

Data supplement to de Vries et al. Influence of baseline severity on antidepressant efficacy for anxiety disorders: meta-analysis and meta-regression. Br J Psychiatry doi: 10.1192/bjp.bp.115.173450

Drug class	Drug	GAD	SAD	OCD	PTSD	PD	Total
SSRIs	Escitalopram	3	-	-	-	-	3
	Paroxetine	3	3	3	3	3**	15
	Paroxetine CR	-	1	-	-	3	4
	Fluoxetine	-	-	3	-	2	2
	Sertraline	-	1*	4	4	4	13
	Fluvoxamine	-	-	2	-	-	2
	Fluvoxamine CR	-	2	1	-	-	3
SNRIs	Duloxetine	3	-	-	-	-	3
	Venlafaxine XR	2	2	-	-	4	8
Total indications		4	5	5	2	5	21
Total trials		11	9	13	7	16	56

Table DS1 Number of trials included, by disorder and drug.

"-" indicates disorder-drug combinations that have not been approved

* 3 trials of sertraline for SAD were submitted to the FDA, but 2 were excluded due to non-matching outcome measures

** 4 trials of paroxetine for PD were submitted to the FDA, but 1 was excluded due to a non-matching outcome measure

	Participants			Baseline scores (range)	
	Placebo	Drug	Total	Placebo	Drug
GAD	1 628	2 219	3 847	23.9 (22.1 – 25.9)	24.0 (22.5 – 26.0)
SAD	1 255	1 379	2 634	85.8 (73.3 – 93.9)	86.7 (78.0 – 95.9)
OCD	976	1 583	2 559	24.5 (22.6 – 26.3)	24.4 (22.6 – 26.6)
PTSD	829	981	1 810	74.3 (72.0 – 78.4)	74.4 (72.0 – 77.4)
PD	1 698	2 162	3 860	10.6 (6.2 – 19.2)	11.5 (6.9 – 17.6)
Overall	6 386	8 324	14 710		

Table DS2 Participant numbers and baseline scores by disorder and group. Baseline scores for GAD are based on the HAM-A, for SAD on the LSAS, for OCD on the Y-BOCS, for PTSD on the CAPS-2 and for PD on the number of panic attacks in the 2 weeks before baseline.

Disorder	Drug	Study ID	Placebo				Drug				
			N	Baseline	Change	Change SD	Dosage (mg)	N	Baseline	Change	Change SD
GAD	Escitalopram	SCT-MD-05	128	22.1	7.7	6.8	10 – 20	124	22.8	9.6	6.7
		SCT-MD-06	138	22.6	7.6	5.9	10 – 20	143	22.6	9.2	6.0
		SCT-MD-07	153	23.2	7.4	7.4	10 – 20	154	23.6	11.3	7.4
	Paroxetine	641	180	23.9	9.6	9.4	20 40	188 197	23.8 23.3	12.5 12.2	8.2 8.4
		642	163	23.6	9.5	8.9	20 – 50	161	23.9	11.8	8.9
		637	183	25.9	11.3	10.8	20 – 50	181	26.0	12.4	10.8
	Duloxetine	F1J-MC-HMBR	173	25.8	8.4	8.8	60 120	165 169	25.1 25.1	12.8 12.5	8.7 8.7
		F1J-MC-HMDT	158	23.5	5.9	8.8	60 – 120	161	22.5	8.1	8.9
		F1J-MC-HMDU	158	25.0	9.2	8.4	60 – 120	149	25.8	11.8	8.4
	Venlafaxine XR	210	96	24.1	9.5	8.3	75 150 225	86 81 86	24.7 24.5 23.6	11.1 11.7 12.1	8.8 7.8 7.5
		214	98	23.7	8	7.2	75 150	87 87	23.7 23.0	10.6 9.8	7.6 8.0
SAD	Fluvoxamine	3107	125	89.3	13.2	24.1	100 – 300	110	90.0	26.6	23.4
		3108	148	93.9	26.2	34.4	100 – 300	126	95.9	34.6	33.2
	Paroxetine	502	145	86.1	15.6	32.8	20 – 50	136	87.6	29.4	32.9

