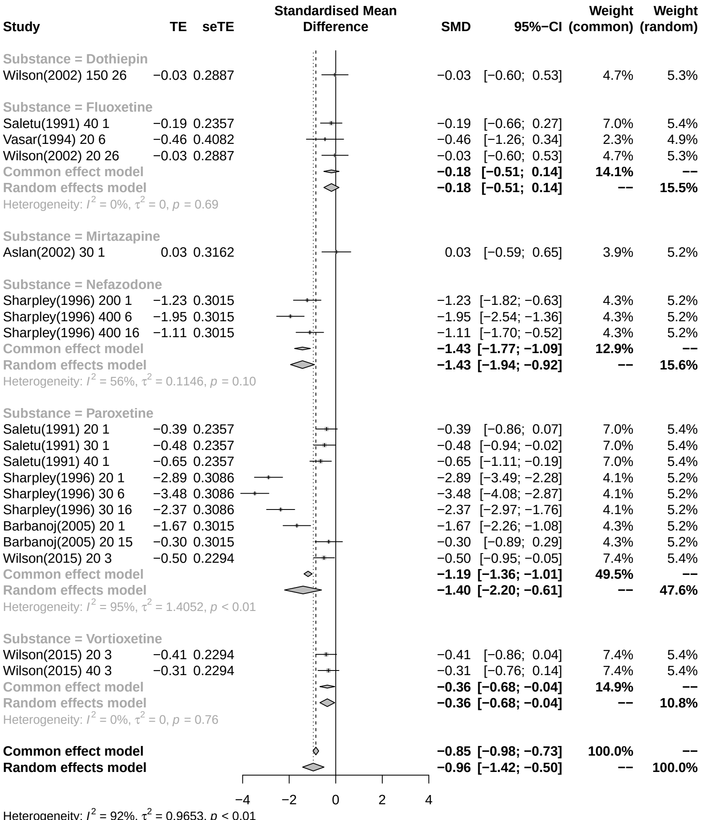
Healthy Population TST vs Placebo

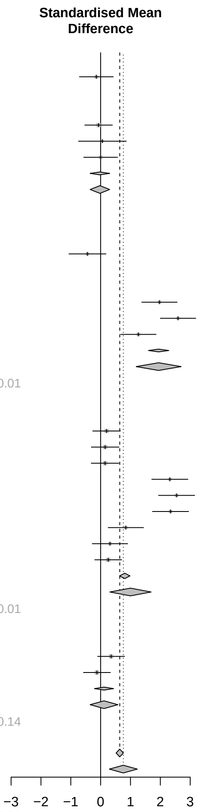


Heterogeneity: I^2 = 92%, τ^2 = 0.9653, p < 0.01

Test for subgroup differences (common effect): χ^2_5 = 66.30, df = 5 (p < 0.01)

Test for subgroup differences (random effects): χ^2_5 = 26.65, df = 5 (p < 0.01)

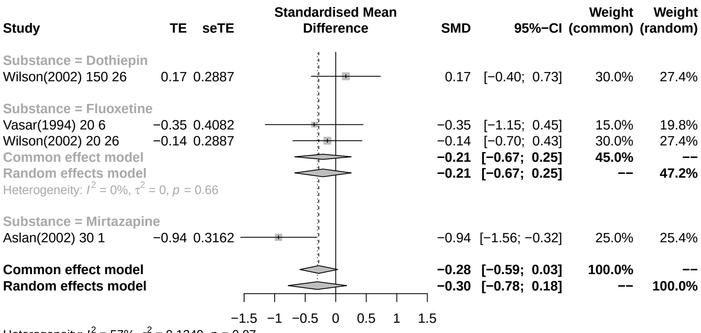
Healthy Population Sleep Latency (min) vs Placebo



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Dothiepin						
Wilson(2002) 150 26	−0.14	0.2887	−0.14	[−0.71; 0.42]	4.7%	5.3%
Substance = Fluoxetine						
Saletu(1991) 40 1	−0.07	0.2357	−0.07	[−0.53; 0.39]	7.0%	5.4%
Vasar(1994) 20 6	0.06	0.4082	0.06	[−0.74; 0.86]	2.3%	4.9%
Wilson(2002) 20 26	0.00	0.2887	0.00	[−0.57; 0.57]	4.7%	5.3%
Common effect model			**−0.02**	**[−0.35; 0.30]**	**14.1%**	**−−**
Random effects model			**−0.02**	**[−0.35; 0.30]**	**−−**	**15.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.96						
Substance = Mirtazapine						
Aslan(2002) 30 1	−0.44	0.3162	−0.44	[−1.06; 0.18]	3.9%	5.2%
Substance = Nefazodone						
Sharpley(1996) 200 1	1.97	0.3015	1.97	[1.38; 2.56]	4.3%	5.2%
Sharpley(1996) 400 6	2.59	0.3015	2.59	[2.00; 3.18]	4.3%	5.2%
Sharpley(1996) 400 16	1.26	0.3015	1.26	[0.67; 1.86]	4.3%	5.2%
Common effect model			**1.94**	**[1.60; 2.28]**	**12.9%**	**−−**
Random effects model			**1.94**	**[1.19; 2.69]**	**−−**	**15.6%**
Heterogeneity: I^2 = 79%, τ^2 = 0.3504, p < 0.01						
Substance = Paroxetine						
Saletu(1991) 20 1	0.20	0.2357	0.20	[−0.26; 0.66]	7.0%	5.4%
Saletu(1991) 30 1	0.15	0.2357	0.15	[−0.31; 0.61]	7.0%	5.4%
Saletu(1991) 40 1	0.15	0.2357	0.15	[−0.31; 0.61]	7.0%	5.4%
Sharpley(1996) 20 1	2.32	0.3086	2.32	[1.71; 2.92]	4.1%	5.2%
Sharpley(1996) 30 6	2.54	0.3086	2.54	[1.94; 3.15]	4.1%	5.2%
Sharpley(1996) 30 16	2.34	0.3086	2.34	[1.74; 2.95]	4.1%	5.2%
Barbanoj(2005) 20 1	0.84	0.3015	0.84	[0.25; 1.43]	4.3%	5.2%
Barbanoj(2005) 20 15	0.31	0.3015	0.31	[−0.28; 0.90]	4.3%	5.2%
Wilson(2015) 20 3	0.25	0.2294	0.25	[−0.20; 0.70]	7.4%	5.4%
Common effect model			**0.81**	**[0.63; 0.98]**	**49.5%**	**−−**
Random effects model			**1.00**	**[0.31; 1.69]**	**−−**	**47.6%**
Heterogeneity: I^2 = 93%, τ^2 = 1.0438, p < 0.01						
Substance = Vortioxetine						
Wilson(2015) 20 3	0.35	0.2294	0.35	[−0.10; 0.80]	7.4%	5.4%
Wilson(2015) 40 3	−0.12	0.2294	−0.12	[−0.57; 0.33]	7.4%	5.4%
Common effect model			**0.11**	**[−0.20; 0.43]**	**14.9%**	**−−**
Random effects model			**0.11**	**[−0.35; 0.58]**	**−−**	**10.8%**
Heterogeneity: I^2 = 53%, τ^2 = 0.0603, p = 0.14						
Common effect model			**0.64**	**[0.52; 0.76]**	**100.0%**	**−−**
Random effects model			**0.76**	**[0.29; 1.23]**	**−−**	**100.0%**

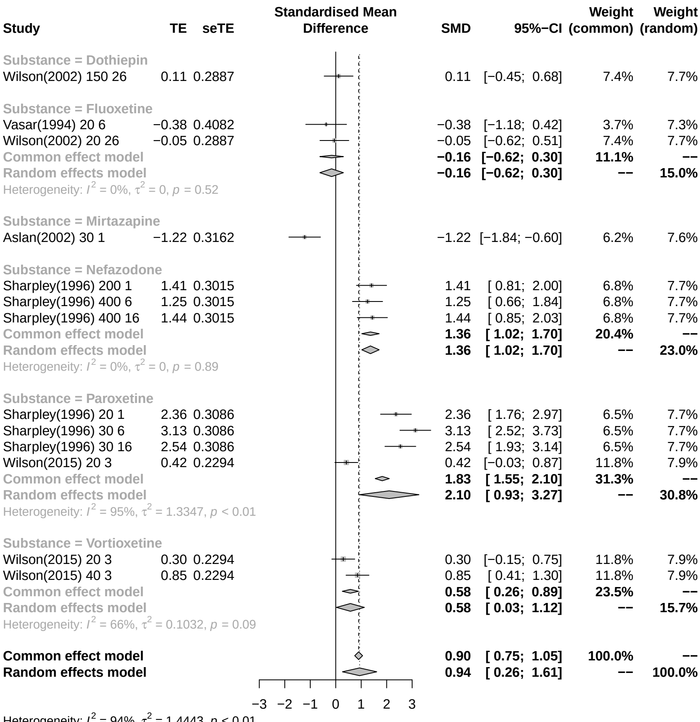
Heterogeneity: I^2 = 92%, τ^2 = 0.9974, p < 0.01
Test for subgroup differences (common effect): χ^2_3 = 105.10, df = 5 (p < 0.01)
Test for subgroup differences (random effects): χ^2_5 = 33.23, df = 5 (p < 0.01)

Healthy Population no. wake periods vs Placebo



Heterogeneity: I^2 = 57%, τ^2 = 0.1349, p = 0.07
Test for subgroup differences (common effect): χ^2_2 = 6.78, df = 2 (p = 0.03)
Test for subgroup differences (random effects): χ^2_2 = 6.78, df = 2 (p = 0.03)

Healthy Population WASO vs Placebo

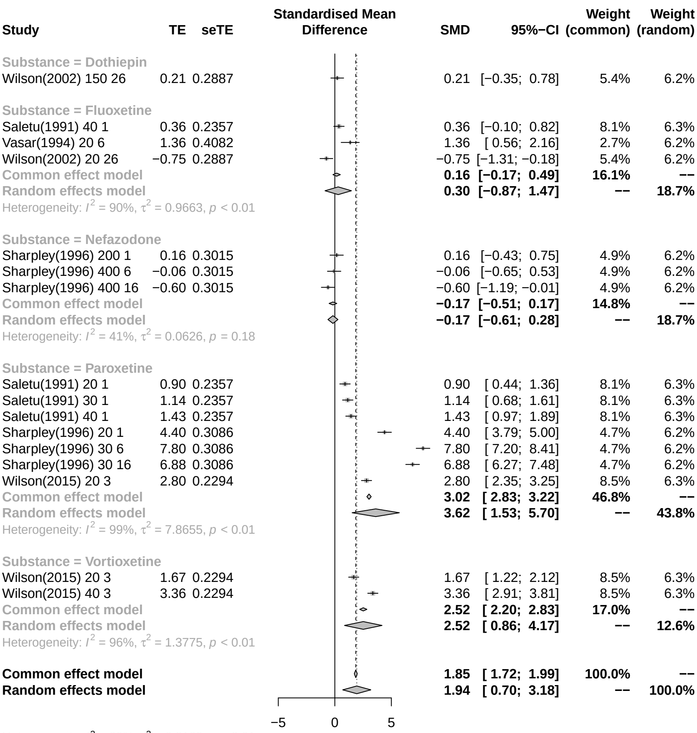


Heterogeneity: I^2 = 94%, τ^2 = 1.4443, p < 0.01

Test for subgroup differences (common effect): χ^2_5 = 126.94, df = 5 (p < 0.01)

Test for subgroup differences (random effects): χ^2_5 = 71.08, df = 5 (p < 0.01)

Healthy Population REM latency min vs Placebo

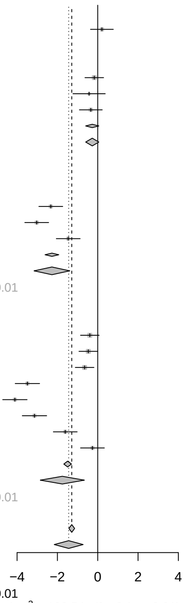


Heterogeneity: I^2 = 99%, τ^2 = 6.3162, p < 0.01

Test for subgroup differences (common effect): χ^2_4 = 430.49, df = 4 (p < 0.01)

Test for subgroup differences (random effects): χ^2_4 = 20.46, df = 4 (p < 0.01)

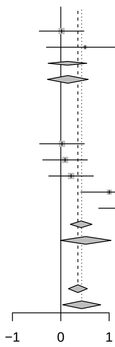
Healthy Population SE % vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Dothiepin							
Wilson(2002) 150 26	0.21	0.2887		0.21	[−0.36; 0.77]	6.4%	6.7%
Substance = Fluoxetine							
Saletu(1991) 40 1	−0.17	0.2357		−0.17	[−0.63; 0.29]	9.5%	6.8%
Vasar(1994) 20 6	−0.43	0.4082		−0.43	[−1.23; 0.37]	3.2%	6.4%
Wilson(2002) 20 26	−0.34	0.2887		−0.34	[−0.91; 0.22]	6.4%	6.7%
Common effect model				**−0.27**	**[−0.60; 0.06]**	**19.1%**	**––**
Random effects model				**−0.27**	**[−0.60; 0.06]**	**––**	**19.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.82							
Substance = Nefazodone							
Sharpley(1996) 200 1	−2.33	0.3015		−2.33	[−2.92; −1.74]	5.8%	6.7%
Sharpley(1996) 400 6	−3.03	0.3015		−3.03	[−3.62; −2.44]	5.8%	6.7%
Sharpley(1996) 400 16	−1.46	0.3015		−1.46	[−2.05; −0.87]	5.8%	6.7%
Common effect model				**−2.27**	**[−2.61; −1.93]**	**17.5%**	**––**
Random effects model				**−2.27**	**[−3.16; −1.39]**	**––**	**20.0%**
Heterogeneity: I^2 = 85%, τ^2 = 0.5222, p < 0.01							
Substance = Paroxetine							
Saletu(1991) 20 1	−0.39	0.2357		−0.39	[−0.85; 0.07]	9.5%	6.8%
Saletu(1991) 30 1	−0.47	0.2357		−0.47	[−0.93; −0.01]	9.5%	6.8%
Saletu(1991) 40 1	−0.65	0.2357		−0.65	[−1.11; −0.19]	9.5%	6.8%
Sharpley(1996) 20 1	−3.49	0.3086		−3.49	[−4.09; −2.88]	5.6%	6.6%
Sharpley(1996) 30 6	−4.11	0.3086		−4.11	[−4.71; −3.50]	5.6%	6.6%
Sharpley(1996) 30 16	−3.14	0.3086		−3.14	[−3.74; −2.53]	5.6%	6.6%
Barbanoj(2005) 20 1	−1.61	0.3015		−1.61	[−2.20; −1.02]	5.8%	6.7%
Barbanoj(2005) 20 15	−0.26	0.3015		−0.26	[−0.85; 0.33]	5.8%	6.7%
Common effect model				**−1.49**	**[−1.68; −1.30]**	**57.0%**	**––**
Random effects model				**−1.76**	**[−2.85; −0.66]**	**––**	**53.5%**
Heterogeneity: I^2 = 97%, τ^2 = 2.4038, p < 0.01							
Common effect model				**−1.29**	**[−1.43; −1.15]**	**100.0%**	**––**
Random effects model				**−1.44**	**[−2.16; −0.72]**	**––**	**100.0%**

Heterogeneity: I^2 = 96%, τ^2 = 1.9181, p < 0.01
Test for subgroup differences (common effect): χ^2_3 = 100.54, df = 3 (p < 0.01)
Test for subgroup differences (random effects): χ^2_3 = 28.06, df = 3 (p < 0.01)

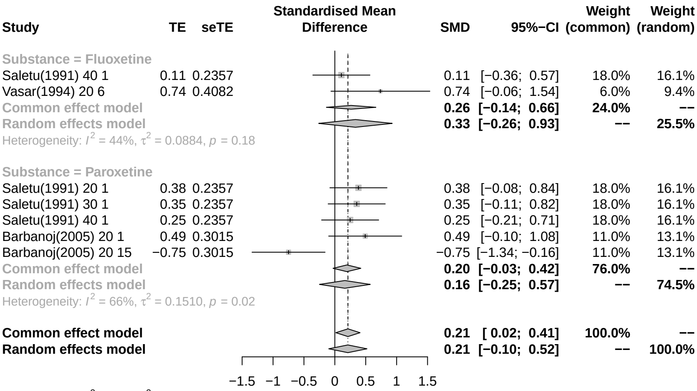
Healthy Population stage 2 % SPT vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Fluoxetine							
Saletu(1991) 40 1	0.02	0.2357		0.02	[−0.45; 0.48]	18.0%	15.5%
Vasar(1994) 20 6	0.50	0.4082		0.50	[−0.30; 1.30]	6.0%	10.9%
Common effect model				**0.14**	**[−0.26; 0.54]**	**24.0%**	**––**
Random effects model				**0.15**	**[−0.28; 0.57]**	**––**	**26.3%**
Heterogeneity: I^2 = 6%, τ^2 = 0.0075, p = 0.30							
Substance = Paroxetine							
Saletu(1991) 20 1	0.02	0.2357		0.02	[−0.44; 0.49]	18.0%	15.5%
Saletu(1991) 30 1	0.09	0.2357		0.09	[−0.37; 0.55]	18.0%	15.5%
Saletu(1991) 40 1	0.21	0.2357		0.21	[−0.25; 0.67]	18.0%	15.5%
Barbanoj(2005) 20 1	1.00	0.3015		1.00	[0.41; 1.60]	11.0%	13.6%
Barbanoj(2005) 20 15	1.37	0.3015		1.37	[0.78; 1.97]	11.0%	13.6%
Common effect model				**0.42**	**[0.20; 0.65]**	**76.0%**	**––**
Random effects model				**0.52**	**[−0.01; 1.04]**	**––**	**73.7%**
Heterogeneity: I^2 = 79%, τ^2 = 0.2868, p < 0.01							
Common effect model				**0.35**	**[0.16; 0.55]**	**100.0%**	**––**
Random effects model				**0.43**	**[0.04; 0.83]**	**––**	**100.0%**

Heterogeneity: I^2 = 73%, τ^2 = 0.2070, p < 0.01
Test for subgroup differences (common effect): χ^2_1 = 1.47, df = 1 (p = 0.23)
Test for subgroup differences (random effects): χ^2_1 = 1.17, df = 1 (p = 0.28)

Healthy Population stage SWS % SPT vs Placebo

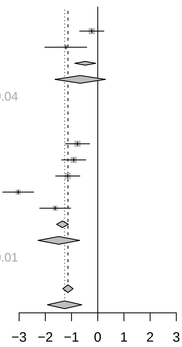


Heterogeneity: I^2 = 56%, τ^2 = 0.0989, p = 0.03

Test for subgroup differences (common effect): χ^2_1 = 0.08, df = 1 (p = 0.77)

