Supplement to paper "Efficacy of new-generation antidepressants assessed with the Montgomery-Asberg Depression Rating Scale, the gold standard clinician rating scale: A meta-analysis of randomized controlled trials"

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1 Meta-analysis across all antidepressants

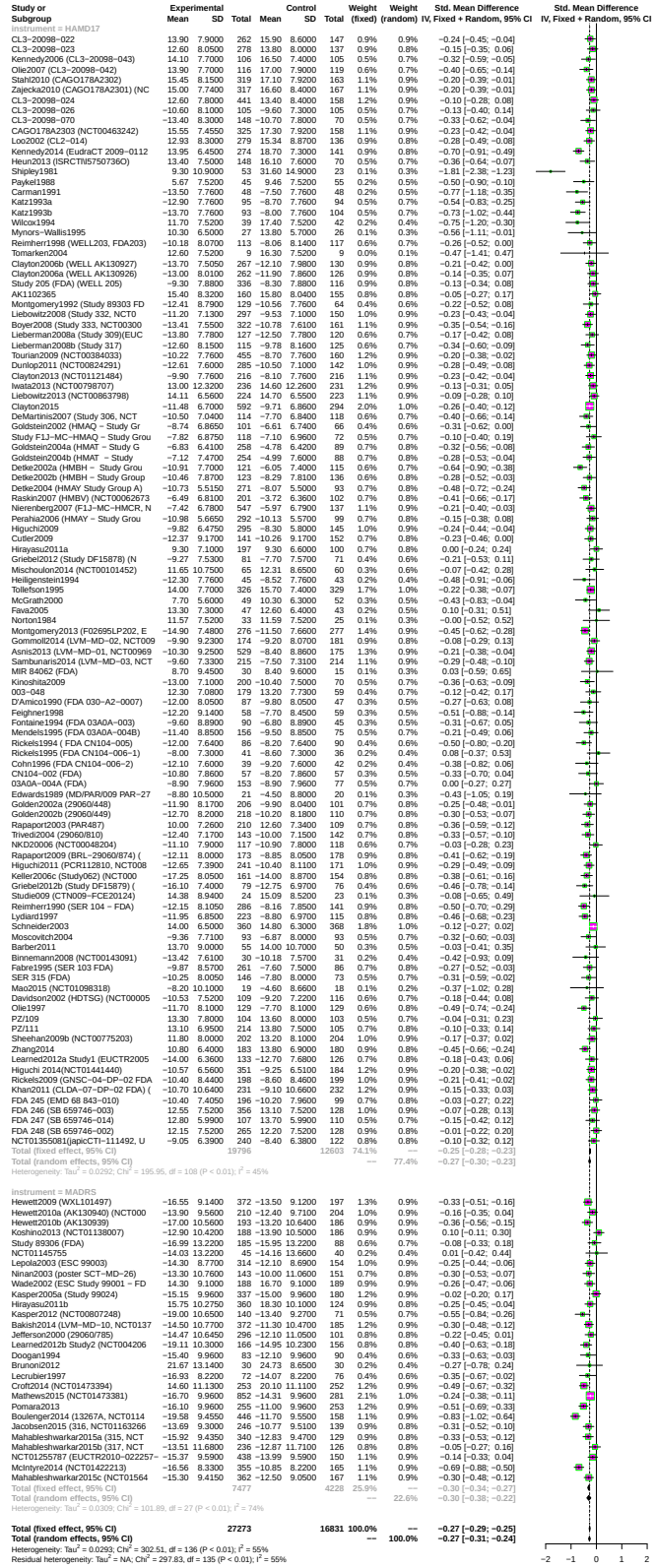

Figure 1: Meta-analytic results for all AD, separated by type of instrument.