		382	92	83.5	14.5	25.2	20 – 50	90	78	30.5	25.2
		454	92	73.3	15.0	31.1	20	89	79.8	31.4	29.5
							40	88	77.5	24.5	30.3
							60	91	76.9	25.2	30.0
	Paroxetine CR	790	184	78.6	17.6	24.4	12.5 – 37.5	185	78.3	31	24.6
	Sertraline	R-0601	196	93.2	21.4	26.6	50 – 200	205	90.8	31.3	26.8
	Venlafaxine XR	387	138	86.8	19.9	26.1	75 – 225	133	91.1	31	25.6
		393	135	87.4	22.1	30.9	75 – 225	126	90.8	32.8	30.2
OCD	Fluoxetine	HCEP study 1	47	23.0	1.2	4.5	20	47	22.9	5.5	7.1
							40	45	22.4	4.3	5.3
							60	47	23.1	4.2	6.7
		HCEP study 2	41	26.1	0.6	4.6	20	39	24.4	3.5	5.9
							40	41	25.4	6.9	8.1
							60	42	26.0	9.1	9.4
	Fluvoxamine	5529	80	22.8	1.7	?	100 – 300	79	23.3	4.9	?
		5534	77	23.8	1.7	4.9	100 – 300	78	22.6	4.0	6.3
	Fluvoxamine CR	3103	119	26.3	5.9	7.6	100 – 300	113	26.6	8.7	7.5
	Paroxetine	116	88	25.6	3.4	6.8	40	83	25.4	6.3	6.7
							60	83	25.3	7.3	6.7
		118	75	24.7	4.6	7.5	20 – 60	79	23.3	5.6	7.5
	136	99	26.3	3.9	?	20 – 60	198	25.7	6.9	?	
	Sertraline	237/248	44	22.6	1.5	?	50 – 200	43	23.4	3.8	?

		371/372	84	23.4	3.4	?	50 100 200	79 81 80	23.2	6.0	?
		546	79	25	3.6	?	50 - 200	85	25.2	6.5	?
		495	87	25.7	5.0	?	50 - 200	83	25.6	5.4	?
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PTSD	Sertraline	641	82	73.8	15.4	28.1	50 - 200	84	72.1	13.1	27.5
		682	94	72.0	27.9	?	50 - 200	94	72.0	27.4	?
		640	104	73.5	26.2	23.8	50 - 200	98	73.9	33	23.9
		671	90	75.1	23.2	27.1	50 - 200	93	76.6	33	27.2
	Paroxetine	651	167	74.4	25.3	25.8	20 40	166 156	75.3 74.3	39.6 37.9	25.8 28.7
		648	133	73.2	24.7	23.1	20 - 50	136	74.3	35.5	23.3
		627	159	78.4	26.2	24.0	20 - 50	154	77.4	30.8	26.1
PD	Drug	Study ID	Placebo				Drug				
			N	Baseline	Change	Remission	Dosage (mg)	N	Baseline	Change	Remission
	Fluoxetine	HCJC	90	7.6	4.4	28	20 - 60	90	7.9	5.8	42
		HCJB	104	6.2	3.8	44	20 - 60	107	6.9	5.4	62
	Paroxetine	120	69	11.6	5.5	43.9	40	72	9.6	8.2	75.8
		187	123	12.3	5.7	33	20 - 60	123	11.9	8.1	51
		223	68	7.9	4.7	63	10 - 60	77	8.8	6.7	59
	Paroxetine CR	494	129	11.1	?	50.4	25 - 75	122	9.9	?	68.9
		495	136	8.9	?	51.5	25 - 75	123	11.5	?	56.9
		497	130	8.7	?	56.2	25 - 75	132	9.0	?	62.1
	Sertraline	629	87	10.4	5.6	46	50 - 200	79	12.8	10.1	62
		630	88	11.2	4.5	?	50 - 200	88	12.1	9.4	?
		529					50 100	42 41	20.3 21.3	17.5 16.5	?