Test for subgroup differences (random effects): χ^2_1 = 0.22, df = 1 (p = 0.64)

Healthy Population stage REM % SPT vs Placebo



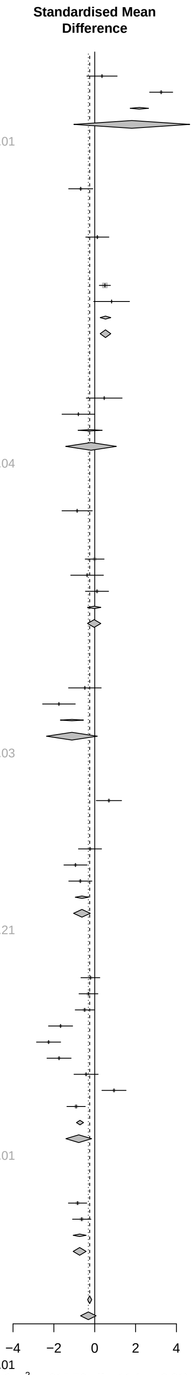
Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Fluoxetine						
Saletu(1991) 40 1	−0.23	0.2357	−0.23	[−0.69; 0.23]	18.0%	14.7%
Vasar(1994) 20 6	−1.22	0.4082	−1.22	[−2.02; −0.42]	6.0%	12.9%
Common effect model			**−0.48**	**[−0.88; −0.08]**	**24.0%**	**––**
Random effects model			**−0.67**	**[−1.63; 0.30]**	**––**	**27.6%**
Heterogeneity: I^2 = 77%, τ^2 = 0.3789, p = 0.04						
Substance = Paroxetine						
Saletu(1991) 20 1	−0.77	0.2357	−0.77	[−1.24; −0.31]	18.0%	14.7%
Saletu(1991) 30 1	−0.92	0.2357	−0.92	[−1.38; −0.45]	18.0%	14.7%
Saletu(1991) 40 1	−1.14	0.2357	−1.14	[−1.61; −0.68]	18.0%	14.7%
Barbanoj(2005) 20 1	−3.04	0.3015	−3.04	[−3.63; −2.45]	11.0%	14.1%
Barbanoj(2005) 20 15	−1.62	0.3015	−1.62	[−2.21; −1.03]	11.0%	14.1%
Common effect model			**−1.35**	**[−1.57; −1.12]**	**76.0%**	**––**
Random effects model			**−1.48**	**[−2.28; −0.69]**	**––**	**72.4%**
Heterogeneity: I^2 = 91%, τ^2 = 0.7511, p < 0.01						
Common effect model			**−1.14**	**[−1.33; −0.94]**	**100.0%**	**––**
Random effects model			**−1.26**	**[−1.92; −0.61]**	**––**	**100.0%**

Heterogeneity: I^2 = 90%, τ^2 = 0.7077, p < 0.01

Test for subgroup differences (common effect): χ^2_1 = 13.79, df = 1 (p < 0.01)

Test for subgroup differences (random effects): χ^2_1 = 1.64, df = 1 (p = 0.20)

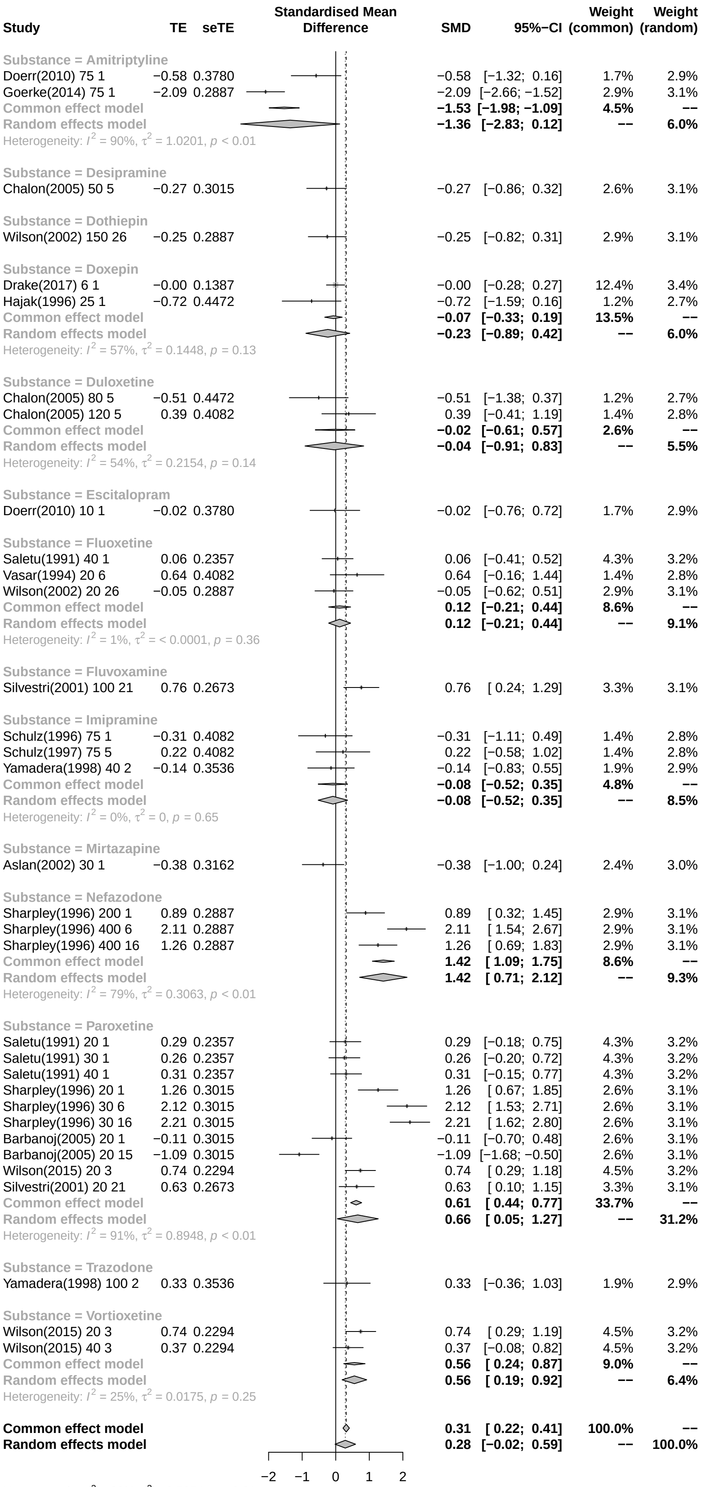
Healthy Population TST



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Amitriptyline						
Doerr(2010) 75 1	0.36	0.3780	0.36	[−0.38; 1.10]	1.9%	3.3%
Goerke(2014) 75 1	3.25	0.2887	3.25	[2.69; 3.82]	3.2%	3.5%
Common effect model			**2.18**	**[1.74; 2.63]**	**5.0%**	**−−**
Random effects model			**1.81**	**[−1.02; 4.65]**	**−−**	**6.8%**
Heterogeneity: I^2 = 97%, τ^2 = 4.0783, p < 0.01						
Substance = Desipramine						
Chalon(2005) 50 5	−0.69	0.3015	−0.69	[−1.28; −0.10]	2.9%	3.5%
Substance = Dothiepin						
Wilson(2002) 150 26	0.13	0.2887	0.13	[−0.44; 0.69]	3.2%	3.5%
Substance = Doxepin						
Drake(2017) 6 1	0.50	0.1387	0.50	[0.23; 0.77]	13.8%	3.7%
Hajak(1996) 25 1	0.83	0.4472	0.83	[−0.05; 1.70]	1.3%	3.2%
Common effect model			**0.53**	**[0.27; 0.79]**	**15.1%**	**−−**
Random effects model			**0.53**	**[0.27; 0.79]**	**−−**	**6.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.48						
Substance = Duloxetine						
Chalon(2005) 80 5	0.46	0.4472	0.46	[−0.41; 1.34]	1.3%	3.2%
Chalon(2005) 120 5	−0.80	0.4082	−0.80	[−1.60; −0.00]	1.6%	3.2%
Common effect model			**−0.23**	**[−0.82; 0.37]**	**2.9%**	**−−**
Random effects model			**−0.18**	**[−1.42; 1.06]**	**−−**	**6.4%**
Heterogeneity: I^2 = 77%, τ^2 = 0.6170, p = 0.04						
Substance = Escitalopram						
Doerr(2010) 10 1	−0.86	0.3780	−0.86	[−1.60; −0.12]	1.9%	3.3%
Substance = Fluoxetine						
Saletu(1991) 40 1	−0.00	0.2357	−0.00	[−0.47; 0.46]	4.8%	3.6%
Vasar(1994) 20 6	−0.37	0.4082	−0.37	[−1.17; 0.43]	1.6%	3.2%
Wilson(2002) 20 26	0.11	0.2887	0.11	[−0.45; 0.68]	3.2%	3.5%
Common effect model			**−0.03**	**[−0.35; 0.30]**	**9.5%**	**−−**
Random effects model			**−0.03**	**[−0.35; 0.30]**	**−−**	**10.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.62						
Substance = Imipramine						
Schulz(1996) 75 1	−0.48	0.4082	−0.48	[−1.28; 0.32]	1.6%	3.2%
Schulz(1997) 75 5	−1.75	0.4082	−1.75	[−2.55; −0.95]	1.6%	3.2%
Common effect model			**−1.12**	**[−1.68; −0.55]**	**3.2%**	**−−**
Random effects model			**−1.12**	**[−2.36; 0.13]**	**−−**	**6.5%**
Heterogeneity: I^2 = 79%, τ^2 = 0.6390, p = 0.03						
Substance = Mirtazapine						
Aslan(2002) 30 1	0.69	0.3162	0.69	[0.07; 1.31]	2.7%	3.4%
Substance = Nefazodone						
Sharpley(1996) 200 1	−0.23	0.2887	−0.23	[−0.80; 0.33]	3.2%	3.5%
Sharpley(1996) 400 6	−0.94	0.2887	−0.94	[−1.51; −0.38]	3.2%	3.5%
Sharpley(1996) 400 16	−0.70	0.2887	−0.70	[−1.27; −0.14]	3.2%	3.5%
Common effect model			**−0.63**	**[−0.95; −0.30]**	**9.5%**	**−−**
Random effects model			**−0.63**	**[−1.04; −0.22]**	**−−**	**10.5%**
Heterogeneity: I^2 = 36%, τ^2 = 0.0477, p = 0.21						
Substance = Paroxetine						
Saletu(1991) 20 1	−0.21	0.2357	−0.21	[−0.67; 0.25]	4.8%	3.6%
Saletu(1991) 30 1	−0.31	0.2357	−0.31	[−0.77; 0.16]	4.8%	3.6%
Saletu(1991) 40 1	−0.49	0.2357	−0.49	[−0.96; −0.03]	4.8%	3.6%
Sharpley(1996) 20 1	−1.67	0.3015	−1.67	[−2.26; −1.08]	2.9%	3.5%
Sharpley(1996) 30 6	−2.26	0.3015	−2.26	[−2.85; −1.67]	2.9%	3.5%
Sharpley(1996) 30 16	−1.75	0.3015	−1.75	[−2.34; −1.16]	2.9%	3.5%
Barbanoj(2005) 20 1	−0.42	0.3015	−0.42	[−1.01; 0.17]	2.9%	3.5%
Barbanoj(2005) 20 15	0.94	0.3015	0.94	[0.35; 1.53]	2.9%	3.5%
Wilson(2015) 20 3	−0.91	0.2294	−0.91	[−1.36; −0.46]	5.0%	3.6%
Common effect model			**−0.72**	**[−0.89; −0.55]**	**34.0%**	**−−**
Random effects model			**−0.78**	**[−1.41; −0.15]**	**−−**	**31.7%**
Heterogeneity: I^2 = 91%, τ^2 = 0.8562, p < 0.01						
Substance = Vortioxetine						
Wilson(2015) 20 3	−0.84	0.2294	−0.84	[−1.29; −0.39]	5.0%	3.6%
Wilson(2015) 40 3	−0.64	0.2294	−0.64	[−1.09; −0.19]	5.0%	3.6%
Common effect model			**−0.74**	**[−1.06; −0.42]**	**10.1%**	**−−**
Random effects model			**−0.74**	**[−1.06; −0.42]**	**−−**	**7.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.53						
Common effect model			**−0.25**	**[−0.35; −0.15]**	**100.0%**	**−−**
Random effects model			**−0.31**	**[−0.69; 0.07]**	**−−**	**100.0%**

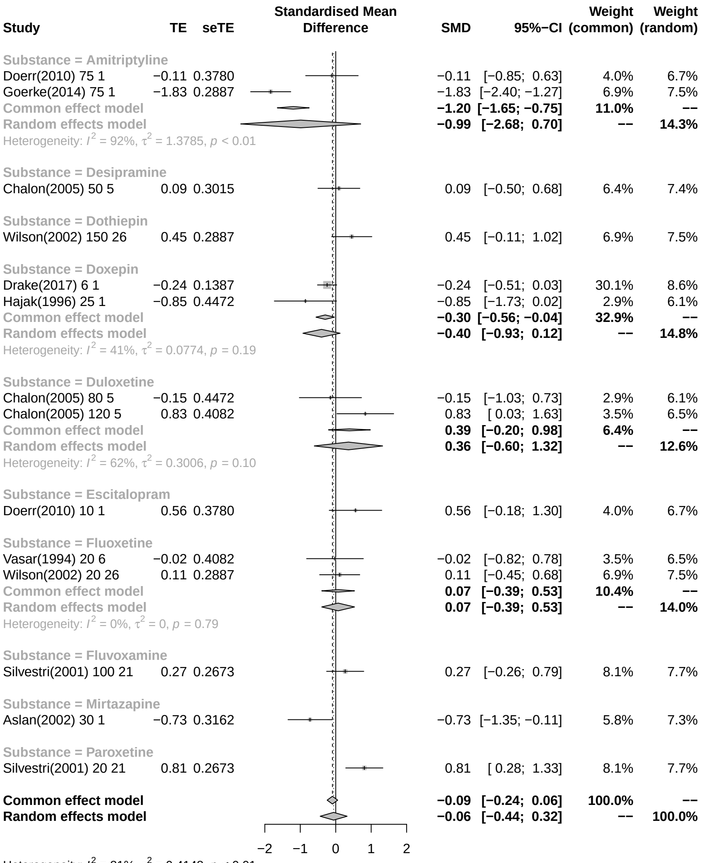
Heterogeneity: I^2 = 92%, τ^2 = 0.9961, p < 0.01
Test for subgroup differences (common effect): χ^2_{11} = 215.70, df = 11 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{11} = 67.69, df = 11 (p < 0.01)

Healthy Population Sleep Latency (min)



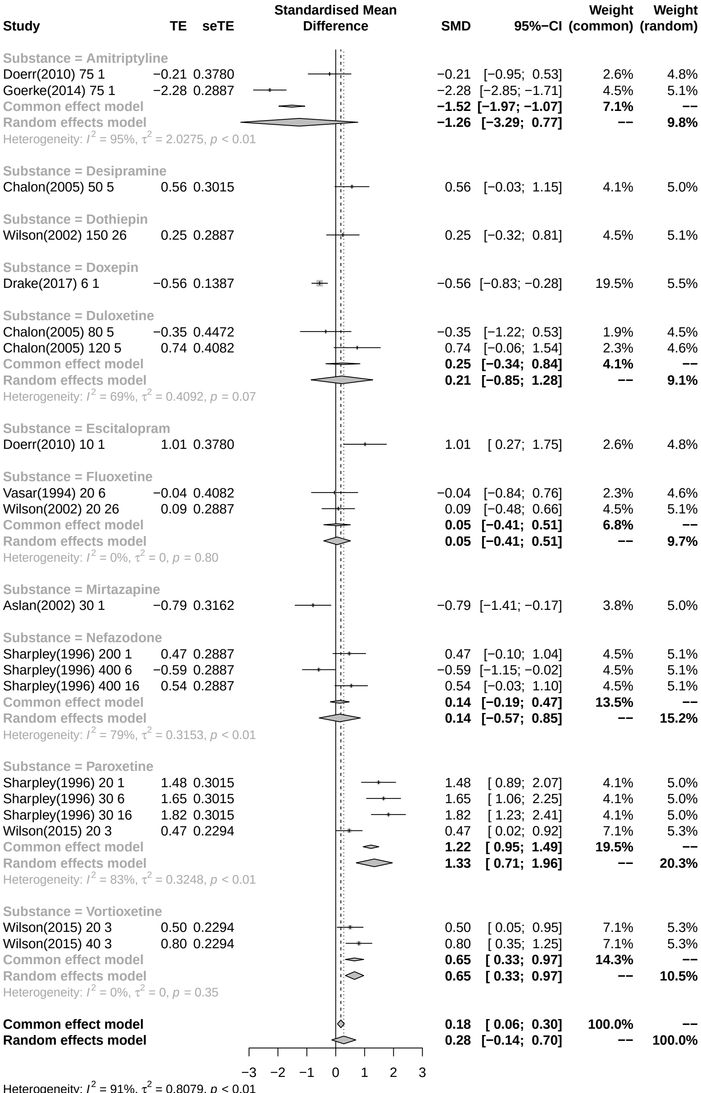
Heterogeneity: I^2 = 89%, τ^2 = 0.7054, p < 0.01
Test for subgroup differences (common effect): χ^2_{13} = 153.50, df = 13 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{13} = 38.49, df = 13 (p < 0.01)