2 Meta-analyses for individual Antidepressants

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (fixed)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
instrument = HAMD17									
Reimherr1998 (WELL203, FDA203)	−10.18	8.0700	113	−8.06	8.1400	117	8.8%	10.1%	−0.26 [−0.52; 0.00]
Tomarken2004	12.60	7.5200	9	16.30	7.5200	9	0.7%	1.1%	−0.47 [−1.41; 0.47]
Clayton2006b (WELL AK130927)	−13.20	6.9400	134	−12.10	7.9800	130	10.2%	11.1%	−0.15 [−0.39; 0.09]
Clayton2006a (WELL AK130926)	−13.10	7.9500	129	−11.90	7.8600	126	9.8%	10.8%	−0.15 [−0.40; 0.09]
Study 205 (FDA) (WELL 205)	−9.30	7.8800	336	−8.30	7.8800	116	13.3%	13.0%	−0.13 [−0.34; 0.08]
AK1102365	15.40	8.3200	160	15.80	8.0400	155	12.2%	12.3%	−0.05 [−0.27; 0.17]
Total (fixed effect, 95% CI)			**881**			**653**	**54.9%**	−−	**−0.14 [−0.25; −0.04]**
Total (random effects, 95% CI)							−−	**58.4%**	**−0.15 [−0.23; −0.06]**
Heterogeneity: $Tau^2 = 0.0040$; $Chi^2 = 1.98$, df = 5 (P = 0.85); $I^2 = 0\%$									
instrument = MADRS									
Hewett2009 (WXL101497)	−16.00	9.0300	187	−13.50	9.1200	197	14.7%	13.7%	−0.27 [−0.48; −0.07]
Hewett2010a (AK130940) (NCT000	−13.90	9.5600	210	−12.40	9.7100	204	15.9%	14.3%	−0.16 [−0.35; 0.04]
Koshino2013 (NCT01138007)	−12.90	10.4200	188	−13.90	10.5000	186	14.4%	13.6%	0.10 [−0.11; 0.30]
Total (fixed effect, 95% CI)			**585**			**587**	**45.1%**	−−	**−0.11 [−0.23; 0.00]**
Total (random effects, 95% CI)							−−	**41.6%**	**−0.11 [−0.58; 0.36]**
Heterogeneity: $Tau^2 = 0.0247$; $Chi^2 = 6.73$, df = 2 (P = 0.03); $I^2 = 70\%$									
Total (fixed effect, 95% CI)			**1466**			**1240**	**100.0%**	−−	**−0.13 [−0.21; −0.05]**
Total (random effects, 95% CI)							−−	**100.0%**	**−0.13 [−0.23; −0.04]**
Heterogeneity: $Tau^2 = 0.0091$; $Chi^2 = 8.85$, df = 8 (P = 0.36); $I^2 = 10\%$									
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 8.71$, df = 7 (P = 0.27); $I^2 = 20\%$									