						200	44	11.5	7.3	?
	514	38	19.2	9.3	?	50 200	38 36	14.1 15.4	6.3 9.3	?
Venlafaxine XR	398	156	9.1	?	34.4	75 150	158 159	11.0 11.4	?	54.1
	399	157	11.1	?	46.5	75 225	156 160	15.7 12.1	?	61.4
	353	155	12.1	?	40.6	75 – 225	155	13.3	?	64.1
	391	168	11.1	?	52.4	75 – 225	160	12.4	?	70.0
										51.0
										55.0

Table DS3 Sample sizes, baseline scores, change scores and remission rates (where applicable) for all included trials.

	Predictor	β [95% CI]	P-value
<i>GAD</i>	<i>Intercept</i>	0.316 [0.226, 0.406]	<0.001
	<i>Baseline</i>	-0.007 [-0.100, 0.085]	0.860
<i>SAD</i>	<i>Intercept</i>	0.426 [0.332, 0.520]	<0.001
	<i>Baseline</i>	-0.064 [-0.162, 0.035]	0.170
<i>OCD</i>	<i>Intercept</i>	0.396 [0.280, 0.512]	<0.001
	<i>Baseline</i>	-0.021 [-0.140, 0.099]	0.707
<i>PTSD</i>	<i>Intercept</i>	0.267 [-0.038, 0.496]	0.030
	<i>Baseline</i>	0.084 [-0.161, 0.329]	0.418
<i>PD</i>	<i>Intercept</i>	0.279 [0.191, 0.366]	<0.001
	<i>Baseline</i>	-0.002 [-0.106, 0.101]	0.960

Table DS4 Results of secondary meta-regression analysis of Hedges' g (drug-placebo difference) with baseline severity as predictor. P-values in bold are significant at $\alpha = 0.05$, while p-values in bold and italics are significant at $\alpha = 0.01$.

	Predictor	Model 1 (with interaction)		Model 2 (without interaction)	
		β [95% CI]	P-value	β [95% CI]	P-value
<i>GAD</i>	<i>Group</i>	0.35 [0.17, 0.52]	<0.001	0.34 [0.17, 0.51]	<0.001
	<i>Baseline</i>	0.11 [-0.03, 0.25]	0.13	0.13 [0.04, 0.23]	0.007
	<i>G x B</i>	0.05 [-0.13, 0.23]	0.574	--	--
<i>SAD</i>	<i>Group</i>	0.47 [0.35, 0.59]	<0.001	0.45 [0.33, 0.58]	<0.001
	<i>Baseline</i>	0.15 [0.04, 0.25]	0.011	0.10 [0.02, 0.18]	0.012
	<i>G x B</i>	-0.08 [-0.23, 0.07]	0.29	--	--
<i>OCD</i>	<i>Group</i>	0.35 [0.23, 0.47]	<0.001	0.36 [0.23, 0.48]	<0.001
	<i>Baseline</i>	0.14 [0.03, 0.25]	0.013	0.18 [0.10, 0.27]	<0.001
	<i>G x B</i>	0.09 [-0.08, 0.25]	0.28	--	--
<i>PTSD</i>	<i>Group</i>	0.21 [-0.03, 0.45]	0.08	0.21 [-0.03, 0.44]	0.08
	<i>Baseline</i>	0.17 [-0.06, 0.40]	0.14	0.20 [0.05, 0.35]	0.013
	<i>G x B</i>	0.06 [-0.26, 0.37]	0.71	--	--
<i>PD</i>	<i>Group</i>	0.13 [0.06, 0.20]	0.001	0.13 [0.06, 0.20]	0.001
	<i>Baseline</i>	0.00 [-0.07, 0.07]	0.97	-0.03 [-0.07, 0.02]	0.20
	<i>G x B</i>	-0.05 [-0.13, 0.04]	0.30	--	--

Table DS5 Results of secondary meta-regression analysis of standardized change scores (Hedges' g) or remission rate (PD only) with treatment group, baseline severity and their interaction as predictors, using an expanded set of trials. P-values in bold are significant at $\alpha = 0.05$, while p-values in bold and italics are significant at $\alpha = 0.01$.