Healthy Population no. wake periods



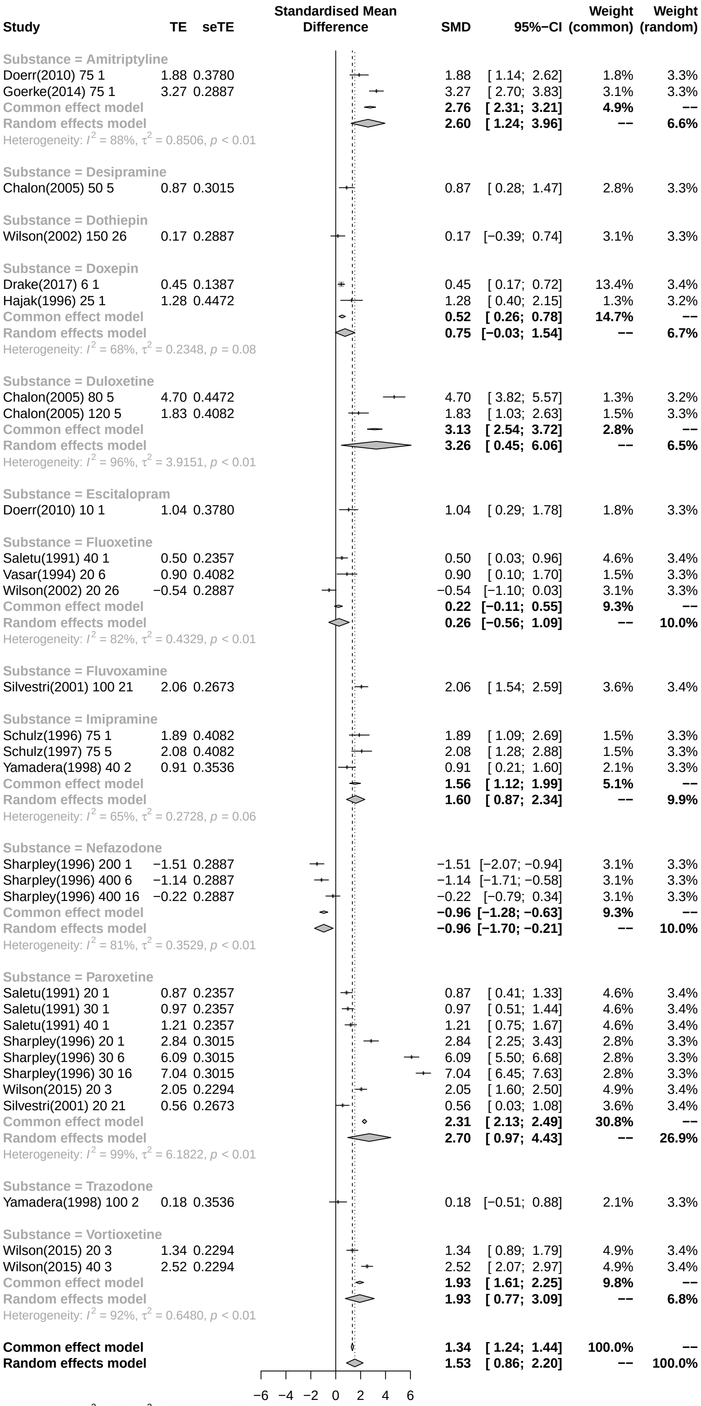
Heterogeneity: I^2 = 81%, τ^2 = 0.4148, p < 0.01
Test for subgroup differences (common effect): χ^2_9 = 52.59, df = 9 (p < 0.01)
Test for subgroup differences (random effects): χ^2_9 = 22.42, df = 9 (p < 0.01)

Healthy Population WASO



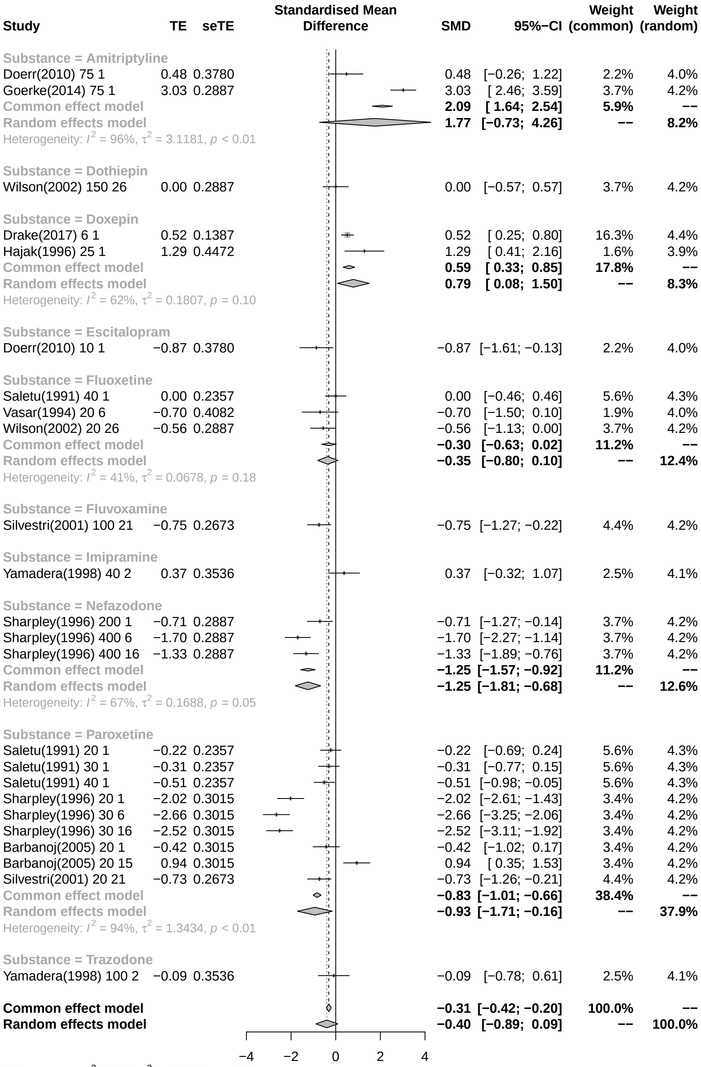
Heterogeneity: I^2 = 91%, τ^2 = 0.8079, p < 0.01
Test for subgroup differences (common effect): χ^2_{10} = 163.90, df = 10 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{10} = 67.07, df = 10 (p < 0.01)

Healthy Population REM latency min



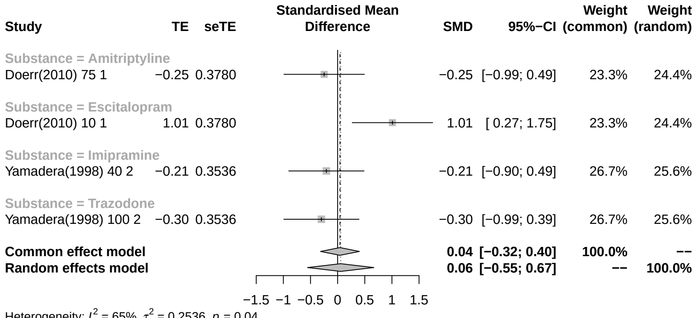
Heterogeneity: I^2 = 97%, τ^2 = 3.3876, p < 0.01
Test for subgroup differences (common effect): χ^2_{12} = 511.86, df = 12 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{12} = 75.01, df = 12 (p < 0.01)

Healthy Population SE %



Heterogeneity: I^2 = 94%, τ^2 = 1.4004, p < 0.01
Test for subgroup differences (common effect): χ^2_9 = 231.08, df = 9 (p < 0.01)
Test for subgroup differences (random effects): χ^2_9 = 34.62, df = 9 (p < 0.01)

Healthy Population stage wake % SPT

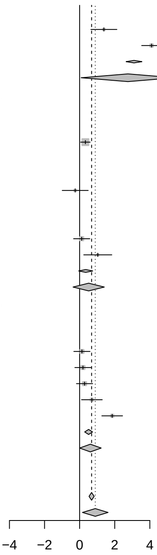


Heterogeneity: I^2 = 65%, τ^2 = 0.2536, p = 0.04

Test for subgroup differences (common effect): χ^2_3 = 8.58, df = 3 (p = 0.04)

Test for subgroup differences (random effects): χ^2_3 = 8.58, df = 3 (p = 0.04)

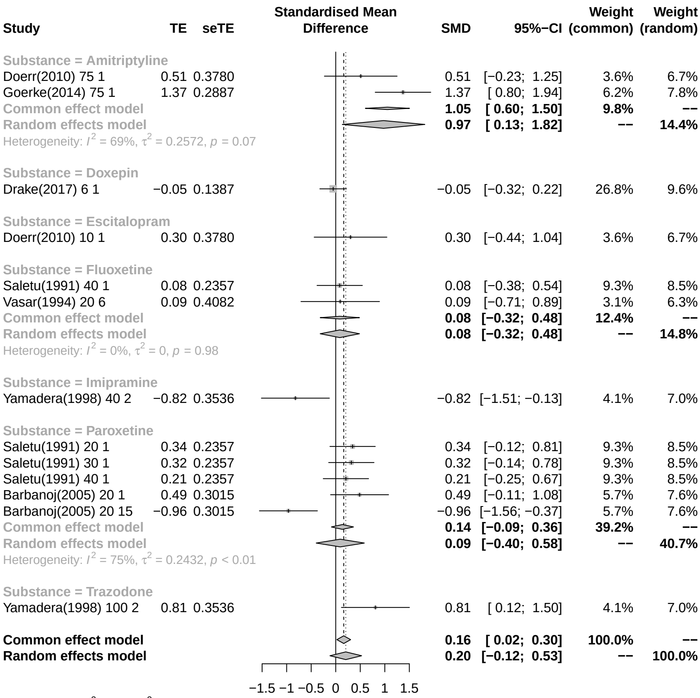
Healthy Population stage 2 % SPT



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Amitriptyline						
Doerr(2010) 75 1	1.38	0.3780	1.38	[0.64; 2.12]	3.9%	8.8%
Goerke(2014) 75 1	4.10	0.2887	4.10	[3.53; 4.67]	6.7%	9.1%
Common effect model			**3.10**	**[2.65; 3.55]**	**10.7%**	**−−**
Random effects model			**2.75**	**[0.09; 5.42]**	**−−**	**17.9%**
Heterogeneity: I^2 = 97%, τ^2 = 3.5818, p < 0.01						
Substance = Doxepin						
Drake(2017) 6 1	0.33	0.1387	0.33	[0.06; 0.60]	29.2%	9.5%
Substance = Escitalopram						
Doerr(2010) 10 1	−0.25	0.3780	−0.25	[−0.99; 0.49]	3.9%	8.8%
Substance = Fluoxetine						
Saletu(1991) 40 1	0.12	0.2357	0.12	[−0.35; 0.58]	10.1%	9.3%
Vasar(1994) 20 6	1.03	0.4082	1.03	[0.23; 1.83]	3.4%	8.6%
Common effect model			**0.35**	**[−0.05; 0.75]**	**13.5%**	**−−**
Random effects model			**0.51**	**[−0.38; 1.41]**	**−−**	**17.9%**
Heterogeneity: I^2 = 74%, τ^2 = 0.3092, p = 0.05						
Substance = Paroxetine						
Saletu(1991) 20 1	0.13	0.2357	0.13	[−0.33; 0.59]	10.1%	9.3%
Saletu(1991) 30 1	0.19	0.2357	0.19	[−0.27; 0.65]	10.1%	9.3%
Saletu(1991) 40 1	0.28	0.2357	0.28	[−0.18; 0.74]	10.1%	9.3%
Barbanoj(2005) 20 1	0.70	0.3015	0.70	[0.11; 1.29]	6.2%	9.1%
Barbanoj(2005) 20 15	1.85	0.3015	1.85	[1.26; 2.45]	6.2%	9.1%
Common effect model			**0.51**	**[0.29; 0.74]**	**42.7%**	**−−**
Random effects model			**0.61**	**[−0.00; 1.23]**	**−−**	**46.0%**
Heterogeneity: I^2 = 84%, τ^2 = 0.4248, p < 0.01						
Common effect model			**0.68**	**[0.53; 0.83]**	**100.0%**	**−−**
Random effects model			**0.89**	**[0.16; 1.62]**	**−−**	**100.0%**

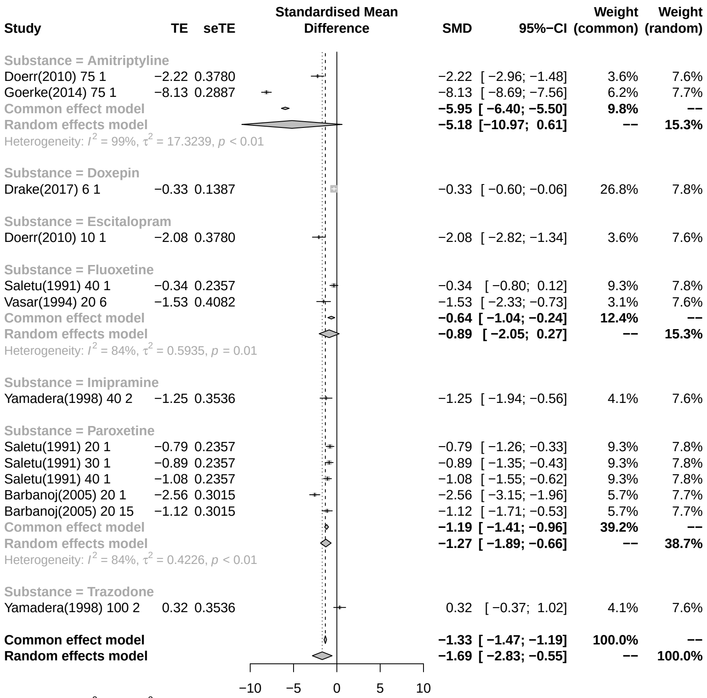
Heterogeneity: I^2 = 95%, τ^2 = 1.4364, p < 0.01
Test for subgroup differences (common effect): χ^2_4 = 128.46, df = 4 (p < 0.01)
Test for subgroup differences (random effects): χ^2_4 = 6.51, df = 4 (p = 0.16)

Healthy Population stage SWS % SPT



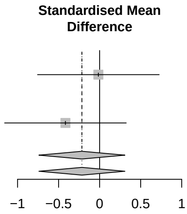
Heterogeneity: I^2 = 75%, τ^2 = 0.2643, p < 0.01
Test for subgroup differences (common effect): χ^2_6 = 28.90, df = 6 (p < 0.01)
Test for subgroup differences (random effects): χ^2_6 = 16.34, df = 6 (p = 0.01)

Healthy Population stage REM % SPT



Heterogeneity: I^2 = 98%, τ^2 = 4.3215, p < 0.01
Test for subgroup differences (common effect): χ^2_6 = 497.32, df = 6 (p < 0.01)
Test for subgroup differences (random effects): χ^2_6 = 36.60, df = 6 (p < 0.01)

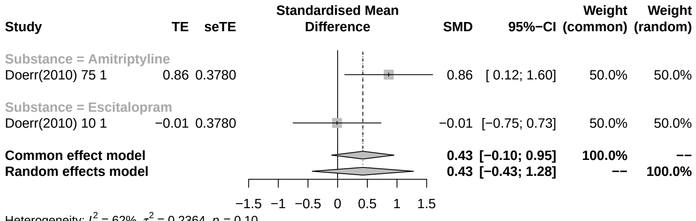
Healthy Population REM density %



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Amitriptyline							
Doerr(2010) 75 1	−0.02	0.3780		−0.02	[−0.76; 0.73]	50.0%	50.0%
Substance = Escitalopram							
Doerr(2010) 10 1	−0.42	0.3780		−0.42	[−1.16; 0.32]	50.0%	50.0%
Common effect model				**−0.22**	**[−0.74; 0.31]**	**100.0%**	**––**
Random effects model				**−0.22**	**[−0.74; 0.31]**	**––**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.45
Test for subgroup differences (common effect): χ^2_1 = 0.56, df = 1 (p = 0.45)
Test for subgroup differences (random effects): χ^2_1 = 0.56, df = 1 (p = 0.45)

Healthy Population PLMS Index

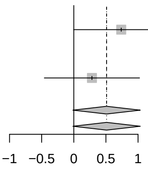


Heterogeneity: I^2 = 62%, τ^2 = 0.2364, p = 0.10

Test for subgroup differences (common effect): χ^2_1 = 2.66, df = 1 (p = 0.10)

Test for subgroup differences (random effects): χ^2_1 = 2.66, df = 1 (p = 0.10)

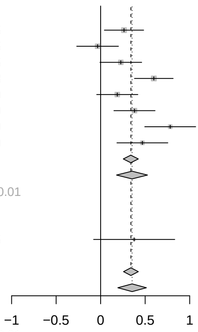
Healthy Population PLMS Index_Ar./h



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Amitriptyline							
Doerr(2010) 75 1	0.74	0.3780		0.74	[−0.00; 1.48]	50.0%	50.0%
Substance = Escitalopram							
Doerr(2010) 10 1	0.28	0.3780		0.28	[−0.46; 1.02]	50.0%	50.0%
Common effect model				**0.51**	**[−0.01; 1.03]**	**100.0%**	**––**
Random effects model				**0.51**	**[−0.01; 1.03]**	**––**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.39
Test for subgroup differences (common effect): χ^2_1 = 0.73, df = 1 (p = 0.39)
Test for subgroup differences (random effects): χ^2_1 = 0.73, df = 1 (p = 0.39)

Insomnia Population TST vs Placebo



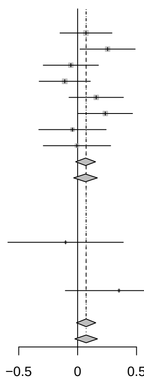
Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Krystal(2010) 1 1	0.26	0.1125		0.26	[0.04; 0.48]	14.2%	12.2%
Krystal(2010) 1 29	−0.03	0.1195		−0.03	[−0.27; 0.20]	12.6%	11.8%
Krystal(2010) 1 85	0.23	0.1195		0.23	[−0.01; 0.46]	12.6%	11.8%
Krystal(2010) 3 1	0.60	0.1108		0.60	[0.38; 0.81]	14.6%	12.3%
Krystal(2010) 3 29	0.19	0.1179		0.19	[−0.04; 0.42]	12.9%	11.9%
Krystal(2010) 3 85	0.38	0.1179		0.38	[0.15; 0.61]	12.9%	11.9%
Hajak(2001) 25 1	0.78	0.1459		0.78	[0.50; 1.07]	8.4%	10.5%
Hajak(2001) 25 28	0.47	0.1459		0.47	[0.18; 0.75]	8.4%	10.5%
Common effect model				**0.34**	**[0.25; 0.42]**	**96.7%**	**––**
Random effects model				**0.35**	**[0.18; 0.53]**	**––**	**93.0%**
Heterogeneity: I^2 = 75%, τ^2 = 0.0476, p < 0.01							
Substance = Trimipramine							
Riemann(2002) 200 28	0.38	0.2325		0.38	[−0.08; 0.83]	3.3%	7.0%
Common effect model				**0.34**	**[0.26; 0.42]**	**100.0%**	**––**
Random effects model				**0.35**	**[0.19; 0.51]**	**––**	**100.0%**

Heterogeneity: I^2 = 72%, τ^2 = 0.0423, p < 0.01

Test for subgroup differences (common effect): χ^2_1 = 0.03, df = 1 (p = 0.87)

Test for subgroup differences (random effects): χ^2_1 = 0.01, df = 1 (p = 0.92)