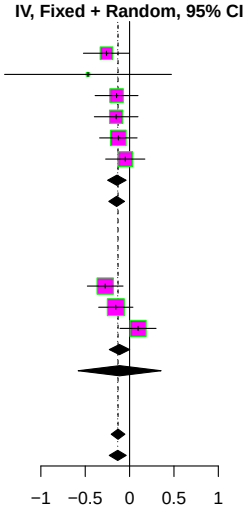

Figure 2: Meta-analytic results for bupropion, separated by type of instrument.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (fixed)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
instrument = HAMD17									
Tourian2009 (NCT00384033)	−10.30	7.7600	157	−8.70	7.7600	160	7.5%	6.5%	−0.21 [−0.43; 0.02]
Goldstein2002 (HMAQ − Study Gr	−9.73	6.8400	68	−6.61	6.7400	66	3.1%	4.7%	−0.46 [−0.80; −0.11]
Study F1J−MC−HMAQ − Study Grou	−8.00	6.7500	81	−7.10	6.9600	72	3.6%	5.0%	−0.13 [−0.45; 0.19]
Goldstein2004a (HMAT − Study G	−6.25	6.3800	171	−4.78	6.4200	89	5.6%	5.9%	−0.23 [−0.49; 0.03]
Goldstein2004b (HMAT − Study	−8.02	7.4200	170	−4.99	7.6000	88	5.4%	5.9%	−0.40 [−0.66; −0.14]
Detke2002a (HMBH − Study Grou	−10.91	7.7000	121	−6.05	7.4000	115	5.4%	5.8%	−0.64 [−0.90; −0.38]
Detke2002b (HMBH − Study Group	−10.46	7.8700	123	−8.29	7.8100	136	6.1%	6.1%	−0.28 [−0.52; −0.03]
Detke2004 (HMAY Study Group A)	−10.64	5.5000	186	−8.07	5.5000	93	5.8%	6.0%	−0.47 [−0.72; −0.21]
Raskin2007 (HMBV) (NCT00062673	−6.49	6.8100	201	−3.72	6.3600	102	6.3%	6.2%	−0.41 [−0.66; −0.17]
Nierenberg2007 (F1J−MC−HMCR, N	−7.61	6.9400	273	−5.97	6.7900	137	8.7%	6.7%	−0.24 [−0.44; −0.03]
Perahia2006 (HMAY − Study Grou	−11.35	5.6200	195	−10.13	5.5700	99	6.2%	6.1%	−0.22 [−0.46; 0.03]
Higuchi2009	−10.25	6.0500	147	−8.30	5.8000	145	6.9%	6.3%	−0.33 [−0.56; −0.10]
Cutler2009	−12.37	9.1700	141	−10.26	9.1700	152	6.9%	6.3%	−0.23 [−0.46; 0.00]
Total (fixed effect, 95% CI)			**2034**			**1454**	**77.6%**	−−	**−0.32 [−0.39; −0.25]**
Total (random effects, 95% CI)							−−	**77.5%**	**−0.32 [−0.40; −0.24]**
Heterogeneity: Tau^2 = 0.0102; Chi^2 = 13.57, df = 12 (P = 0.33); I^2 = 12%									
instrument = MADRS									
NCT01145755	−14.03	13.2200	45	−14.16	13.6600	40	2.0%	3.8%	0.01 [−0.42; 0.44]
Boulenger2014 (13267A, NCT0114	−21.15	9.3000	146	−11.70	9.5500	158	6.4%	6.2%	−1.00 [−1.24; −0.76]
Mahableshwarkar2015a (315, NCT	−16.90	9.4800	115	−12.83	9.4700	129	5.7%	5.9%	−0.43 [−0.68; −0.17]
Mahableshwarkar2015c (NCT01564	−15.80	9.5700	187	−12.50	9.0500	167	8.3%	6.6%	−0.35 [−0.56; −0.14]
Total (fixed effect, 95% CI)			**493**			**494**	**22.4%**	−−	**−0.52 [−0.65; −0.40]**
Total (random effects, 95% CI)							−−	**22.5%**	**−0.46 [−1.12; 0.19]**
Heterogeneity: Tau^2 = 0.1449; Chi^2 = 24.35, df = 3 (P < 0.01); I^2 = 88%									
Total (fixed effect, 95% CI)			**2527**			**1948**	**100.0%**	−−	**−0.36 [−0.42; −0.30]**
Total (random effects, 95% CI)							−−	**100.0%**	**−0.36 [−0.47; −0.25]**
Heterogeneity: Tau^2 = 0.0357; Chi^2 = 45.76, df = 16 (P < 0.01); I^2 = 65%									
Residual heterogeneity: Tau^2 = NA; Chi^2 = 37.92, df = 15 (P < 0.01); I^2 = 60%									

