1 suicide			
	humerus fracture, 1 accidental		attempt, 1 loss of consciusness			
	injury, 1 fall, 1 urinary		related to high blood alcohol			
600-B-367-EU	retention, 1 trismus	* out of 165	levels	* out of 83		
	7 anorgasmia, 4 ejaculation					
	delayed, 4 erectile dysfunction,					
Alvarez 2012	1 brain tumor	* out of 113	2 sexual dysfunction	* out of 105		
	1 pregnancy, 1 discontinuation					
Claghorn 1990	symptoms	2 out of 79	None mentioned	0 out of 80		
			1 hospitalisation for			
			depression, 1 QT-			
			prolongation, 1 intentional			
			overdose, 1 infection			
Cunningham 1994	3 hypertension, 1 albuminuria	4 out of 72	(mononucleosis)	4 out of 76		
	16 anorexia, 12 abnormal					
Cunningham 1997	ejaculation,	* out of 193	4 anorexia	4 out of 100		
	6 anorexia, 2 impotence, 1					
	extrauterine pregnancy, 1					
EudraCT 2004-000562-13	cervix carcinoma	* out of 127	2 anorexia, 1 panic attack	* out of 120		
	1 rash with mucosal lesions, 1					
	grand mal seizure, 1					
Guelfi 1995	hypertension, 1 fall	4 out of 46	None mentioned	0 out of 47		
			9 anxiety, 3 depression, 1			
			seizure, 1 syncope, 1			
	6 anxiety, 1 syncope, 1 suicide		convulsion, 1 blood TSH			
Hewett 2009	attemtp	* out of 187	increase	* out of 197		
	9 anorexia, 1 worsening of					
	depression, 1 pyelonephritis, 1		2 anorexia, 1 suicidal			
Hewett 2010	QTc-prologation, 1 gastritis	* out of 198	depression	* out of 187		
	7 hypotension, 1 suicide, 1		1 hypotension, 1 suicide, 1			
Higuchi 2016	méniéres disease	* out of 354	anemia	* out of 183		
Learned 2012	3 anxiety	3 out of 133	5 anxiety, 1 ovarian cyst	* out of 126		
Lieberman 2008 (225 mg)	18 anorexia, 4 impotence	* out of 117	1 anorexia, 1 impotence	* out of 123		
	13 anxiety, 11 sexual					
Mendels 1993	dysfunction	* out of 234	1 anxiety	1 out of 78		
Nemeroff 2007	10 anxiety	1 out of 100	1 anxiety	1 out of 102		
Rudolph 1998	40 anorexia, 10 anxiety	* out of 266	2 anorexia	2 out of 92		
Rudolph 1999	9 anorexia	9 out of 100	4 anorexia	4 out of 98		
Schatzberg 2006	9 libido decreased, 2 anxiety	* out of 100	4 anxiety, 1 libido decreased	* out of 96		
	12 anxiety, 2 suicidal ideation,		4 anxiety, 2 suicidal ideation, 2			
	1 worsening of depression, 1		worsening of depression, 1			
Sheehan 2009	intentional overdose	*out of 95	allergic reaction, 1 nose bleed	* out of 95		
	1 suicide attempt, 1					
	discontinuation symptoms, 1					
Schweizer 1994	maculopapular rash	3 out of 73	1 leukopenia	1 out of 78		
Silverstone 1999	13 anorexia	13 out of 128	3 anorexia	3 out of 119		
	15 anorexia, 8 abnormal					
	ejaculation/orgasm (men), 5					
	impotence, 4 anorgasmia		4 anorexia, 1 anorgasmia			
	(women), 2 abnormal		(women), 1 abnormal			
Thase 1997	ejaculation/orgasm (women)	* out of 95	ejaculation/orgasm (men)	* out of 102		

* The overall proportion of serious adverse events was unclear.

# Supplementary Table 8: Individual non-serious adverse events

	Number of							
	trials							Number
	reporting	Venlafaxine	Venlafaxine	Control	Control	Relative risk		needed to
Events	the event	events	analysed	events	analysed	(95% CI)	P-value	harm
Nausea	23	981	3270	275	2394	2.72 (2.26,3.28)	< 0.01	5
Dry mouth	21	481	2884	165	2198	2.16 (1.71,2.74)	< 0.01	10
Dizziness	20	454	3051	129	2160	2.49 (1.90,3.26)	< 0.01	11
Somnolence	18	415	2768	125	1888	2.23 (1.78,2.78)	< 0.01	11
Sweating	20	314	2660	60	2118	3.99 (2.88,5.54)	< 0.01	11
Constipation	18	310	2595	94	1892	2.24 (1.64,3.04)	< 0.01	14
Nervousness	11	157	1360	47	949	2.20 (1.43,3.40)	< 0.01	15
Insomnia	19	340	2853	140	2064	1.73 (1.37,2.19)	< 0.01	19
Asthenia	16	173	2132	75	1696	1.78 (1.30,2.43)	< 0.01	27
Tremor	11	69	1287	23	1156	2.30 (1.22,4.32)	0.01	29
Appetite decreased	3	21	589	6	405	2.52 (1.04,6.09)	0.04	47
Abdominal pain	4	24	844	29	573	0.58 (0.22,1.57)	0.28	
Abnormal dreams	2	21	358	1	183	2.97 (0.51,17.25)	0.23	
Abnormal vision	7	33	765	14	671	1.95 (0.85,4.47)	0.11	
Abnormality of accommod	3	11	283	3	206	2.39 (0.72,7.99)	0.16	
Agitation	5	15	518	4	428	2.24 (0.55,9.03)	0.26	
Back pain	3	7	394	14	299	0.44 (0.18,1.07)	0.07	
Blood pressure increased	2	14	456	7	279	1.36 (0.50,3.70)	0.55	
Bronchitis	2	3	211	0	130	1.84 (0.26,13.00)	0.54	
Coughing	2	4	267	5	179	0.59 (0.15,2.23)	0.43	
Diarrhoea	14	126	1838	105	1449	1.00 (0.78,1.28)	0.99	
Dyspepsia	6	40	700	51	602	0.72 (0.44,1.16)	0.17	
Flatulence	2	0	172	1	90	0.39 (0.05,3.22)	0.38	
Headache	17	502	2384	384	1776	1.01 (0.69,1.17)	0.93	
Hypercholesterolemia	2	1	211	2	130	0.51 (0.08,3.07)	0.46	
Hypochromic anaemia	2	2	211	0	130	1.50 (0.21,10.91)	0.69	
Increased salivation	2	2	211	0	130	1.50 (0.21,10.91)	0.69	
Infection	6	49	771	37	533	0.93 (0.61,1.43)	0.75	
Influenza	5	16	611	17	511	0.80 (0.30,2.14)	0.66	
Malaise	2	20	519	6	266	1.31 (0.37,4.69)	0.67	
Nasopharyngitis	4	88	798	66	601	0.83 (0.57,1.19)	0.31	
Neck pain	2	2	211	1	130	1.02 (0.19,5.46)	0.98	
Pain	2	6	211	2	130	1.49 (0.28,7.93)	0.64	