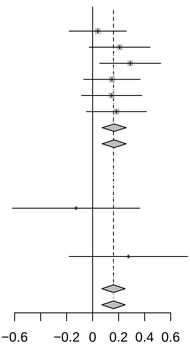
Insomnia Population Sleep Latency (min) vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Krystal(2010) 1 1	0.07	0.1125		0.07	[−0.15; 0.29]	13.8%	13.0%
Krystal(2010) 1 29	0.25	0.1195		0.25	[0.02; 0.49]	12.2%	12.0%
Krystal(2010) 1 85	−0.06	0.1195		−0.06	[−0.29; 0.18]	12.2%	12.0%
Krystal(2010) 3 1	−0.11	0.1108		−0.11	[−0.33; 0.11]	14.2%	13.3%
Krystal(2010) 3 29	0.16	0.1179		0.16	[−0.07; 0.39]	12.6%	12.2%
Krystal(2010) 3 85	0.23	0.1179		0.23	[0.00; 0.47]	12.6%	12.2%
Hajak(2001) 25 1	−0.04	0.1459		−0.04	[−0.33; 0.24]	8.2%	8.9%
Hajak(2001) 25 28	−0.01	0.1459		−0.01	[−0.29; 0.28]	8.2%	8.9%
Common effect model				**0.07**	**[−0.02; 0.15]**	**94.0%**	**––**
Random effects model				**0.07**	**[−0.03; 0.17]**	**––**	**92.5%**
Heterogeneity: I^2 = 27%, τ^2 = 0.0060, p = 0.22							
Substance = Trazodone							
Roth(2011) 50 7	−0.10	0.2500		−0.10	[−0.59; 0.39]	2.8%	3.5%
Substance = Trimipramine							
Riemann(2002) 200 28	0.35	0.2325		0.35	[−0.10; 0.81]	3.2%	4.0%
Common effect model				**0.07**	**[−0.01; 0.15]**	**100.0%**	**––**
Random effects model				**0.07**	**[−0.02; 0.17]**	**––**	**100.0%**

Heterogeneity: I^2 = 22%, τ^2 = 0.0057, p = 0.24
Test for subgroup differences (common effect): χ^2_2 = 1.94, df = 2 (p = 0.38)
Test for subgroup differences (random effects): χ^2_2 = 1.94, df = 2 (p = 0.38)

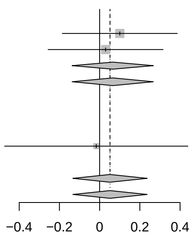
Insomnia Population no. wake periods vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Krystal(2010) 1 1	0.04	0.1125		0.04	[−0.18; 0.26]	16.5%	16.5%
Krystal(2010) 1 29	0.21	0.1195		0.21	[−0.03; 0.44]	14.6%	14.6%
Krystal(2010) 1 85	0.29	0.1195		0.29	[0.05; 0.52]	14.6%	14.6%
Krystal(2010) 3 1	0.15	0.1108		0.15	[−0.07; 0.37]	17.0%	17.0%
Krystal(2010) 3 29	0.15	0.1179		0.15	[−0.08; 0.38]	15.0%	15.0%
Krystal(2010) 3 85	0.18	0.1179		0.18	[−0.05; 0.41]	15.0%	15.0%
Common effect model				**0.17**	**[0.07; 0.26]**	**92.8%**	**––**
Random effects model				**0.17**	**[0.07; 0.26]**	**––**	**92.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.77							
Substance = Trazodone							
Roth(2011) 50 7	−0.13	0.2500		−0.13	[−0.62; 0.36]	3.3%	3.3%
Substance = Trimipramine							
Riemann(2002) 200 28	0.28	0.2325		0.28	[−0.18; 0.73]	3.9%	3.9%
Common effect model				**0.16**	**[0.07; 0.25]**	**100.0%**	**––**
Random effects model				**0.16**	**[0.07; 0.25]**	**––**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.77
Test for subgroup differences (common effect): χ^2_2 = 1.58, df = 2 (p = 0.45)
Test for subgroup differences (random effects): χ^2_2 = 1.58, df = 2 (p = 0.45)

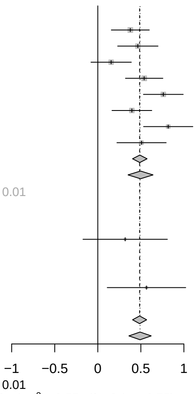
Insomnia Population REM latency min vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	0.10	0.1459		0.10	[−0.19; 0.39]	41.8%	41.8%
Hajak(2001) 25 28	0.03	0.1459		0.03	[−0.26; 0.32]	41.8%	41.8%
Common effect model				**0.06**	**[−0.14; 0.27]**	**83.6%**	**−−**
Random effects model				**0.06**	**[−0.14; 0.27]**	**−−**	**83.6%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73							
Substance = Trimipramine							
Riemann(2002) 200 28	−0.02	0.2325		−0.02	[−0.47; 0.44]	16.4%	16.4%
Common effect model				**0.05**	**[−0.13; 0.24]**	**100.0%**	**−−**
Random effects model				**0.05**	**[−0.13; 0.24]**	**−−**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.90
Test for subgroup differences (common effect): χ^2_1 = 0.10, df = 1 (p = 0.75)
Test for subgroup differences (random effects): χ^2_1 = 0.10, df = 1 (p = 0.75)

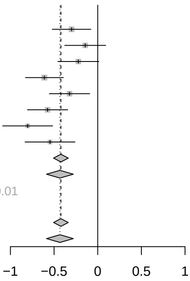
Insomnia Population SE % vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Krystal(2010) 1 1	0.38	0.1125		0.38	[0.16; 0.60]	13.8%	12.0%
Krystal(2010) 1 29	0.47	0.1195		0.47	[0.23; 0.70]	12.2%	11.4%
Krystal(2010) 1 85	0.16	0.1195		0.16	[−0.08; 0.39]	12.2%	11.4%
Krystal(2010) 3 1	0.54	0.1108		0.54	[0.32; 0.76]	14.2%	12.1%
Krystal(2010) 3 29	0.76	0.1179		0.76	[0.53; 0.99]	12.6%	11.6%
Krystal(2010) 3 85	0.40	0.1179		0.40	[0.16; 0.63]	12.6%	11.6%
Hajak(2001) 25 1	0.82	0.1459		0.82	[0.53; 1.10]	8.2%	9.7%
Hajak(2001) 25 28	0.51	0.1459		0.51	[0.22; 0.79]	8.2%	9.7%
Common effect model				**0.49**	**[0.40; 0.57]**	**94.0%**	**––**
Random effects model				**0.50**	**[0.35; 0.64]**	**––**	**89.4%**
Heterogeneity: I^2 = 65%, τ^2 = 0.0285, p < 0.01							
Substance = Trazodone							
Roth(2011) 50 7	0.32	0.2500		0.32	[−0.17; 0.81]	2.8%	5.0%
Substance = Trimipramine							
Riemann(2002) 200 28	0.57	0.2325		0.57	[0.11; 1.02]	3.2%	5.6%
Common effect model				**0.49**	**[0.40; 0.57]**	**100.0%**	**––**
Random effects model				**0.49**	**[0.36; 0.62]**	**––**	**100.0%**

Heterogeneity: I^2 = 56%, τ^2 = 0.0238, p = 0.01
Test for subgroup differences (common effect): χ^2_2 = 0.57, df = 2 (p = 0.75)
Test for subgroup differences (random effects): χ^2_2 = 0.59, df = 2 (p = 0.75)

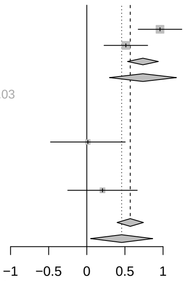
Insomnia Population WASO vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Krystal(2010) 1 1	−0.30	0.1125		−0.30	[−0.52; −0.08]	14.7%	13.2%
Krystal(2010) 1 29	−0.14	0.1195		−0.14	[−0.38; 0.09]	13.0%	12.8%
Krystal(2010) 1 85	−0.22	0.1195		−0.22	[−0.46; 0.01]	13.0%	12.8%
Krystal(2010) 3 1	−0.61	0.1108		−0.61	[−0.83; −0.39]	15.1%	13.3%
Krystal(2010) 3 29	−0.32	0.1179		−0.32	[−0.55; −0.09]	13.4%	12.9%
Krystal(2010) 3 85	−0.57	0.1179		−0.57	[−0.81; −0.34]	13.4%	12.9%
Hajak(2001) 25 1	−0.80	0.1459		−0.80	[−1.09; −0.52]	8.7%	11.1%
Hajak(2001) 25 28	−0.55	0.1459		−0.55	[−0.83; −0.26]	8.7%	11.1%
Common effect model				**−0.42**	**[−0.51; −0.34]**	**100.0%**	**––**
Random effects model				**−0.43**	**[−0.59; −0.28]**	**––**	**100.0%**
Heterogeneity: I^2 = 69%, τ^2 = 0.0337, p < 0.01							
Common effect model				**−0.42**	**[−0.51; −0.34]**	**100.0%**	**––**
Random effects model				**−0.43**	**[−0.59; −0.28]**	**––**	**100.0%**

Heterogeneity: I^2 = 69%, τ^2 = 0.0337, p < 0.01
Test for subgroup differences (common effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)

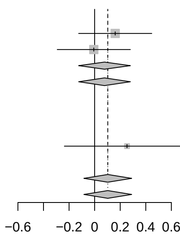
Insomnia Population stage 2 % SPT vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	0.96	0.1459		0.96	[0.67; 1.25]	36.6%	27.6%
Hajak(2001) 25 28	0.51	0.1459		0.51	[0.23; 0.80]	36.6%	27.6%
Common effect model				**0.74**	**[0.53; 0.94]**	**73.2%**	**−−**
Random effects model				**0.74**	**[0.30; 1.18]**	**−−**	**55.3%**
Heterogeneity: I^2 = 79%, τ^2 = 0.0790, p = 0.03							
Substance = Trazodone							
Roth(2011) 50 7	0.01	0.2500		0.01	[−0.48; 0.50]	12.5%	21.9%
Substance = Trimipramine							
Riemann(2002) 200 28	0.21	0.2325		0.21	[−0.25; 0.66]	14.4%	22.8%
Common effect model				**0.57**	**[0.40; 0.74]**	**100.0%**	**−−**
Random effects model				**0.46**	**[0.05; 0.86]**	**−−**	**100.0%**

Heterogeneity: I^2 = 80%, τ^2 = 0.1349, p < 0.01
Test for subgroup differences (common effect): χ^2_2 = 10.00, df = 2 (p < 0.01)
Test for subgroup differences (random effects): χ^2_2 = 5.16, df = 2 (p = 0.08)

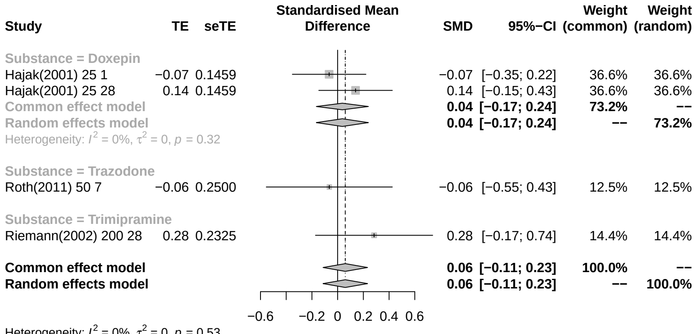
Insomnia Population stage SWS % SPT vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	0.16	0.1459		0.16	[−0.13; 0.45]	42.7%	42.7%
Hajak(2001) 25 28	−0.01	0.1459		−0.01	[−0.29; 0.28]	42.7%	42.7%
Common effect model				**0.08**	**[−0.13; 0.28]**	**85.5%**	**––**
Random effects model				**0.08**	**[−0.13; 0.28]**	**––**	**85.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42							
Substance = Trazodone							
Roth(2011) 50 7	0.25	0.2500		0.25	[−0.24; 0.74]	14.5%	14.5%
Common effect model				**0.10**	**[−0.08; 0.29]**	**100.0%**	**––**
Random effects model				**0.10**	**[−0.08; 0.29]**	**––**	**100.0%**

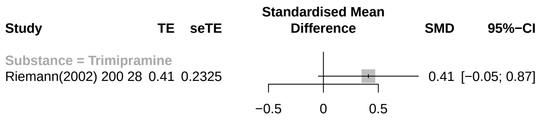
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58
Test for subgroup differences (common effect): χ^2_1 = 0.42, df = 1 (p = 0.52)
Test for subgroup differences (random effects): χ^2_1 = 0.42, df = 1 (p = 0.52)

Insomnia Population stage REM % SPT vs Placebo

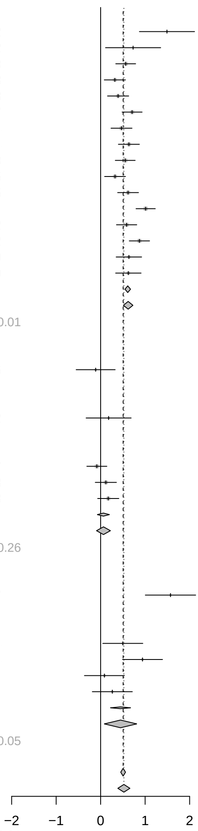


Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.53
Test for subgroup differences (common effect): χ^2_2 = 1.22, df = 2 (p = 0.54)
Test for subgroup differences (random effects): χ^2_2 = 1.22, df = 2 (p = 0.54)

Insomnia Population stage wake % SPT vs Placebo



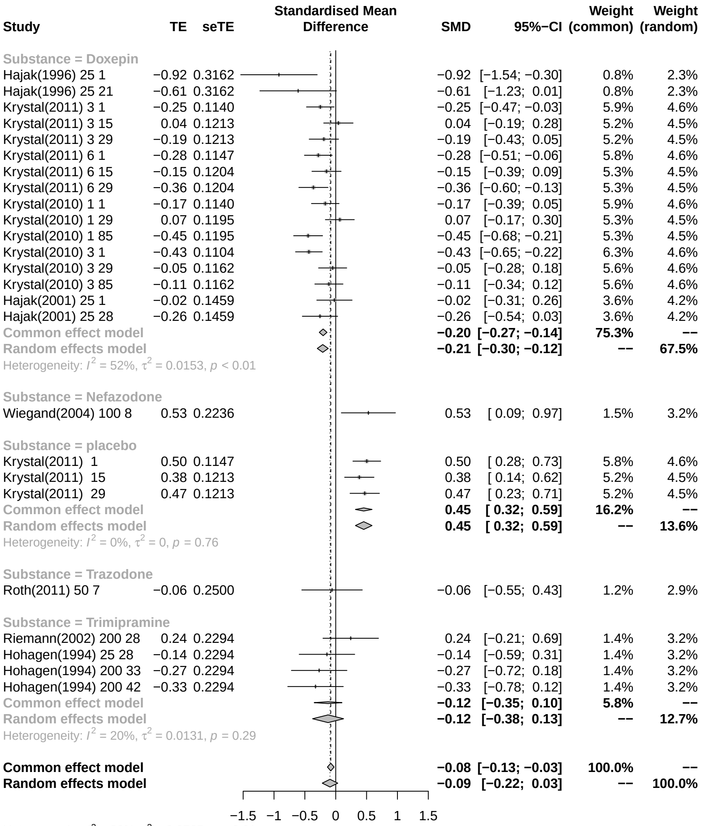
Insomnia Population TST



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin						
Hajak(1996) 25 1	1.49	0.3162	1.49	[0.87; 2.11]	0.8%	2.4%
Hajak(1996) 25 21	0.73	0.3162	0.73	[0.11; 1.35]	0.8%	2.4%
Krystal(2011) 3 1	0.56	0.1140	0.56	[0.34; 0.79]	5.8%	4.4%
Krystal(2011) 3 15	0.32	0.1213	0.32	[0.08; 0.56]	5.1%	4.3%
Krystal(2011) 3 29	0.39	0.1213	0.39	[0.15; 0.63]	5.1%	4.3%
Krystal(2011) 6 1	0.71	0.1147	0.71	[0.48; 0.93]	5.7%	4.4%
Krystal(2011) 6 15	0.47	0.1204	0.47	[0.23; 0.70]	5.2%	4.3%
Krystal(2011) 6 29	0.63	0.1204	0.63	[0.40; 0.87]	5.2%	4.3%
Krystal(2010) 1 1	0.55	0.1140	0.55	[0.33; 0.78]	5.8%	4.4%
Krystal(2010) 1 29	0.32	0.1195	0.32	[0.09; 0.56]	5.3%	4.3%
Krystal(2010) 1 85	0.62	0.1195	0.62	[0.38; 0.85]	5.3%	4.3%
Krystal(2010) 3 1	1.01	0.1104	1.01	[0.80; 1.23]	6.2%	4.4%
Krystal(2010) 3 29	0.58	0.1162	0.58	[0.36; 0.81]	5.6%	4.4%
Krystal(2010) 3 85	0.87	0.1162	0.87	[0.64; 1.10]	5.6%	4.4%
Hajak(2001) 25 1	0.63	0.1459	0.63	[0.35; 0.92]	3.6%	4.1%
Hajak(2001) 25 28	0.62	0.1459	0.62	[0.34; 0.91]	3.6%	4.1%
Common effect model			**0.61**	**[0.55; 0.67]**	**74.7%**	**−−**
Random effects model			**0.62**	**[0.51; 0.73]**	**−−**	**65.2%**
Heterogeneity: I^2 = 66%, τ^2 = 0.0291, p < 0.01						
Substance = Nefazodone						
Wiegand(2004) 100 8	−0.11	0.2236	−0.11	[−0.55; 0.33]	1.5%	3.3%
Substance = Paroxetine						
Nowell(1999) 20 42	0.18	0.2582	0.18	[−0.33; 0.69]	1.1%	2.9%
Substance = placebo						
Krystal(2011) 1	−0.09	0.1147	−0.09	[−0.31; 0.14]	5.7%	4.4%
Krystal(2011) 15	0.12	0.1213	0.12	[−0.12; 0.35]	5.1%	4.3%
Krystal(2011) 29	0.17	0.1213	0.17	[−0.07; 0.41]	5.1%	4.3%
Common effect model			**0.06**	**[−0.07; 0.20]**	**16.0%**	**−−**
Random effects model			**0.06**	**[−0.09; 0.22]**	**−−**	**13.0%**
Heterogeneity: I^2 = 25%, τ^2 = 0.0050, p = 0.26						
Substance = Trazodone						
Paterson(2009) 100 56	1.57	0.2887	1.57	[1.00; 2.14]	0.9%	2.7%
Substance = Trimipramine						
Riemann(2002) 200 28	0.50	0.2294	0.50	[0.05; 0.95]	1.4%	3.2%
Hohagen(1994) 25 28	0.94	0.2294	0.94	[0.49; 1.39]	1.4%	3.2%
Hohagen(1994) 200 33	0.09	0.2294	0.09	[−0.36; 0.54]	1.4%	3.2%
Hohagen(1994) 200 42	0.26	0.2294	0.26	[−0.19; 0.71]	1.4%	3.2%
Common effect model			**0.45**	**[0.22; 0.67]**	**5.7%**	**−−**
Random effects model			**0.45**	**[0.08; 0.81]**	**−−**	**12.9%**
Heterogeneity: I^2 = 62%, τ^2 = 0.0844, p = 0.05						
Common effect model			**0.51**	**[0.45; 0.56]**	**100.0%**	**−−**
Random effects model			**0.52**	**[0.39; 0.66]**	**−−**	**100.0%**