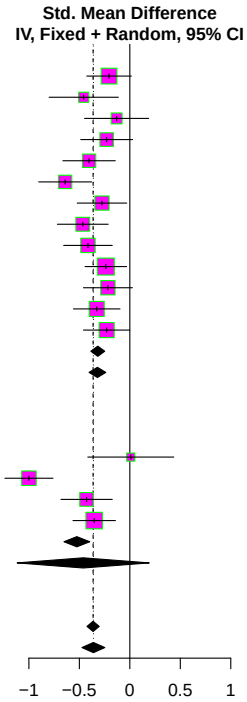

Figure 3: Meta-analytic results for duloxetine and separated by type of instrument.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (fixed)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
instrument = HAMD17									
Clayton2006b (WELL AK130927)	−14.20	8.0700	133	−12.10	7.9800	130	8.0%	8.3%	−0.26 [−0.50; −0.02]
Clayton2006a (WELL AK130926)	−12.90	8.0700	133	−11.90	7.8600	126	7.9%	8.3%	−0.13 [−0.37; 0.12]
Nierenberg2007 (F1J−MC−HMCR, N	−7.22	6.6200	274	−5.97	6.7900	137	11.2%	10.0%	−0.19 [−0.39; 0.02]
Hirayasu2011a	9.30	7.1000	197	9.30	6.6000	100	8.2%	8.4%	0.00 [−0.24; 0.24]
Griebel2012 (Study DF15878) (N	−9.27	7.5300	81	−7.70	7.5700	71	4.6%	5.9%	−0.21 [−0.53; 0.11]
Mischoulon2014 (NCT00101452)	11.65	10.7500	65	12.31	8.6500	60	3.8%	5.1%	−0.07 [−0.42; 0.28]
Total (fixed effect, 95% CI)			**883**			**624**	**43.8%**	−−	**−0.15 [−0.25; −0.04]**
Total (random effects, 95% CI)							−−	**46.0%**	**−0.15 [−0.25; −0.04]**
Heterogeneity: Tau^2 = 0.0029; Chi^2 = 2.79, df = 5 (P = 0.73); I^2 = 0%									
instrument = MADRS									
Lepola2003 (ESC 99003)	−15.00	8.7100	155	−12.10	8.6900	154	9.4%	9.1%	−0.33 [−0.56; −0.11]
Ninan2003 (poster SCT−MD−26)	−13.30	10.7600	143	−10.00	11.0600	151	8.9%	8.9%	−0.30 [−0.53; −0.07]
Wade2002 (ESC Study 99001 − FD	14.30	9.1000	188	16.70	9.1000	189	11.5%	10.1%	−0.26 [−0.47; −0.06]
Kasper2005a (Study 99024)	−15.50	9.9600	173	−15.00	9.9600	180	10.8%	9.8%	−0.05 [−0.26; 0.16]
Hirayasu2011b	15.90	10.5500	239	18.30	10.1000	124	10.0%	9.4%	−0.23 [−0.45; −0.01]
Kasper2012 (NCT00807248)	−19.00	10.6500	140	−13.40	9.2700	71	5.6%	6.7%	−0.55 [−0.84; −0.26]
Total (fixed effect, 95% CI)			**1038**			**869**	**56.2%**	−−	**−0.26 [−0.35; −0.17]**
Total (random effects, 95% CI)							−−	**54.0%**	**−0.27 [−0.43; −0.11]**
Heterogeneity: Tau^2 = 0.0147; Chi^2 = 8.22, df = 5 (P = 0.14); I^2 = 39%									
Total (fixed effect, 95% CI)			**1921**			**1493**	**100.0%**	−−	**−0.21 [−0.28; −0.14]**
Total (random effects, 95% CI)							−−	**100.0%**	**−0.21 [−0.30; −0.12]**
Heterogeneity: Tau^2 = 0.0114; Chi^2 = 13.71, df = 11 (P = 0.25); I^2 = 20%									
Residual heterogeneity: Tau^2 = NA; Chi^2 = 11.01, df = 10 (P = 0.36); I^2 = 9%									