Supplementary references

References for additional studies included in sensitivity analysis

- [1] Allgulander C., Dahl A.A., Austin C., Morris P.L.P., Sogaard J.A., Fayyad R., et al. 2004. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry*. 161(9):1642–9.
- [2] Baldwin D.S., Huusom A.K.T., Maehlum E. 2006. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. *Br J Psychiatry*. 189(October):264–72.
- [3] Bandelow B., Chouinard G., Bobes J., Ahokas A., Eggens I., Liu S., et al. 2010. Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study. *Int J Neuropsychopharmacol*. 13(3):305–20.
- [4] Brawman-Mintzer O., Knapp R.G., Rynn M., Carter R.E., Rickels K. 2006. Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 67:874–81.
- [5] Hackett D., Haudiquet V., Salinas E. 2003. A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. *Eur Psychiatry*. 18(4):182–7.
- [6] Kasper S., Herman B., Nivoli G., Van Ameringen M., Petralia A., Mandel F.S., et al. 2009. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial. *Int Clin Psychopharmacol*. 24(2):87–96.
- [7] Merideth C., Cutler A.J., She F., Eriksson H. 2012. Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder. *Int Clin Psychopharmacol*. 27(1):40–54.
- [8] Nicolini H., Bakish D., Duenas H., Spann M., Erickson J., Hallberg C., et al. 2009. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. *Psychol Med*. 39(2):267–76.
- [9] Nimatoudis I., Zissis N.P., Kogeorgos J., Theodoropoulou S., Vidalis A., Kaprinis G. 2004. Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo controlled study. *Int Clin Psychopharmacol*. 19(6):331–6.

- [10] Allgulander C. 1999. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. *Acta Psychiatr Scand.* 100(3):193–8.
- [11] Allgulander C., Mangano R., Zhang J., Dahl A. a., Lepola U., Sjödin I., et al. 2004. Efficacy of venlafaxine ER in patients with social anxiety disorder: A double-blind, placebo-controlled, parallel-group comparison with paroxetine. *Hum Psychopharmacol.* 19(6):387–96.
- [12] Asakura S., Tajima O., Koyama T. 2007. Fluvoxamine treatment of generalized social anxiety disorder in Japan: a randomized double-blind, placebo-controlled study. *Int J Neuropsychopharmacol.* 10(2):263–74.
- [13] Clark D.M., Ehlers A., McManus F., Hackmann A., Fennell M., Campbell H., et al. 2003. Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. *J Consult Clin Psychol.* 71(6):1058–67.
- [14] Kasper S., Stein D.J., Loft H., Nil R. 2005. Escitalopram in the treatment of social anxiety disorder. *Br J Psychiatry.* 186(3):222–6.
- [15] Kobak K.A., Greist J.H., Jefferson J.W., Katzelnick D.J. 2002. Fluoxetine in social phobia: a double-blind, placebo-controlled pilot study. *J Clin Psychopharmacol.* 22(3):257–62.
- [16] Lader M., Stender K., Bürger V., Nil R. 2004. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety.* 19(4):241–8.
- [17] Liebowitz M.R., Gelenberg A.J., Munjack D. 2005. Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry.* 62(2):190–8.
- [18] Stein M.B., Fyer A.J., Davidson J.R., Pollack M.H., Wiita B. 1999. Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *Am J Psychiatry.* 156(5):756–60.
- [19] Van Vliet I.M., den Boer J.A., Westenberg H.G. 1994. Psychopharmacological treatment of social phobia; a double blind placebo controlled study with fluvoxamine. *Psychopharmacology (Berl).* 115(1-2):128–34.
- [20] Jenike M.A., Hyman S., Baer L., Holland A., Minichiello W.E., Buttolph L., et al. 1990. A controlled trial of fluvoxamine in obsessive-compulsive disorder: implications for a serotonergic theory. *Am J Psychiatry.* 147(9):1209–15.
- [21] Jenike M.A., Baer L., Summergrad P., Minichiello W.E., Holland A., Seymour R. 1990. Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. *Am J Psychiatry.* 147:923–8.