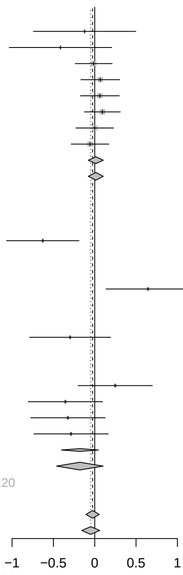
Heterogeneity: I^2 = 81%, τ^2 = 0.0973, p < 0.01
Test for subgroup differences (common effect): χ^2_5 = 75.44, df = 5 (p < 0.01)
Test for subgroup differences (random effects): χ^2_5 = 55.28, df = 5 (p < 0.01)

Insomnia Population Sleep Latency (min)



Heterogeneity: I^2 = 80%, τ^2 = 0.0765, p < 0.01
Test for subgroup differences (common effect): χ^2_4 = 83.18, df = 4 (p < 0.01)
Test for subgroup differences (random effects): χ^2_4 = 71.67, df = 4 (p < 0.01)

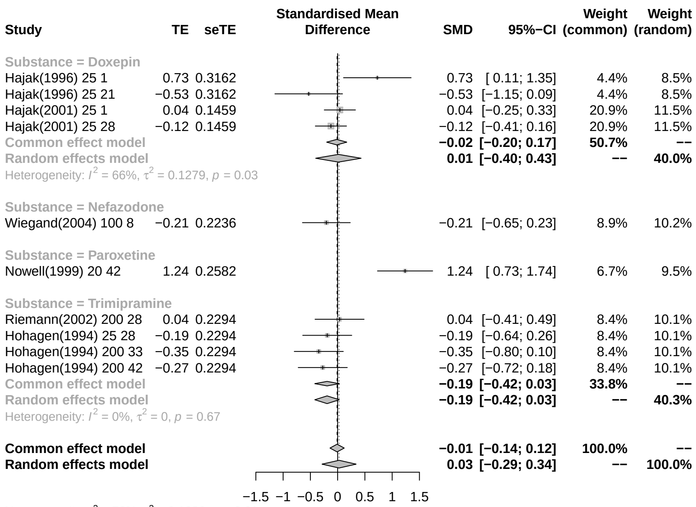
Insomnia Population no. wake periods



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(1996) 25 1	−0.12	0.3162		−0.12	[−0.74; 0.50]	1.7%	2.7%
Hajak(1996) 25 21	−0.41	0.3162		−0.41	[−1.03; 0.21]	1.7%	2.7%
Krystal(2010) 1 1	−0.01	0.1140		−0.01	[−0.24; 0.21]	13.0%	10.8%
Krystal(2010) 1 29	0.07	0.1195		0.07	[−0.17; 0.30]	11.8%	10.4%
Krystal(2010) 1 85	0.06	0.1195		0.06	[−0.17; 0.30]	11.8%	10.4%
Krystal(2010) 3 1	0.09	0.1104		0.09	[−0.12; 0.31]	13.8%	11.2%
Krystal(2010) 3 29	0.00	0.1162		0.00	[−0.23; 0.23]	12.5%	10.6%
Krystal(2010) 3 85	−0.06	0.1162		−0.06	[−0.28; 0.17]	12.5%	10.6%
Common effect model				**0.01**	**[−0.08; 0.10]**	**78.6%**	**−−**
Random effects model				**0.01**	**[−0.08; 0.10]**	**−−**	**69.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.85							
Substance = Nefazodone							
Wiegand(2004) 100 8	−0.63	0.2236		−0.63	[−1.07; −0.19]	3.4%	4.7%
Substance = Paroxetine							
Nowell(1999) 20 42	0.64	0.2582		0.64	[0.14; 1.15]	2.5%	3.8%
Substance = Trazodone							
Roth(2011) 50 7	−0.30	0.2500		−0.30	[−0.79; 0.19]	2.7%	4.0%
Substance = Trimipramine							
Riemann(2002) 200 28	0.25	0.2294		0.25	[−0.20; 0.70]	3.2%	4.5%
Hohagen(1994) 25 28	−0.36	0.2294		−0.36	[−0.80; 0.09]	3.2%	4.5%
Hohagen(1994) 200 33	−0.32	0.2294		−0.32	[−0.77; 0.12]	3.2%	4.5%
Hohagen(1994) 200 42	−0.29	0.2294		−0.29	[−0.74; 0.16]	3.2%	4.5%
Common effect model				**−0.18**	**[−0.40; 0.05]**	**12.8%**	**−−**
Random effects model				**−0.18**	**[−0.46; 0.10]**	**−−**	**18.2%**
Heterogeneity: I^2 = 36%, τ^2 = 0.0293, p = 0.20							
Common effect model				**−0.03**	**[−0.11; 0.05]**	**100.0%**	**−−**
Random effects model				**−0.05**	**[−0.16; 0.06]**	**−−**	**100.0%**

Heterogeneity: I^2 = 45%, τ^2 = 0.0156, p = 0.03
Test for subgroup differences (common effect): χ^2_4 = 17.68, df = 4 (p < 0.01)
Test for subgroup differences (random effects): χ^2_4 = 17.00, df = 4 (p < 0.01)

Insomnia Population REM latency min

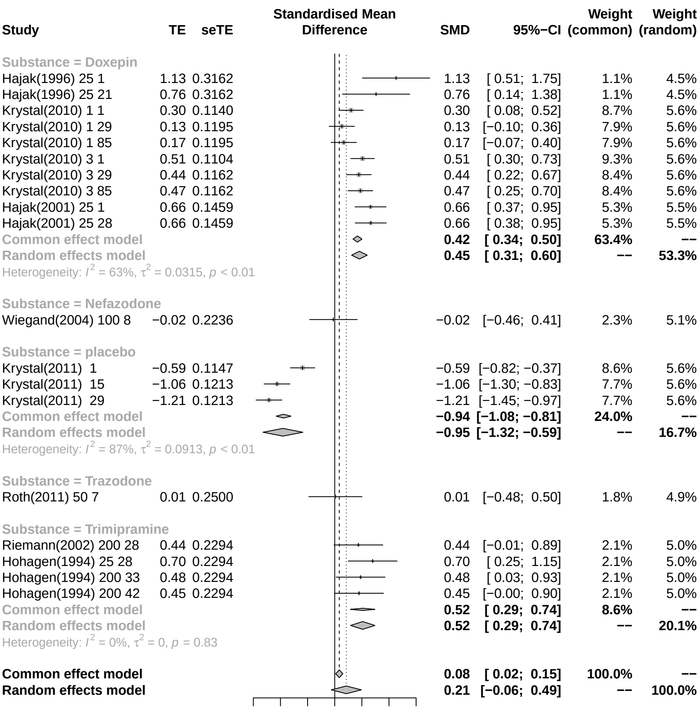


Heterogeneity: I^2 = 76%, τ^2 = 0.1986, p < 0.01

Test for subgroup differences (common effect): χ^2_3 = 26.65, df = 3 (p < 0.01)

Test for subgroup differences (random effects): χ^2_3 = 26.64, df = 3 (p < 0.01)

Insomnia Population SE %

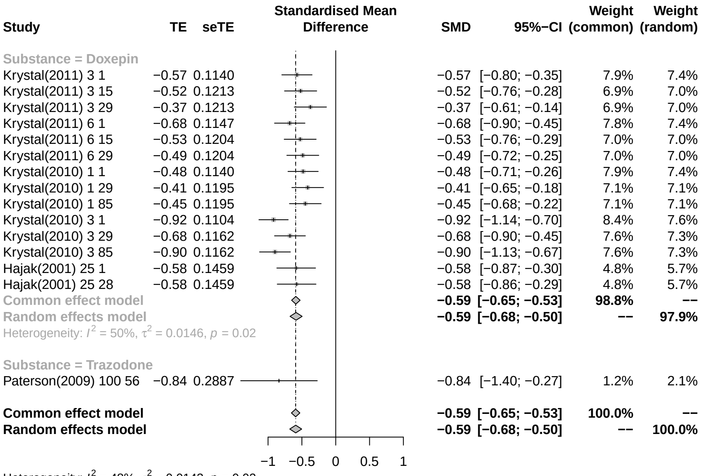


Heterogeneity: I^2 = 95%, τ^2 = 0.3426, p < 0.01

Test for subgroup differences (common effect): χ^2_4 = 300.81, df = 4 (p < 0.01)

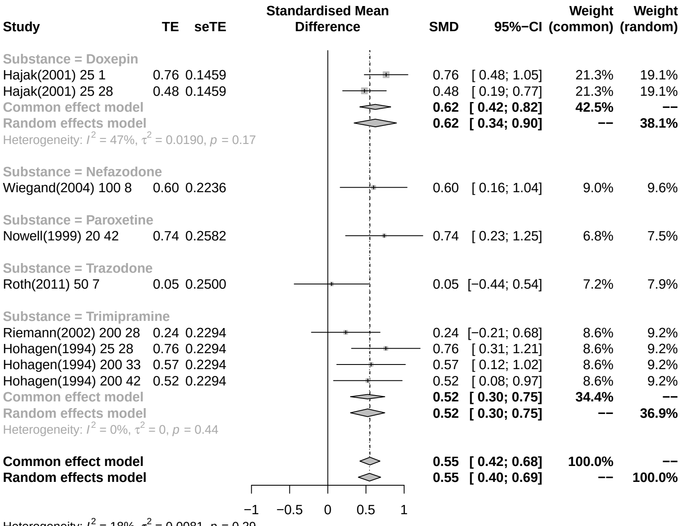
Test for subgroup differences (random effects): χ^2_4 = 56.15, df = 4 (p < 0.01)

Insomnia Population WASO



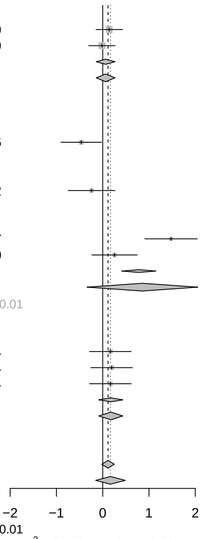
Heterogeneity: I^2 = 48%, τ^2 = 0.0143, p = 0.02
Test for subgroup differences (common effect): χ^2_1 = 0.74, df = 1 (p = 0.39)
Test for subgroup differences (random effects): χ^2_1 = 0.75, df = 1 (p = 0.39)

Insomnia Population stage 2 % SPT



Heterogeneity: I^2 = 18%, τ^2 = 0.0081, p = 0.29
Test for subgroup differences (common effect): χ^2_4 = 5.14, df = 4 (p = 0.27)
Test for subgroup differences (random effects): χ^2_4 = 4.87, df = 4 (p = 0.30)

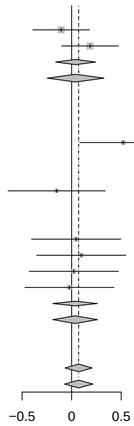
Insomnia Population stage SWS % SPT



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	0.14	0.1459		0.14	[−0.15; 0.43]	22.0%	12.6%
Hajak(2001) 25 28	−0.02	0.1459		−0.02	[−0.30; 0.27]	22.0%	12.6%
Common effect model				**0.06**	**[−0.14; 0.26]**	**43.9%**	**––**
Random effects model				**0.06**	**[−0.14; 0.26]**	**––**	**25.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.45							
Substance = Nefazodone							
Wiegand(2004) 100 8	−0.46	0.2236		−0.46	[−0.90; −0.03]	9.3%	11.1%
Substance = Paroxetine							
Nowell(1999) 20 42	−0.24	0.2582		−0.24	[−0.75; 0.26]	7.0%	10.4%
Substance = Trazodone							
Paterson(2009) 100 56	1.48	0.2887		1.48	[0.91; 2.04]	5.6%	9.8%
Roth(2011) 50 7	0.26	0.2500		0.26	[−0.23; 0.75]	7.5%	10.6%
Common effect model				**0.78**	**[0.41; 1.15]**	**13.1%**	**––**
Random effects model				**0.86**	**[−0.34; 2.05]**	**––**	**20.3%**
Heterogeneity: I^2 = 90%, τ^2 = 0.6719, p < 0.01							
Substance = Trimipramine							
Hohagen(1994) 25 28	0.16	0.2294		0.16	[−0.29; 0.61]	8.9%	11.0%
Hohagen(1994) 200 33	0.19	0.2294		0.19	[−0.26; 0.64]	8.9%	11.0%
Hohagen(1994) 200 42	0.17	0.2294		0.17	[−0.28; 0.62]	8.9%	11.0%
Common effect model				**0.17**	**[−0.09; 0.43]**	**26.6%**	**––**
Random effects model				**0.17**	**[−0.09; 0.43]**	**––**	**33.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00							
Common effect model				**0.12**	**[−0.02; 0.25]**	**100.0%**	**––**
Random effects model				**0.17**	**[−0.15; 0.49]**	**––**	**100.0%**

Heterogeneity: I^2 = 75%, τ^2 = 0.1898, p < 0.01
Test for subgroup differences (common effect): χ^2_3 = 21.42, df = 4 (p < 0.01)
Test for subgroup differences (random effects): χ^2_4 = 9.13, df = 4 (p = 0.06)

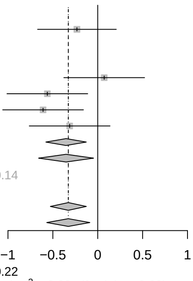
Insomnia Population stage REM % SPT



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	−0.11	0.1459		−0.11	[−0.39; 0.18]	22.8%	21.7%
Hajak(2001) 25 28	0.19	0.1459		0.19	[−0.10; 0.47]	22.8%	21.7%
Common effect model				**0.04**	**[−0.16; 0.24]**	**45.6%**	**––**
Random effects model				**0.04**	**[−0.25; 0.33]**	**––**	**43.5%**
Heterogeneity: I^2 = 50%, τ^2 = 0.0211, p = 0.16							
Substance = Nefazodone							
Wiegand(2004) 100 8	0.52	0.2236		0.52	[0.08; 0.96]	9.7%	10.1%
Substance = Trazodone							
Roth(2011) 50 7	−0.15	0.2500		−0.15	[−0.64; 0.34]	7.8%	8.1%
Substance = Trimipramine							
Riemann(2002) 200 28	0.04	0.2294		0.04	[−0.40; 0.49]	9.2%	9.6%
Hohagen(1994) 25 28	0.10	0.2294		0.10	[−0.35; 0.55]	9.2%	9.6%
Hohagen(1994) 200 33	0.02	0.2294		0.02	[−0.43; 0.47]	9.2%	9.6%
Hohagen(1994) 200 42	−0.02	0.2294		−0.02	[−0.47; 0.43]	9.2%	9.6%
Common effect model				**0.04**	**[−0.19; 0.26]**	**36.9%**	**––**
Random effects model				**0.04**	**[−0.19; 0.26]**	**––**	**38.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99							
Common effect model				**0.07**	**[−0.07; 0.21]**	**100.0%**	**––**
Random effects model				**0.07**	**[−0.07; 0.21]**	**––**	**100.0%**

Heterogeneity: I^2 = 2%, τ^2 = 0.0035, p = 0.41
Test for subgroup differences (common effect): χ^2_3 = 5.02, df = 3 (p = 0.17)
Test for subgroup differences (random effects): χ^2_3 = 4.97, df = 3 (p = 0.17)

Insomnia Population stage wake % SPT



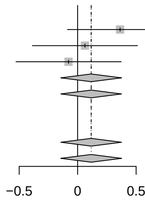
Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Nefazodone							
Wiegand(2004) 100 8	−0.23	0.2236		−0.23	[−0.67; 0.21]	20.8%	20.6%
Substance = Trimipramine							
Riemann(2002) 200 28	0.07	0.2294		0.07	[−0.38; 0.52]	19.8%	19.9%
Hohagen(1994) 25 28	−0.56	0.2294		−0.56	[−1.01; −0.11]	19.8%	19.9%
Hohagen(1994) 200 33	−0.61	0.2294		−0.61	[−1.06; −0.16]	19.8%	19.9%
Hohagen(1994) 200 42	−0.31	0.2294		−0.31	[−0.76; 0.14]	19.8%	19.9%
Common effect model				**−0.35**	**[−0.58; −0.13]**	**79.2%**	**––**
Random effects model				**−0.35**	**[−0.66; −0.05]**	**––**	**79.4%**
Heterogeneity: I^2 = 46%, τ^2 = 0.0445, p = 0.14							
Common effect model				**−0.33**	**[−0.53; −0.13]**	**100.0%**	**––**
Random effects model				**−0.33**	**[−0.57; −0.09]**	**––**	**100.0%**

Heterogeneity: I^2 = 31%, τ^2 = 0.0228, p = 0.22

Test for subgroup differences (common effect): χ^2_1 = 0.23, df = 1 (p = 0.63)

Test for subgroup differences (random effects): χ^2_1 = 0.20, df = 1 (p = 0.66)

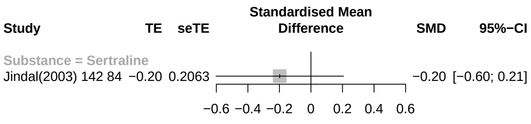
Insomnia Population REM density %



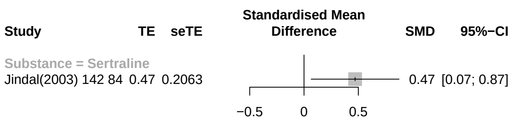
Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Trimipramine							
Hohagen(1994) 25 28	0.36	0.2294		0.36	[−0.09; 0.81]	33.3%	33.3%
Hohagen(1994) 200 33	0.06	0.2294		0.06	[−0.39; 0.51]	33.3%	33.3%
Hohagen(1994) 200 42	−0.08	0.2294		−0.08	[−0.53; 0.37]	33.3%	33.3%
Common effect model				**0.12**	**[−0.14; 0.38]**	**100.0%**	**−−**
Random effects model				**0.12**	**[−0.14; 0.38]**	**−−**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.38							
Common effect model				**0.12**	**[−0.14; 0.38]**	**100.0%**	**−−**
Random effects model				**0.12**	**[−0.14; 0.38]**	**−−**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.38
Test for subgroup differences (common effect): χ^2_0 = 0.00, df = 0 (p = NA)
Test for subgroup differences (random effects): χ^2_0 = 0.00, df = 0 (p = NA)