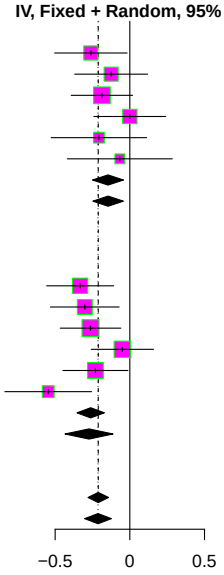

Figure 4: Meta-analytic results for escitalopram, separated by type of instrument.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (fixed)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
instrument = HAMD17									
CL3−20098−023	12.20	8.1000	137	13.80	8.0000	137	5.2%	5.2%	−0.20 [−0.44; 0.04]
CAGO178A2303 (NCT00463242)	14.00	7.5300	163	17.30	7.9200	158	6.0%	5.7%	−0.43 [−0.65; −0.20]
Loo2002 (CL2−014)	13.09	8.3700	144	15.34	8.8700	136	5.3%	5.2%	−0.26 [−0.50; −0.03]
Goldstein2004a (HMAT − Study G	−7.40	6.4400	87	−4.78	6.4200	89	3.3%	3.8%	−0.41 [−0.70; −0.11]
Goldstein2004b (HMAT − Study	−6.22	7.5200	84	−4.99	7.6000	88	3.3%	3.7%	−0.16 [−0.46; 0.14]
Detke2004 (HMAY Study Group A)	−10.83	5.5300	85	−8.07	5.5000	93	3.3%	3.7%	−0.50 [−0.80; −0.20]
Perahia2006 (HMAY − Study Grou	−10.61	5.7100	97	−10.13	5.5700	99	3.8%	4.1%	−0.08 [−0.36; 0.20]
Higuchi2009	−9.40	6.9000	148	−8.30	5.8000	145	5.6%	5.4%	−0.17 [−0.40; 0.06]
Edwards1989 (MD/PAR/009 PAR−27	−8.80	10.5000	21	−4.50	8.8000	20	0.8%	1.1%	−0.43 [−1.05; 0.19]
Golden2002a (29060/448)	−11.90	8.1700	206	−9.90	8.0400	101	5.2%	5.1%	−0.25 [−0.48; −0.01]
Golden2002b (29060/449)	−12.70	8.2000	218	−10.20	8.1800	110	5.5%	5.4%	−0.30 [−0.53; −0.07]
Rapaport2003 (PAR487)	10.00	7.2600	210	12.60	7.3400	109	5.4%	5.3%	−0.36 [−0.59; −0.12]
Trivedi2004 (29060/810)	−12.40	7.1700	143	−10.00	7.1500	142	5.4%	5.3%	−0.33 [−0.57; −0.10]
NKD20006 (NCT00048204)	−11.10	7.9000	117	−10.90	7.8000	118	4.5%	4.7%	−0.03 [−0.28; 0.23]
Rapaport2009 (BRL−29060/874) (	−12.11	8.0000	173	−8.85	8.0500	178	6.6%	6.0%	−0.41 [−0.62; −0.19]
Higuchi2011 (PCR112810, NCT008	−12.65	7.3900	241	−10.40	8.1100	171	7.6%	6.5%	−0.29 [−0.49; −0.09]
Keller2006c (Study062) (NCT000	−17.25	8.0500	161	−14.00	8.8700	154	5.9%	5.6%	−0.38 [−0.61; −0.16]
Griebel2012b (Study DF15879) (	−16.10	7.4000	79	−12.75	6.9700	76	2.9%	3.4%	−0.46 [−0.78; −0.14]
Total (fixed effect, 95% CI)			2514			2124	85.5%	−−	−0.30 [−0.36; −0.24]
Total (random effects, 95% CI)							−−	85.4%	−0.30 [−0.36; −0.23]
Heterogeneity: $Tau^2 = 0.0082$; $Chi^2 = 16.13$, df = 17 (P = 0.51); $I^2 = 0\%$									
instrument = MADRS									
Hirayasu2011b	15.60	10.0000	121	18.30	10.1000	124	4.7%	4.8%	−0.27 [−0.52; −0.02]
Jefferson2000 (29060/785)	−13.80	10.8300	97	−12.10	11.0500	101	3.8%	4.1%	−0.15 [−0.43; 0.12]
Learned2012b Study2 (NCT004206	−19.11	10.3000	166	−14.95	10.2300	156	6.0%	5.7%	−0.40 [−0.63; −0.18]
Total (fixed effect, 95% CI)			384			381	14.5%	−−	−0.30 [−0.44; −0.15]
Total (random effects, 95% CI)							−−	14.6%	−0.29 [−0.60; 0.02]
Heterogeneity: $Tau^2 = 0.0061$; $Chi^2 = 1.96$, df = 2 (P = 0.38); $I^2 = 0\%$									
Total (fixed effect, 95% CI)			**2898**			**2505**	**100.0%**	**−−**	**−0.30 [−0.35; −0.24]**
Total (random effects, 95% CI)							**−−**	**100.0%**	**−0.30 [−0.35; −0.24]**
Heterogeneity: $Tau^2 = 0.0076$; $Chi^2 = 18.08$, df = 20 (P = 0.58); $I^2 = 0\%$									
Residual heterogeneity: $Tau^2 = NA$; $Chi^2 = 18.08$, df = 19 (P = 0.52); $I^2 = 0\%$									