- [22] Jenike M.A., Baer L., Minichiello W.E., Rauch S.L., Buttolph M.L. 1997. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. *Am J Psychiatry*. 154(9):1261–4.
- [23] Kamijima K., Murasaki M., Asai M., Higuchi T., Nakajima T., Taga C., et al. 2004. Paroxetine in the treatment of obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study in Japanese patients. *Psychiatry Clin Neurosci*. 58:427–33.
- [24] Montgomery S.A., Kasper S., Stein D.J., Bang Hedegaard K., Lemming O.M. 2001. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 16(2):75–86.
- [25] Nakatani E., Nakagawa A., Nakao T., Yoshizato C., Nabeyama M., Kudo A., et al. 2005. A randomized controlled trial of Japanese patients with obsessive-compulsive disorder--effectiveness of behavior therapy and fluvoxamine. *Psychother Psychosom*. 74(5):269–76.
- [26] Davidson J., Baldwin D., Stein D.J., Kuper E., Benattia I., Ahmed S., et al. 2006. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry*. 63(10):1158–65.
- [27] Marshall R.D., Lewis-Fernandez R., Blanco C., Simpson H.B., Lin S.-H., Vermes D., et al. 2006. A controlled trial of paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults. *Depress Anxiety*. 0:1–8.
- [28] Martenyi F., Brown E.B., Zhang H., Prakash A., Koke S.C. 2002. Fluoxetine versus placebo in posttraumatic stress disorder. *J Clin Psychiatry*. 63:199–206.
- [29] Martenyi F., Brown E.B., Caldwell C.D. 2007. Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study. *J Clin Psychopharmacol*. 27(2):166–70.
- [30] Tucker P., Potter-Kimball R., Wyatt D.B., Parker D.E., Burgin C., Jones D.E., et al. 2003. Can physiologic assessment and side effects tease out differences in PTSD trials? A double-blind comparison of citalopram, sertraline, and placebo. *Psychopharmacol Bull*. 37(3):135–49.
- [31] Van Der Kolk B.A., Spinazzola J., Blaustein M.E., Hopper J.W., Hopper E.K., Korn D.L., et al. 2007. A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: treatment effects and long-term maintenance. *J Clin Psychiatry*. 68(1):37–46.
- [32] Asnis G.M., Hameedi F. a, Goddard a W., Potkin S.G., Black D., Jameel M., et al. 2001. Fluvoxamine in the treatment of panic disorder: a multi-center, double-blind, placebo-controlled study in outpatients. *Psychiatry Res*. 103(1):1–14.

- [33] De Beurs E., van Balkom A.J.L.M., Lange A., Koele P., van Dyck R. 1995. Treatment of panic disorder with agoraphobia: comparison of fluvoxamine, placebo, and psychological panic management combined with exposure and of exposure in vivo alone. *Am J Psychiatry*. 152(5):683–91.
- [34] Nair N.P., Bakish D., Saxena B., Amin M., Schwartz G., West T.E. 1996. Comparison of fluvoxamine, imipramine, and placebo in the treatment of outpatients with panic disorder. *Anxiety*. 2(4):192–8.
- [35] Pollack M.H., Worthington III J.J., Otto M.W., Maki K.M., Smoller J.W., Manfro G.G., et al. 1996. Venlafaxine for panic disorder: results from a double-blind, placebo-controlled study. *Psychopharmacol Bull*. 32(4):667–70.
- [36] Stahl S.M, Gergel I., Li D. 2003. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 64:1322–7.
- [37] Stein M.B., Ron Norton G., Walker J.R., Chartier M.J., Graham R. 2000. Do selective serotonin re-uptake inhibitors enhance the efficacy of very brief cognitive behavioral therapy for panic disorder? A pilot study. *Psychiatry Res*. 94(3):191–200.