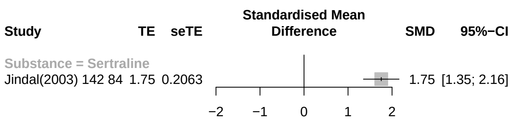
Depressed Population TST vs Placebo



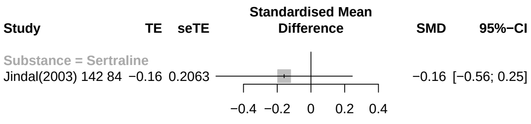
Depressed Population Sleep Latency (min) vs Placebo



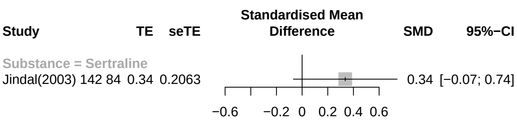
Depressed Population REM latency min vs Placebo



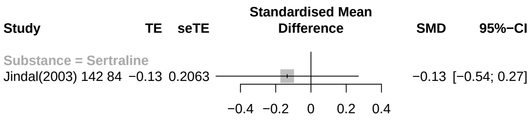
Depressed Population SE % vs Placebo



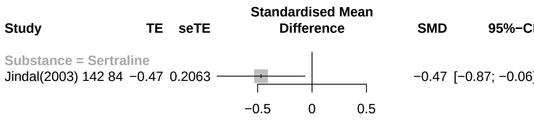
Depressed Population stage 2 % SPT vs Placebo



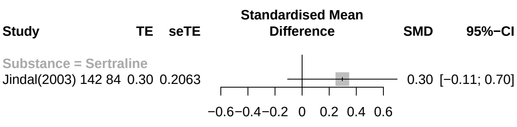
Depressed Population stage SWS % SPT vs Placebo



Depressed Population stage REM % SPT vs Placebo

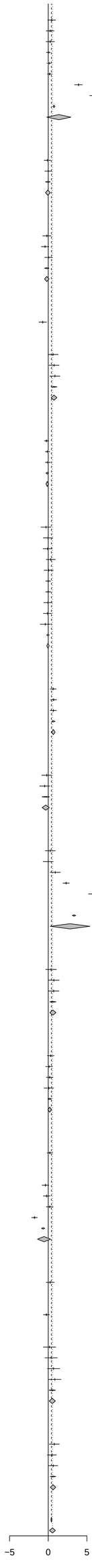


Depressed Population REM density % vs Placebo



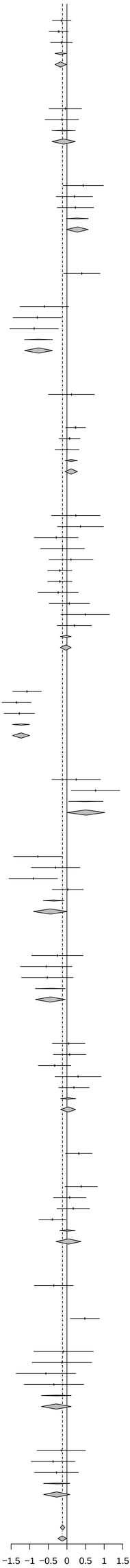
Depressed Population TST

Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine							
Quera(2007) 25 7	0.44	0.2582		0.44	[−0.07; 0.95]	1.3%	1.6%
Quera(2007) 25 14	0.24	0.2582		0.24	[−0.26; 0.75]	1.3%	1.6%
Quera(2007) 25 42	0.26	0.2774		0.26	[−0.29; 0.80]	1.1%	1.6%
Quera−Salva(2011) 25 14	0.02	0.1280		0.02	[−0.23; 0.28]	5.4%	1.7%
Quera−Salva(2011) 50 42	0.09	0.1313		0.09	[−0.17; 0.34]	5.1%	1.7%
Quera−Salva(2011) 50 168	0.17	0.1491		0.17	[−0.12; 0.46]	4.0%	1.7%
Mi(2020) 25 7	3.91	0.2582		3.91	[3.41; 4.42]	1.3%	1.6%
Mi(2020) 25 54	5.87	0.2582		5.87	[5.36; 6.37]	1.3%	1.6%
Common effect model				**0.74**	**[0.61; 0.86]**	**20.8%**	**––**
Random effects model				**1.37**	**[−0.18; 2.92]**	**––**	**13.0%**
Heterogeneity: I^2 = 99%, τ^2 = 4.9253, p < 0.01							
Substance = Bupropion							
Ott(2002) 300 1	−0.10	0.2236		−0.10	[−0.54; 0.34]	1.8%	1.6%
Schramm(2014) 150 3	−0.00	0.2294		−0.00	[−0.45; 0.45]	1.7%	1.6%
Common effect model				**−0.05**	**[−0.37; 0.26]**	**3.4%**	**––**
Random effects model				**−0.05**	**[−0.37; 0.26]**	**––**	**3.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.77							
Substance = Citalopram							
Göder(2011) 18 7	−0.18	0.2774		−0.18	[−0.72; 0.37]	1.1%	1.6%
van Bemmel(1993) 20 1	−0.41	0.2500		−0.41	[−0.90; 0.08]	1.4%	1.6%
van Bemmel(1994) 40 42	0.03	0.2500		0.03	[−0.46; 0.52]	1.4%	1.6%
Common effect model				**−0.19**	**[−0.48; 0.10]**	**4.0%**	**––**
Random effects model				**−0.19**	**[−0.48; 0.10]**	**––**	**4.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.46							
Substance = Clomipramine							
Kupfer(1994) 200 14	−0.72	0.2500		−0.72	[−1.21; −0.23]	1.4%	1.6%
Substance = Doxepin							
Roth(1982) 75 8	0.62	0.3333		0.62	[−0.03; 1.28]	0.8%	1.6%
Roth(1982) 150 15	0.75	0.3333		0.75	[0.10; 1.40]	0.8%	1.6%
Roth(1982) 150 29	0.86	0.3333		0.86	[0.21; 1.51]	0.8%	1.6%
Common effect model				**0.74**	**[0.37; 1.12]**	**2.4%**	**––**
Random effects model				**0.74**	**[0.37; 1.12]**	**––**	**4.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.88							
Substance = Escitalopram							
Quera−Salva(2011) 10 14	−0.22	0.1374		−0.22	[−0.49; 0.05]	4.7%	1.7%
Quera−Salva(2011) 20 42	−0.09	0.1443		−0.09	[−0.37; 0.19]	4.2%	1.7%
Quera−Salva(2011) 20 168	−0.06	0.1644		−0.06	[−0.38; 0.27]	3.2%	1.6%
Common effect model				**−0.13**	**[−0.30; 0.04]**	**12.1%**	**––**
Random effects model				**−0.13**	**[−0.30; 0.04]**	**––**	**5.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.69							
Substance = Fluoxetine							
Hendrickse(1994) 40 84	−0.30	0.3333		−0.30	[−0.95; 0.36]	0.8%	1.6%
Wolf(2001) 20 35	−0.03	0.3162		−0.03	[−0.65; 0.59]	0.9%	1.6%
Winokur(2003) 20 7	−0.08	0.3015		−0.08	[−0.67; 0.51]	1.0%	1.6%
Winokur(2003) 20 14	0.32	0.3015		0.32	[−0.27; 0.92]	1.0%	1.6%
Winokur(2003) 40 56	0.06	0.3015		0.06	[−0.53; 0.65]	1.0%	1.6%
Trivedi(1999) 20 7	−0.01	0.1667		−0.01	[−0.34; 0.32]	3.2%	1.6%
Trivedi(1999) 20 35	−0.01	0.1667		−0.01	[−0.34; 0.32]	3.2%	1.6%
Trivedi(1999) 20 70	−0.04	0.2774		−0.04	[−0.58; 0.50]	1.1%	1.6%
Trivedi(1999) 20 210	−0.10	0.2774		−0.10	[−0.64; 0.45]	1.1%	1.6%
Dorsey(1996) 40 1	−0.39	0.3333		−0.39	[−1.04; 0.27]	0.8%	1.6%
Common effect model				**−0.04**	**[−0.19; 0.12]**	**14.0%**	**––**
Random effects model				**−0.04**	**[−0.19; 0.12]**	**––**	**16.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95							
Substance = Fluvoxamine							
Hao(2019) 100 14	0.63	0.1961		0.63	[0.24; 1.01]	2.3%	1.6%
Hao(2019) 200 28	0.69	0.2000		0.69	[0.30; 1.08]	2.2%	1.6%
Hao(2019) 200 56	0.66	0.2085		0.66	[0.25; 1.07]	2.0%	1.6%
Common effect model				**0.66**	**[0.43; 0.89]**	**6.5%**	**––**
Random effects model				**0.66**	**[0.43; 0.89]**	**––**	**4.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.98							
Substance = Imipramine							
Sonntag(1996) 150 2	−0.19	0.3333		−0.19	[−0.84; 0.46]	0.8%	1.6%
Sonntag(1996) 150 28	−0.46	0.3333		−0.46	[−1.12; 0.19]	0.8%	1.6%
Common effect model				**−0.33**	**[−0.79; 0.14]**	**1.6%**	**––**
Random effects model				**−0.33**	**[−0.79; 0.14]**	**––**	**3.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.56							
Substance = Mirtazapine							
Winokur(2003) 30 7	0.25	0.3333		0.25	[−0.40; 0.91]	0.8%	1.6%
Winokur(2003) 30 14	−0.01	0.3333		−0.01	[−0.67; 0.64]	0.8%	1.6%
Winokur(2003) 45 56	0.91	0.3333		0.91	[0.26; 1.56]	0.8%	1.6%
Zhang(2018) 30 42	2.31	0.2132		2.31	[1.89; 2.73]	1.9%	1.6%
Mi(2020) 30 7	5.71	0.2582		5.71	[5.20; 6.22]	1.3%	1.6%
Mi(2020) 30 54	7.75	0.2582		7.75	[7.24; 8.25]	1.3%	1.6%
Common effect model				**3.33**	**[3.11; 3.55]**	**6.9%**	**––**
Random effects model				**2.82**	**[0.26; 5.39]**	**––**	**9.6%**
Heterogeneity: I^2 = 99%, τ^2 = 10.1516, p < 0.01							
Substance = Moclobemide							
Monti(1990) 150 7	0.36	0.3536		0.36	[−0.33; 1.06]	0.7%	1.6%
Monti(1990) 300 21	0.72	0.3536		0.72	[0.03; 1.41]	0.7%	1.6%
Monti(1990) 300 30	0.70	0.3536		0.70	[0.00; 1.39]	0.7%	1.6%
Common effect model				**0.59**	**[0.19; 0.99]**	**2.1%**	**––**
Random effects model				**0.59**	**[0.19; 0.99]**	**––**	**4.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73							
Substance = Nefazodone							
Argyropoulos(2003d) 500 3	0.32	0.2236		0.32	[−0.12; 0.75]	1.8%	1.6%
Argyropoulos(2003d) 500 10	0.10	0.2236		0.10	[−0.34; 0.53]	1.8%	1.6%
Argyropoulos(2003d) 500 56	0.18	0.2236		0.18	[−0.26; 0.62]	1.8%	1.6%
Armitage(1994) 400 28	0.08	0.3162		0.08	[−0.54; 0.70]	0.9%	1.6%
Common effect model				**0.18**	**[−0.05; 0.41]**	**6.1%**	**––**
Random effects model				**0.18**	**[−0.05; 0.41]**	**––**	**6.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.89							
Substance = Nortriptyline							
Reynolds(1991) 150 39	0.21	0.1826		0.21	[−0.15; 0.57]	2.6%	1.6%
Substance = Paroxetine							
Argyropoulos(2003) 30 3	−0.36	0.2236		−0.36	[−0.80; 0.07]	1.8%	1.6%
Argyropoulos(2003b) 30 10	−0.21	0.2236		−0.21	[−0.64; 0.23]	1.8%	1.6%
Argyropoulos(2003c) 30 56	0.19	0.2236		0.19	[−0.25; 0.63]	1.8%	1.6%
Zhang(2018) 75 42	−1.78	0.1857		−1.78	[−2.14; −1.41]	2.5%	1.6%
Common effect model				**−0.66**	**[−0.87; −0.46]**	**7.8%**	**––**
Random effects model				**−0.55**	**[−1.39; 0.30]**	**––**	**6.5%**
Heterogeneity: I^2 = 95%, τ^2 = 0.7037, p < 0.01							
Substance = Reboxetine							
Göder(2011) 6 7	0.25	0.2673		0.25	[−0.27; 0.78]	1.2%	1.6%
Substance = Sertraline							
Jindal(2003) 142 84	−0.24	0.2000		−0.24	[−0.63; 0.16]	2.2%	1.6%
Substance = Trazodone							
Scharf(1990) 150 1	0.16	0.4082		0.16	[−0.64; 0.96]	0.5%	1.6%
Scharf(1990) 250 7	0.37	0.4082		0.37	[−0.43; 1.17]	0.5%	1.6%
Scharf(1990) 300 14	0.68	0.4082		0.68	[−0.12; 1.48]	0.5%	1.6%
Scharf(1990) 300 35	0.85	0.4082		0.85	[0.05; 1.65]	0.5%	1.6%
Common effect model				**0.52**	**[0.12; 0.92]**	**2.1%**	**––**
Random effects model				**0.52**	**[0.12; 0.92]**	**––**	**6.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64							
Substance = Trimipramine							
Wolf(2001) 150 35	0.78	0.3333		0.78	[0.12; 1.43]	0.8%	1.6%
Sonntag(1996) 200 2	0.47	0.3015		0.47	[−0.13; 1.06]	1.0%	1.6%
Sonntag(1996) 200 28	0.65	0.3015		0.65	[0.06; 1.24]	1.0%	1.6%
Common effect model				**0.62**	**[0.27; 0.97]**	**2.7%**	**––**
Random effects model				**0.62**	**[0.27; 0.97]**	**––**	**4.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.78							
Common effect model				**0.40**	**[0.34; 0.46]**	**100.0%**	**––**
Random effects model				**0.54**	**[0.16; 0.92]**	**––**	**100.0%**



Heterogeneity: I^2 = 97%, τ^2 = 2.2813, p = 0
Test for subgroup differences (common effect): χ^2_{17} = 953.42, df = 17 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{17} = 94.62, df = 17 (p < 0.01)

Depressed Population Sleep Latency (min)