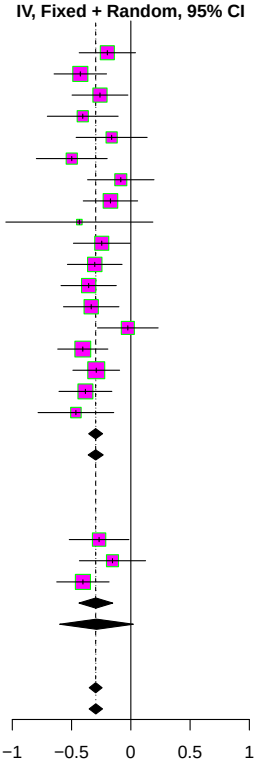

Figure 5: Meta-Analytic results for paroxetine, separated by type of instrument.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (fixed)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
instrument = HAMD17									
Lieberman2008a (Study 309)(EUC	−13.80	7.7800	127	−12.50	7.7800	120	11.6%	12.3%	−0.17 [−0.42; 0.08]
Lieberman2008b (Study 317)	−12.60	8.1500	115	−9.78	8.1600	125	11.2%	11.9%	−0.34 [−0.60; −0.09]
Learned2012a Study1 (EUCTR2005	−14.00	6.3600	133	−12.70	7.6800	126	12.2%	12.8%	−0.18 [−0.43; 0.06]
Higuchi 2014(NCT01441440)	−10.57	6.5600	351	−9.25	6.5100	184	22.7%	20.7%	−0.20 [−0.38; −0.02]
Total (fixed effect, 95% CI)			**726**			**555**	**57.7%**	−−	**−0.22 [−0.33; −0.11]**
Total (random effects, 95% CI)							−−	**57.8%**	**−0.22 [−0.34; −0.10]**
Heterogeneity: Tau^2 = 0.0015; Chi^2 = 1.22, df = 3 (P = 0.75); I^2 = 0%									
instrument = MADRS									
Hewett2009 (WXL101497)	−17.10	9.2500	185	−13.50	9.1200	197	17.7%	17.2%	−0.39 [−0.59; −0.19]
Hewett2010b (AK130939)	−17.00	10.5600	193	−13.20	10.6400	186	17.6%	17.2%	−0.36 [−0.56; −0.15]
Lecrubier1997	−16.93	8.2200	72	−14.07	8.2200	76	6.9%	7.9%	−0.35 [−0.67; −0.02]
Total (fixed effect, 95% CI)			**450**			**459**	**42.3%**	−−	**−0.37 [−0.50; −0.24]**
Total (random effects, 95% CI)							−−	**42.2%**	**−0.37 [−0.43; −0.31]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 0.08, df = 2 (P = 0.96); I^2 = 0%									
Total (fixed effect, 95% CI)			**1176**			**1014**	**100.0%**	−−	**−0.28 [−0.37; −0.20]**
Total (random effects, 95% CI)							−−	**100.0%**	**−0.28 [−0.37; −0.19]**
Heterogeneity: Tau^2 = 0.0034; Chi^2 = 4.25, df = 6 (P = 0.64); I^2 = 0%									
Residual heterogeneity: Tau^2 = NA; Chi^2 = 1.29, df = 5 (P = 0.94); I^2 = 0%									

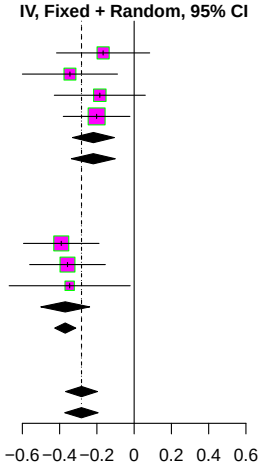

Figure 6: Meta-analytic results for venlafaxine, separated by type of instrument.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (fixed)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
instrument = HAMD17									
Rickels2009 (GNSC−04−DP−02 FDA	−10.40	8.4400	198	−8.60	8.4600	199	10.7%	11.3%	−0.21 [−0.41; −0.02]
Khan2011 (CLDA−07−DP−02 FDA) (	−10.70	10.6400	231	−9.10	10.6600	232	12.5%	11.7%	−0.15 [−0.33; 0.03]
FDA 245 (EMD 68 843−010)	−9.70	7.1400	104	−10.20	7.9600	99	5.5%	9.2%	0.07 [−0.21; 0.34]
FDA 246 (SB 659746−003)	12.80	7.5200	241	13.10	7.5200	128	9.1%	10.8%	−0.04 [−0.25; 0.17]
FDA 247 (SB 659746−014)	12.80	5.9900	107	13.70	5.9900	110	5.9%	9.4%	−0.15 [−0.42; 0.12]
FDA 248 (SB 659746−002)	12.15	7.5200	265	12.20	7.5200	128	9.4%	10.9%	−0.01 [−0.22; 0.20]
Total (fixed effect, 95% CI)			**1146**			**896**	**53.1%**	−−	**−0.10 [−0.18; −0.01]**
Total (random effects, 95% CI)							−−	**63.4%**	**−0.09 [−0.20; 0.01]**
Heterogeneity: Tau^2 = 0.0044; Chi^2 = 4.12, df = 5 (P = 0.53); I^2 = 0%									
instrument = MADRS									
Croft2014 (NCT01473394)	14.60	11.1300	253	20.10	11.1100	252	13.3%	11.9%	−0.49 [−0.67; −0.32]
Mathews2015 (NCT01473381)	−16.91	9.9600	572	−14.31	9.9600	281	20.3%	12.8%	−0.26 [−0.40; −0.12]
Pomara2013	−16.10	9.9600	255	−11.00	9.9600	253	13.3%	11.9%	−0.51 [−0.69; −0.33]
Total (fixed effect, 95% CI)			**1080**			**786**	**46.9%**	−−	**−0.40 [−0.49; −0.30]**
Total (random effects, 95% CI)							−−	**36.6%**	**−0.41 [−0.77; −0.06]**
Heterogeneity: Tau^2 = 0.0132; Chi^2 = 6.22, df = 2 (P = 0.04); I^2 = 68%									
Total (fixed effect, 95% CI)			**2226**			**1682**	**100.0%**	−−	**−0.24 [−0.30; −0.17]**
Total (random effects, 95% CI)							−−	**100.0%**	**−0.21 [−0.36; −0.05]**
Heterogeneity: Tau^2 = 0.0312; Chi^2 = 31.26, df = 8 (P < 0.01); I^2 = 74%									
Residual heterogeneity: Tau^2 = NA; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 = 32%									