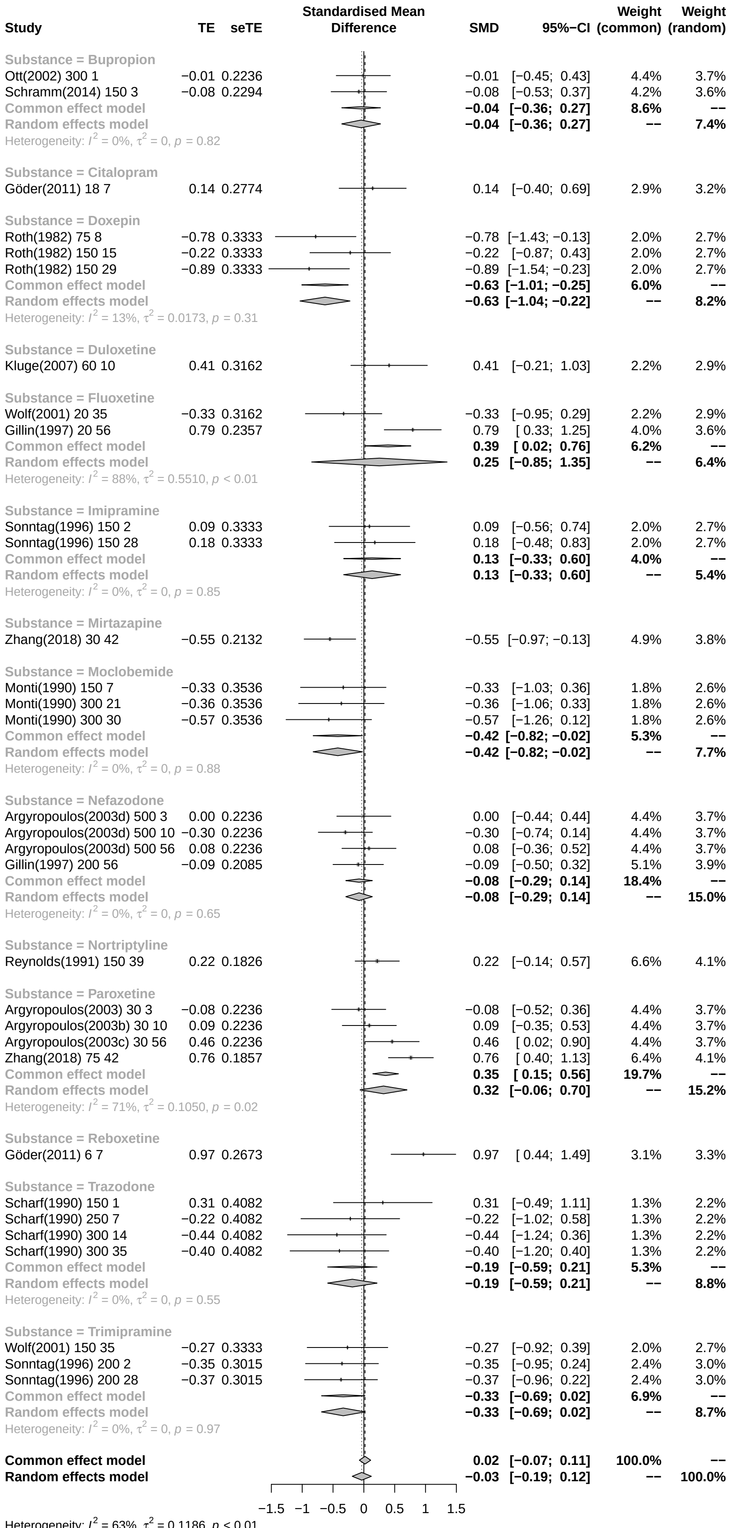


Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine						
Quera−Salva(2011) 25 14	−0.14	0.1280	−0.14	[−0.39; 0.11]	5.6%	2.3%
Quera−Salva(2011) 50 42	−0.22	0.1313	−0.22	[−0.48; 0.04]	5.3%	2.3%
Quera−Salva(2011) 50 168	−0.15	0.1491	−0.15	[−0.44; 0.15]	4.1%	2.2%
Common effect model			**−0.17**	**[−0.32; −0.02]**	**15.1%**	**−−**
Random effects model			**−0.17**	**[−0.32; −0.02]**	**−−**	**6.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.89						
Substance = Bupropion						
Ott(2002) 300 1	−0.04	0.2236	−0.04	[−0.48; 0.39]	1.8%	1.9%
Schramm(2014) 150 3	−0.14	0.2294	−0.14	[−0.59; 0.31]	1.7%	1.9%
Common effect model			**−0.09**	**[−0.40; 0.22]**	**3.6%**	**−−**
Random effects model			**−0.09**	**[−0.40; 0.22]**	**−−**	**3.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.77						
Substance = Citalopram						
Göder(2011) 18 7	0.44	0.2774	0.44	[−0.11; 0.98]	1.2%	1.7%
van Bemmel(1993) 20 1	0.20	0.2500	0.20	[−0.29; 0.69]	1.5%	1.8%
van Bemmel(1994) 40 42	0.23	0.2500	0.23	[−0.26; 0.72]	1.5%	1.8%
Common effect model			**0.28**	**[−0.01; 0.57]**	**4.1%**	**−−**
Random effects model			**0.28**	**[−0.01; 0.57]**	**−−**	**5.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.79						
Substance = Clomipramine						
Kupfer(1994) 200 14	0.40	0.2500	0.40	[−0.09; 0.89]	1.5%	1.8%
Substance = Doxepin						
Roth(1982) 75 8	−0.61	0.3333	−0.61	[−1.26; 0.04]	0.8%	1.4%
Roth(1982) 150 15	−0.80	0.3333	−0.80	[−1.45; −0.14]	0.8%	1.4%
Roth(1982) 150 29	−0.88	0.3333	−0.88	[−1.54; −0.23]	0.8%	1.4%
Common effect model			**−0.76**	**[−1.14; −0.39]**	**2.5%**	**−−**
Random effects model			**−0.76**	**[−1.14; −0.39]**	**−−**	**4.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.84						
Substance = Duloxetine						
Kluge(2007) 60 10	0.12	0.3162	0.12	[−0.50; 0.74]	0.9%	1.5%
Substance = Escitalopram						
Quera−Salva(2011) 10 14	0.23	0.1374	0.23	[−0.04; 0.50]	4.9%	2.3%
Quera−Salva(2011) 20 42	0.07	0.1443	0.07	[−0.21; 0.35]	4.4%	2.3%
Quera−Salva(2011) 20 168	0.00	0.1644	0.00	[−0.32; 0.32]	3.4%	2.2%
Common effect model			**0.11**	**[−0.05; 0.28]**	**12.7%**	**−−**
Random effects model			**0.11**	**[−0.05; 0.28]**	**−−**	**6.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52						
Substance = Fluoxetine						
Hendrickse(1994) 40 84	0.24	0.3333	0.24	[−0.42; 0.89]	0.8%	1.4%
Wolf(2001) 20 35	0.36	0.3162	0.36	[−0.26; 0.98]	0.9%	1.5%
Winokur(2003) 20 7	−0.29	0.3015	−0.29	[−0.88; 0.30]	1.0%	1.6%
Winokur(2003) 20 14	−0.12	0.3015	−0.12	[−0.71; 0.47]	1.0%	1.6%
Winokur(2003) 40 56	0.11	0.3015	0.11	[−0.48; 0.70]	1.0%	1.6%
Trivedi(1999) 20 7	−0.19	0.1667	−0.19	[−0.52; 0.14]	3.3%	2.2%
Trivedi(1999) 20 35	−0.19	0.1667	−0.19	[−0.52; 0.14]	3.3%	2.2%
Trivedi(1999) 20 70	−0.24	0.2774	−0.24	[−0.78; 0.31]	1.2%	1.7%
Trivedi(1999) 20 210	0.06	0.2774	0.06	[−0.48; 0.61]	1.2%	1.7%
Dorsey(1996) 40 1	0.49	0.3333	0.49	[−0.16; 1.15]	0.8%	1.4%
Gillin(1997) 20 56	0.20	0.2357	0.20	[−0.26; 0.66]	1.7%	1.9%
Common effect model			**−0.03**	**[−0.18; 0.12]**	**16.3%**	**−−**
Random effects model			**−0.03**	**[−0.18; 0.12]**	**−−**	**18.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52						
Substance = Fluvoxamine						
Hao(2019) 100 14	−1.07	0.1961	−1.07	[−1.46; −0.69]	2.4%	2.0%
Hao(2019) 200 28	−1.35	0.2000	−1.35	[−1.75; −0.96]	2.3%	2.0%
Hao(2019) 200 56	−1.28	0.2085	−1.28	[−1.69; −0.87]	2.1%	2.0%
Common effect model			**−1.23**	**[−1.46; −1.00]**	**6.8%**	**−−**
Random effects model			**−1.23**	**[−1.46; −1.00]**	**−−**	**6.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58						
Substance = Imipramine						
Sonntag(1996) 150 2	0.25	0.3333	0.25	[−0.41; 0.90]	0.8%	1.4%
Sonntag(1996) 150 28	0.77	0.3333	0.77	[0.11; 1.42]	0.8%	1.4%
Common effect model			**0.51**	**[0.05; 0.97]**	**1.7%**	**−−**
Random effects model			**0.51**	**[−0.00; 1.02]**	**−−**	**2.9%**
Heterogeneity: I^2 = 18%, τ^2 = 0.0240, p = 0.27						
Substance = Mirtazapine						
Winokur(2003) 30 7	−0.78	0.3333	−0.78	[−1.43; −0.13]	0.8%	1.4%
Winokur(2003) 30 14	−0.30	0.3333	−0.30	[−0.96; 0.35]	0.8%	1.4%
Winokur(2003) 45 56	−0.91	0.3333	−0.91	[−1.56; −0.25]	0.8%	1.4%
Zhang(2018) 30 42	0.02	0.2132	0.02	[−0.40; 0.44]	2.0%	2.0%
Common effect model			**−0.36**	**[−0.64; −0.08]**	**4.5%**	**−−**
Random effects model			**−0.45**	**[−0.90; 0.01]**	**−−**	**6.2%**
Heterogeneity: I^2 = 60%, τ^2 = 0.1235, p = 0.06						
Substance = Moclobemide						
Monti(1990) 150 7	−0.26	0.3536	−0.26	[−0.95; 0.43]	0.7%	1.4%
Monti(1990) 300 21	−0.56	0.3536	−0.56	[−1.25; 0.13]	0.7%	1.4%
Monti(1990) 300 30	−0.53	0.3536	−0.53	[−1.22; 0.16]	0.7%	1.4%
Common effect model			**−0.45**	**[−0.85; −0.05]**	**2.2%**	**−−**
Random effects model			**−0.45**	**[−0.85; −0.05]**	**−−**	**4.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.80						
Substance = Nefazodone						
Argyropoulos(2003d) 500 3	0.05	0.2236	0.05	[−0.39; 0.48]	1.8%	1.9%
Argyropoulos(2003d) 500 10	0.07	0.2236	0.07	[−0.37; 0.51]	1.8%	1.9%
Argyropoulos(2003d) 500 56	−0.33	0.2236	−0.33	[−0.77; 0.11]	1.8%	1.9%
Armitage(1994) 400 28	0.30	0.3162	0.30	[−0.32; 0.92]	0.9%	1.5%
Gillin(1997) 200 56	0.19	0.2085	0.19	[−0.22; 0.60]	2.1%	2.0%
Common effect model			**0.03**	**[−0.17; 0.24]**	**8.6%**	**−−**
Random effects model			**0.03**	**[−0.17; 0.24]**	**−−**	**9.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0.0001, p = 0.41						
Substance = Nortriptyline						
Reynolds(1991) 150 39	0.32	0.1826	0.32	[−0.04; 0.68]	2.8%	2.1%
Substance = Paroxetine						
Argyropoulos(2003) 30 3	0.38	0.2236	0.38	[−0.06; 0.82]	1.8%	1.9%
Argyropoulos(2003b) 30 10	0.07	0.2236	0.07	[−0.36; 0.51]	1.8%	1.9%
Argyropoulos(2003c) 30 56	0.17	0.2236	0.17	[−0.27; 0.61]	1.8%	1.9%
Zhang(2018) 75 42	−0.39	0.1857	−0.39	[−0.75; −0.03]	2.7%	2.1%
Common effect model			**0.01**	**[−0.19; 0.22]**	**8.2%**	**−−**
Random effects model			**0.04**	**[−0.29; 0.38]**	**−−**	**7.8%**
Heterogeneity: I^2 = 62%, τ^2 = 0.0716, p = 0.05						
Substance = Reboxetine						
Göder(2011) 6 7	−0.36	0.2673	−0.36	[−0.88; 0.17]	1.3%	1.7%
Substance = Sertraline						
Jindal(2003) 142 84	0.48	0.2000	0.48	[0.09; 0.87]	2.3%	2.0%
Substance = Trazodone						
Scharf(1990) 150 1	−0.09	0.4082	−0.09	[−0.89; 0.71]	0.6%	1.2%
Scharf(1990) 250 7	−0.14	0.4082	−0.14	[−0.94; 0.66]	0.6%	1.2%
Scharf(1990) 300 14	−0.57	0.4082	−0.57	[−1.37; 0.23]	0.6%	1.2%
Scharf(1990) 300 35	−0.35	0.4082	−0.35	[−1.15; 0.45]	0.6%	1.2%
Common effect model			**−0.29**	**[−0.69; 0.11]**	**2.2%**	**−−**
Random effects model			**−0.29**	**[−0.69; 0.11]**	**−−**	**4.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.84						
Substance = Trimipramine						
Wolf(2001) 150 35	−0.15	0.3333	−0.15	[−0.81; 0.50]	0.8%	1.4%
Sonntag(1996) 200 2	−0.37	0.3015	−0.37	[−0.96; 0.22]	1.0%	1.6%
Sonntag(1996) 200 28	−0.28	0.3015	−0.28	[−0.87; 0.31]	1.0%	1.6%
Common effect model			**−0.28**	**[−0.63; 0.08]**	**2.9%**	**−−**
Random effects model			**−0.28**	**[−0.63; 0.08]**	**−−**	**4.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.89						
Common effect model			**−0.12**	**[−0.18; −0.06]**	**100.0%**	**−−**
Random effects model			**−0.13**	**[−0.24; −0.01]**	**−−**	**100.0%**

−1.5 −1 −0.5 0 0.5 1 1.5

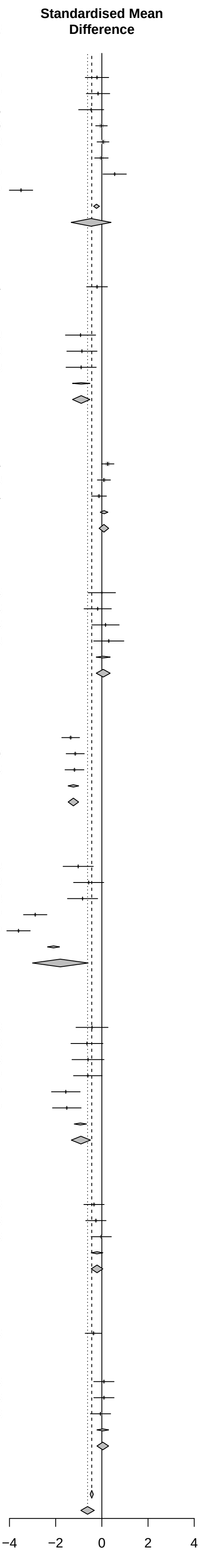
Heterogeneity: I^2 = 70%, τ^2 = 0.1338, p < 0.01
Test for subgroup differences (common effect): χ^2_{18} = 157.31, df = 18 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{18} = 154.66, df = 18 (p < 0.01)

Depressed Population no. wake periods



Heterogeneity: I^2 = 63%, τ^2 = 0.1186, p < 0.01
Test for subgroup differences (common effect): χ^2_{13} = 58.52, df = 13 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{13} = 43.37, df = 13 (p < 0.01)

Depressed Population WASO

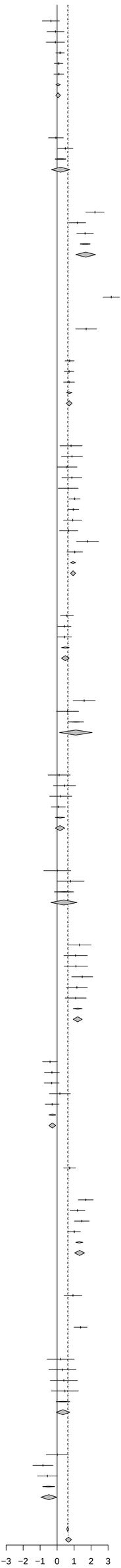


Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine						
Quera(2007) 25 7	−0.21	0.2582	−0.21	[−0.72; 0.30]	1.9%	2.5%
Quera(2007) 25 14	−0.16	0.2582	−0.16	[−0.67; 0.34]	1.9%	2.5%
Quera(2007) 25 42	−0.46	0.2774	−0.46	[−1.01; 0.08]	1.6%	2.5%
Quera−Salva(2011) 25 14	−0.02	0.1280	−0.02	[−0.27; 0.23]	7.6%	2.7%
Quera−Salva(2011) 50 42	0.05	0.1313	0.05	[−0.21; 0.31]	7.3%	2.7%
Quera−Salva(2011) 50 168	−0.02	0.1491	−0.02	[−0.31; 0.27]	5.6%	2.6%
Mi(2020) 25 7	0.55	0.2582	0.55	[0.05; 1.06]	1.9%	2.5%
Mi(2020) 25 54	−3.50	0.2582	−3.50	[−4.01; −2.99]	1.9%	2.5%
Common effect model			**−0.23**	**[−0.36; −0.10]**	**29.7%**	**−−**
Random effects model			**−0.47**	**[−1.33; 0.40]**	**−−**	**20.5%**
Heterogeneity: I^2 = 96%, τ^2 = 1.5041, p < 0.01						
Substance = Bupropion						
Schramm(2014) 150 3	−0.21	0.2294	−0.21	[−0.66; 0.24]	2.4%	2.5%
Substance = Doxepin						
Roth(1982) 75 8	−0.92	0.3333	−0.92	[−1.58; −0.27]	1.1%	2.4%
Roth(1982) 150 15	−0.86	0.3333	−0.86	[−1.52; −0.21]	1.1%	2.4%
Roth(1982) 150 29	−0.90	0.3333	−0.90	[−1.55; −0.24]	1.1%	2.4%
Common effect model			**−0.89**	**[−1.27; −0.52]**	**3.4%**	**−−**
Random effects model			**−0.89**	**[−1.27; −0.52]**	**−−**	**7.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99						
Substance = Escitalopram						
Quera−Salva(2011) 10 14	0.25	0.1374	0.25	[−0.01; 0.52]	6.6%	2.7%
Quera−Salva(2011) 20 42	0.09	0.1443	0.09	[−0.19; 0.37]	6.0%	2.6%
Quera−Salva(2011) 20 168	−0.12	0.1644	−0.12	[−0.45; 0.20]	4.6%	2.6%
Common effect model			**0.10**	**[−0.07; 0.26]**	**17.3%**	**−−**
Random effects model			**0.09**	**[−0.12; 0.30]**	**−−**	**7.9%**
Heterogeneity: I^2 = 36%, τ^2 = 0.0119, p = 0.21						
Substance = Fluoxetine						
Winokur(2003) 20 7	0.00	0.3015	0.00	[−0.59; 0.59]	1.4%	2.4%
Winokur(2003) 20 14	−0.18	0.3015	−0.18	[−0.77; 0.41]	1.4%	2.4%
Winokur(2003) 40 56	0.16	0.3015	0.16	[−0.43; 0.75]	1.4%	2.4%
Dorsey(1996) 40 1	0.30	0.3333	0.30	[−0.35; 0.95]	1.1%	2.4%
Common effect model			**0.06**	**[−0.24; 0.36]**	**5.3%**	**−−**
Random effects model			**0.06**	**[−0.24; 0.36]**	**−−**	**9.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73						
Substance = Fluvoxamine						
Hao(2019) 100 14	−1.35	0.1961	−1.35	[−1.74; −0.97]	3.3%	2.6%
Hao(2019) 200 28	−1.15	0.2000	−1.15	[−1.55; −0.76]	3.1%	2.6%
Hao(2019) 200 56	−1.19	0.2085	−1.19	[−1.59; −0.78]	2.9%	2.6%
Common effect model			**−1.23**	**[−1.46; −1.00]**	**9.3%**	**−−**
Random effects model			**−1.23**	**[−1.46; −1.00]**	**−−**	**7.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.75						
Substance = Mirtazapine						
Winokur(2003) 30 7	−1.02	0.3333	−1.02	[−1.68; −0.37]	1.1%	2.4%
Winokur(2003) 30 14	−0.57	0.3333	−0.57	[−1.22; 0.08]	1.1%	2.4%
Winokur(2003) 45 56	−0.84	0.3333	−0.84	[−1.49; −0.18]	1.1%	2.4%
Mi(2020) 30 7	−2.89	0.2582	−2.89	[−3.39; −2.38]	1.9%	2.5%
Mi(2020) 30 54	−3.61	0.2582	−3.61	[−4.11; −3.10]	1.9%	2.5%
Common effect model			**−2.09**	**[−2.35; −1.83]**	**7.1%**	**−−**
Random effects model			**−1.80**	**[−3.00; −0.59]**	**−−**	**12.2%**
Heterogeneity: I^2 = 96%, τ^2 = 1.7968, p < 0.01						
Substance = Moclobemide						
Monti(1990) 150 7	−0.43	0.3536	−0.43	[−1.12; 0.27]	1.0%	2.4%
Monti(1990) 300 21	−0.65	0.3536	−0.65	[−1.34; 0.05]	1.0%	2.4%
Monti(1990) 300 30	−0.60	0.3536	−0.60	[−1.29; 0.09]	1.0%	2.4%
Monti(1989) 150 4	−0.61	0.3162	−0.61	[−1.23; 0.01]	1.3%	2.4%
Monti(1989) 300 19	−1.56	0.3162	−1.56	[−2.18; −0.94]	1.3%	2.4%
Monti(1989) 300 31	−1.52	0.3162	−1.52	[−2.14; −0.90]	1.3%	2.4%
Common effect model			**−0.93**	**[−1.20; −0.66]**	**6.8%**	**−−**
Random effects model			**−0.91**	**[−1.32; −0.50]**	**−−**	**14.3%**
Heterogeneity: I^2 = 58%, τ^2 = 0.1548, p = 0.03						
Substance = Nefazodone						
Argyropoulos(2003d) 500 3	−0.34	0.2236	−0.34	[−0.78; 0.10]	2.5%	2.6%
Argyropoulos(2003d) 500 10	−0.26	0.2236	−0.26	[−0.70; 0.18]	2.5%	2.6%
Argyropoulos(2003d) 500 56	−0.03	0.2236	−0.03	[−0.47; 0.41]	2.5%	2.6%
Common effect model			**−0.21**	**[−0.46; 0.04]**	**7.5%**	**−−**
Random effects model			**−0.21**	**[−0.46; 0.04]**	**−−**	**7.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.59						
Substance = Nortriptyline						
Reynolds(1991) 150 39	−0.36	0.1826	−0.36	[−0.72; −0.01]	3.8%	2.6%
Substance = Paroxetine						
Argyropoulos(2003) 30 3	0.09	0.2236	0.09	[−0.35; 0.53]	2.5%	2.6%
Argyropoulos(2003b) 30 10	0.09	0.2236	0.09	[−0.35; 0.53]	2.5%	2.6%
Argyropoulos(2003c) 30 56	−0.06	0.2236	−0.06	[−0.50; 0.38]	2.5%	2.6%
Common effect model			**0.04**	**[−0.21; 0.29]**	**7.5%**	**−−**
Random effects model			**0.04**	**[−0.21; 0.29]**	**−−**	**7.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87						
Common effect model			**−0.44**	**[−0.51; −0.37]**	**100.0%**	**−−**
Random effects model			**−0.62**	**[−0.91; −0.33]**	**−−**	**100.0%**