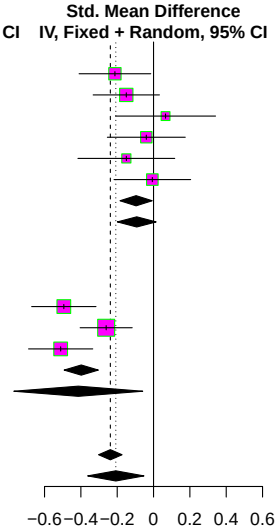

Figure 7: Meta-analytic results for vilazodone, separated by type of instrument.

3 Meta-analyses with raw mean differences

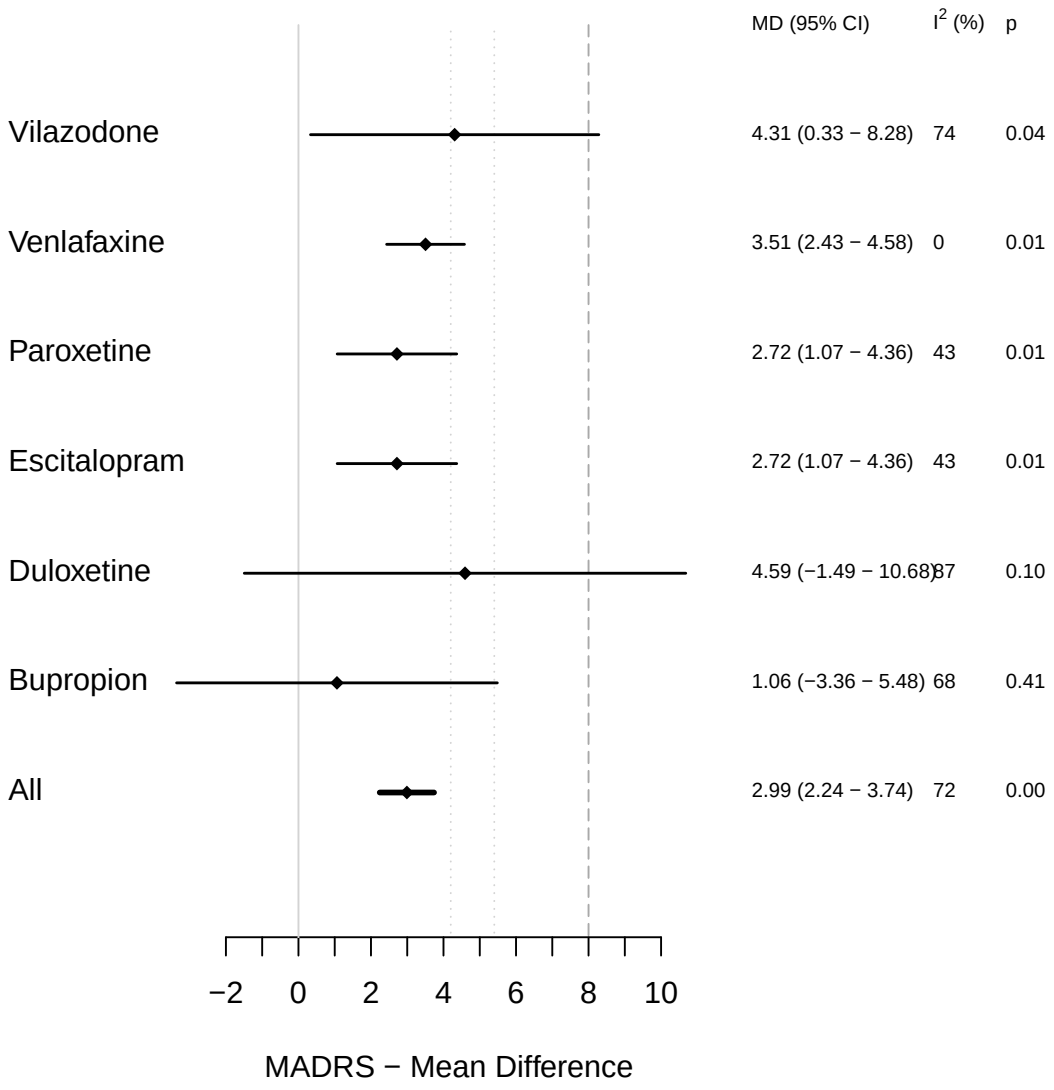

Figure 8: Meta-analytic results for trials using the MADRS and with mean differences as outcome. The vertical gray dashed line is the threshold for clinical significance according to Leucht et al. (2013), the vertical dotted lines are thresholds for minimal important differences according to Barrett et al. (2005) (see article text for details). MD: mean-difference, I^2: heterogenity index (%), p: p-value of meta-analytic result.

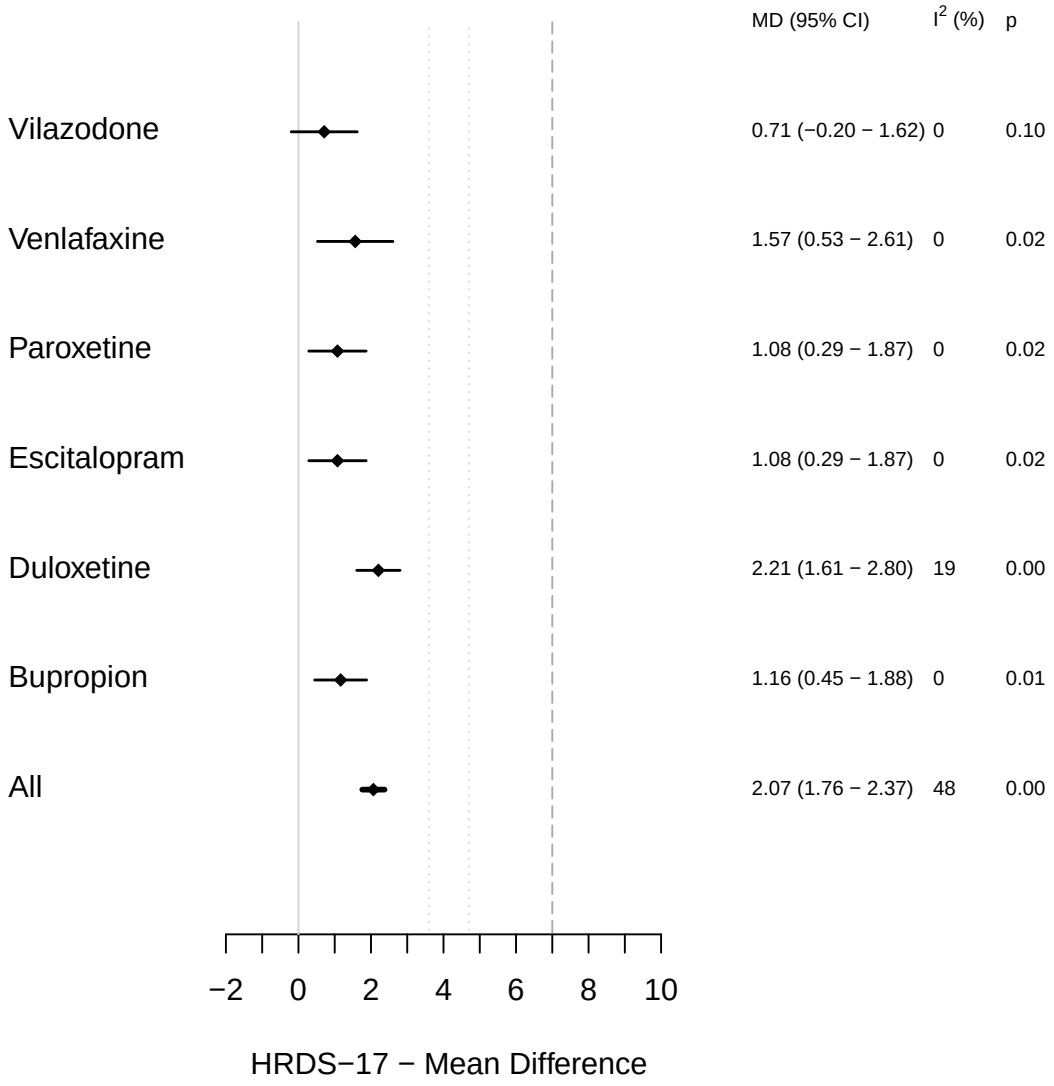

Figure 9: Meta-analytic results for trials using the HDRS-17 and with mean differences as outcome. The vertical gray dashed line is the threshold for clinical significance according to Leucht et al. (2013), the vertical dotted lines are thresholds for minimal important differences according to Barrett et al. (2005) (see article text for details). MD: mean-difference, I^2: heterogenity index (%), p: p-value of meta-analytic result.