Heterogeneity: I^2 = 93%, τ^2 = 0.8193, p < 0.01
Test for subgroup differences (common effect): χ^2_{10} = 299.42, df = 10 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{10} = 112.93, df = 10 (p < 0.01)

Depressed Population REM latency min

Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine						
Quera(2007) 25 7	−0.36	0.2582	−0.36	[−0.87; 0.14]	1.3%	1.6%
Quera(2007) 25 14	−0.10	0.2582	−0.10	[−0.60; 0.41]	1.3%	1.6%
Quera(2007) 25 42	−0.10	0.2774	−0.10	[−0.65; 0.44]	1.1%	1.6%
Quera−Salva(2011) 25 14	0.18	0.1280	0.18	[−0.08; 0.43]	5.3%	1.8%
Quera−Salva(2011) 50 42	0.09	0.1313	0.09	[−0.17; 0.35]	5.1%	1.8%
Quera−Salva(2011) 50 168	0.10	0.1491	0.10	[−0.19; 0.39]	3.9%	1.8%
Common effect model			**0.06**	**[−0.08; 0.19]**	**18.1%**	**−−**
Random effects model			**0.06**	**[−0.08; 0.19]**	**−−**	**10.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.50						
Substance = Bupropion						
Ott(2002) 300 1	−0.07	0.2236	−0.07	[−0.51; 0.37]	1.7%	1.7%
Schramm(2014) 150 3	0.48	0.2294	0.48	[0.03; 0.93]	1.7%	1.7%
Common effect model			**0.20**	**[−0.11; 0.51]**	**3.4%**	**−−**
Random effects model			**0.20**	**[−0.34; 0.75]**	**−−**	**3.3%**
Heterogeneity: I^2 = 67%, τ^2 = 0.1020, p = 0.08						
Substance = Citalopram						
Göder(2011) 18 7	2.23	0.2774	2.23	[1.69; 2.77]	1.1%	1.6%
van Bemmel(1993) 20 1	1.19	0.2500	1.19	[0.70; 1.68]	1.4%	1.6%
van Bemmel(1994) 40 42	1.65	0.2500	1.65	[1.16; 2.14]	1.4%	1.6%
Common effect model			**1.65**	**[1.36; 1.95]**	**3.9%**	**−−**
Random effects model			**1.68**	**[1.10; 2.26]**	**−−**	**4.8%**
Heterogeneity: I^2 = 74%, τ^2 = 0.1971, p = 0.02						
Substance = Clomipramine						
Kupfer(1994) 200 14	3.19	0.2500	3.19	[2.70; 3.68]	1.4%	1.6%
Substance = Duloxetine						
Kluge(2007) 60 10	1.71	0.3162	1.71	[1.09; 2.33]	0.9%	1.5%
Substance = Escitalopram						
Quera−Salva(2011) 10 14	0.73	0.1374	0.73	[0.46; 1.00]	4.6%	1.8%
Quera−Salva(2011) 20 42	0.70	0.1443	0.70	[0.42; 0.98]	4.2%	1.8%
Quera−Salva(2011) 20 168	0.70	0.1644	0.70	[0.38; 1.03]	3.2%	1.7%
Common effect model			**0.71**	**[0.55; 0.88]**	**12.1%**	**−−**
Random effects model			**0.71**	**[0.55; 0.88]**	**−−**	**5.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99						
Substance = Fluoxetine						
Hendrickse(1994) 40 84	0.82	0.3333	0.82	[0.17; 1.47]	0.8%	1.5%
Wolf(2001) 20 35	0.87	0.3162	0.87	[0.26; 1.49]	0.9%	1.5%
Winokur(2003) 20 7	0.58	0.3015	0.58	[−0.01; 1.17]	1.0%	1.5%
Winokur(2003) 20 14	0.87	0.3015	0.87	[0.28; 1.46]	1.0%	1.5%
Winokur(2003) 40 56	0.65	0.3015	0.65	[0.06; 1.24]	1.0%	1.5%
Trivedi(1999) 20 7	1.03	0.1667	1.03	[0.70; 1.36]	3.1%	1.7%
Trivedi(1999) 20 35	0.95	0.1667	0.95	[0.63; 1.28]	3.1%	1.7%
Trivedi(1999) 20 70	0.92	0.2774	0.92	[0.37; 1.46]	1.1%	1.6%
Trivedi(1999) 20 210	0.68	0.2774	0.68	[0.14; 1.22]	1.1%	1.6%
Dorsey(1996) 40 1	1.79	0.3333	1.79	[1.14; 2.44]	0.8%	1.5%
Gillin(1997) 20 56	1.04	0.2357	1.04	[0.58; 1.50]	1.6%	1.7%
Common effect model			**0.94**	**[0.79; 1.09]**	**15.5%**	**−−**
Random effects model			**0.94**	**[0.79; 1.09]**	**−−**	**17.4%**
Heterogeneity: I^2 = 4%, τ^2 = < 0.0001, p = 0.40						
Substance = Fluvoxamine						
Hao(2019) 100 14	0.58	0.1961	0.58	[0.19; 0.96]	2.3%	1.7%
Hao(2019) 200 28	0.43	0.2000	0.43	[0.03; 0.82]	2.2%	1.7%
Hao(2019) 200 56	0.44	0.2085	0.44	[0.03; 0.85]	2.0%	1.7%
Common effect model			**0.48**	**[0.26; 0.71]**	**6.5%**	**−−**
Random effects model			**0.48**	**[0.26; 0.71]**	**−−**	**5.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.84						
Substance = Imipramine						
Sonntag(1996) 150 2	1.59	0.3333	1.59	[0.94; 2.25]	0.8%	1.5%
Sonntag(1996) 150 28	0.61	0.3333	0.61	[−0.04; 1.26]	0.8%	1.5%
Common effect model			**1.10**	**[0.64; 1.56]**	**1.6%**	**−−**
Random effects model			**1.10**	**[0.14; 2.07]**	**−−**	**3.0%**
Heterogeneity: I^2 = 77%, τ^2 = 0.3730, p = 0.04						
Substance = Mirtazapine						
Winokur(2003) 30 7	0.12	0.3333	0.12	[−0.53; 0.77]	0.8%	1.5%
Winokur(2003) 30 14	0.43	0.3333	0.43	[−0.22; 1.09]	0.8%	1.5%
Winokur(2003) 45 56	0.21	0.3333	0.21	[−0.44; 0.86]	0.8%	1.5%
Zhang(2018) 30 42	0.07	0.2132	0.07	[−0.35; 0.49]	1.9%	1.7%
Common effect model			**0.17**	**[−0.11; 0.45]**	**4.3%**	**−−**
Random effects model			**0.17**	**[−0.11; 0.45]**	**−−**	**6.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.83						
Substance = Mitrazepine						
Winokur(2000) 15 7	0.01	0.4082	0.01	[−0.79; 0.81]	0.5%	1.4%
Winokur(2000) 30 14	0.79	0.4082	0.79	[−0.01; 1.59]	0.5%	1.4%
Common effect model			**0.40**	**[−0.16; 0.97]**	**1.0%**	**−−**
Random effects model			**0.40**	**[−0.37; 1.17]**	**−−**	**2.7%**
Heterogeneity: I^2 = 46%, τ^2 = 0.1406, p = 0.17						
Substance = Moclobemide						
Monti(1990) 150 7	1.31	0.3536	1.31	[0.62; 2.01]	0.7%	1.5%
Monti(1990) 300 21	1.09	0.3536	1.09	[0.40; 1.78]	0.7%	1.5%
Monti(1990) 300 30	1.11	0.3536	1.11	[0.42; 1.80]	0.7%	1.5%
Monti(1989) 150 4	1.48	0.3162	1.48	[0.86; 2.10]	0.9%	1.5%
Monti(1989) 300 19	1.16	0.3162	1.16	[0.54; 1.78]	0.9%	1.5%
Monti(1989) 300 31	1.09	0.3162	1.09	[0.47; 1.71]	0.9%	1.5%
Common effect model			**1.21**	**[0.94; 1.48]**	**4.7%**	**−−**
Random effects model			**1.21**	**[0.94; 1.48]**	**−−**	**8.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95						
Substance = Nefazodone						
Argyropoulos(2003d) 500 3	−0.42	0.2236	−0.42	[−0.85; 0.02]	1.7%	1.7%
Argyropoulos(2003d) 500 10	−0.31	0.2236	−0.31	[−0.75; 0.13]	1.7%	1.7%
Argyropoulos(2003d) 500 56	−0.32	0.2236	−0.32	[−0.76; 0.12]	1.7%	1.7%
Armitage(1994) 400 28	0.16	0.3162	0.16	[−0.46; 0.78]	0.9%	1.5%
Gillin(1997) 200 56	−0.29	0.2085	−0.29	[−0.70; 0.12]	2.0%	1.7%
Common effect model			**−0.28**	**[−0.48; −0.08]**	**8.1%**	**−−**
Random effects model			**−0.28**	**[−0.48; −0.08]**	**−−**	**8.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.66						
Substance = Nortriptyline						
Reynolds(1991) 150 39	0.74	0.1826	0.74	[0.38; 1.09]	2.6%	1.7%
Substance = Paroxetine						
Argyropoulos(2003) 30 3	1.69	0.2236	1.69	[1.25; 2.12]	1.7%	1.7%
Argyropoulos(2003b) 30 10	1.20	0.2236	1.20	[0.76; 1.64]	1.7%	1.7%
Argyropoulos(2003c) 30 56	1.45	0.2236	1.45	[1.02; 1.89]	1.7%	1.7%
Zhang(2018) 75 42	1.01	0.1857	1.01	[0.65; 1.38]	2.5%	1.7%
Common effect model			**1.31**	**[1.10; 1.51]**	**7.8%**	**−−**
Random effects model			**1.32**	**[1.03; 1.62]**	**−−**	**6.7%**
Heterogeneity: I^2 = 50%, τ^2 = 0.0461, p = 0.11						
Substance = Reboxetine						
Göder(2011) 6 7	0.93	0.2673	0.93	[0.41; 1.46]	1.2%	1.6%
Substance = Sertraline						
Jindal(2003) 142 84	1.38	0.2000	1.38	[0.99; 1.77]	2.2%	1.7%
Substance = Trazodone						
Scharf(1990) 150 1	0.21	0.4082	0.21	[−0.59; 1.01]	0.5%	1.4%
Scharf(1990) 250 7	0.31	0.4082	0.31	[−0.49; 1.11]	0.5%	1.4%
Scharf(1990) 300 14	0.40	0.4082	0.40	[−0.40; 1.20]	0.5%	1.4%
Scharf(1990) 300 35	0.46	0.4082	0.46	[−0.34; 1.26]	0.5%	1.4%
Common effect model			**0.34**	**[−0.06; 0.74]**	**2.1%**	**−−**
Random effects model			**0.34**	**[−0.06; 0.74]**	**−−**	**5.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.98						
Substance = Trimipramine						
Wolf(2001) 150 35	0.01	0.3333	0.01	[−0.64; 0.66]	0.8%	1.5%
Sonntag(1996) 200 2	−0.84	0.3015	−0.84	[−1.43; −0.24]	1.0%	1.5%
Sonntag(1996) 200 28	−0.57	0.3015	−0.57	[−1.16; 0.02]	1.0%	1.5%
Common effect model			**−0.50**	**[−0.85; −0.14]**	**2.7%**	**−−**
Random effects model			**−0.48**	**[−0.96; −0.01]**	**−−**	**4.6%**
Heterogeneity: I^2 = 45%, τ^2 = 0.0785, p = 0.16						
Common effect model			**0.62**	**[0.57; 0.68]**	**100.0%**	**−−**
Random effects model			**0.67**	**[0.49; 0.85]**	**−−**	**100.0%**



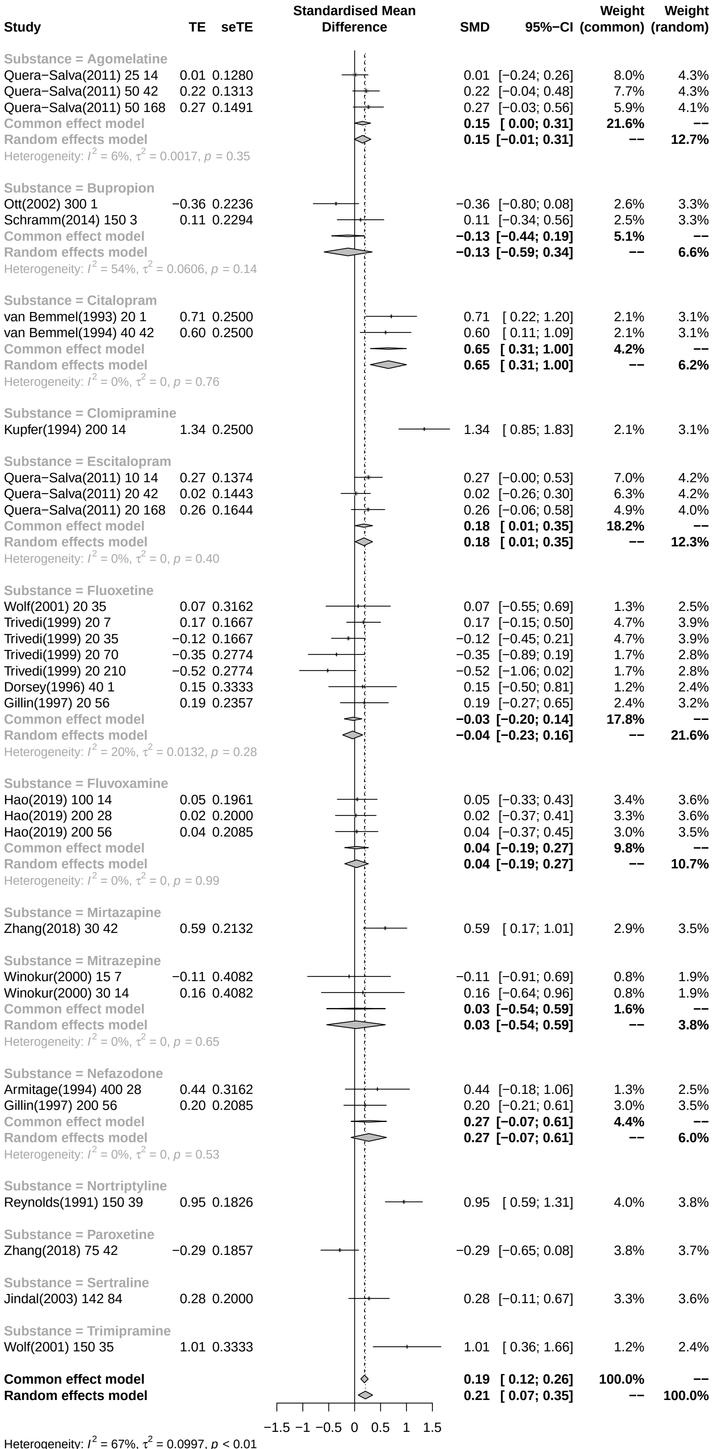
Heterogeneity: I^2 = 88%, τ^2 = 0.4548, p < 0.01
Test for subgroup differences (common effect): χ^2_{18} = 465.69, df = 18 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{18} = 382.71, df = 18 (p < 0.01)

Depressed Population SE %

Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine						
Quera(2007) 25 7	0.46	0.2582	0.46	[−0.04; 0.97]	1.3%	1.7%
Quera(2007) 25 14	0.28	0.2582	0.28	[−0.22; 0.79]	1.3%	1.7%
Quera(2007) 25 42	0.51	0.2774	0.51	[−0.04; 1.05]	1.1%	1.7%
Quera−Salva(2011) 25 14	0.05	0.1280	0.05	[−0.20; 0.30]	5.4%	1.7%
Quera−Salva(2011) 50 42	0.09	0.1313	0.09	[−0.16; 0.35]	5.1%	1.7%
Quera−Salva(2011) 50 168	0.15	0.1491	0.15	[−0.14; 0.44]	4.0%	1.7%
Mi(2020) 25 7	2.24	0.2582	2.24	[1.73; 2.74]	1.3%	1.7%
Mi(2020) 25 54	3.26	0.2582	3.26	[2.75; 3.77]	1.3%	1.7%
Common effect model			**0.49**	**[0.36; 0.61]**	**20.8%**	**−−**
Random effects model			**0.87**	**[0.05; 1.69]**	**−−**	**13.7%**
Heterogeneity: I^2 = 96%, τ^2 = 1.3664, p < 0.01						
Substance = Bupropion						
Ott(2002) 300 1	−0.09	0.2236	−0.09	[−0.53; 0.34]	1.8%	1.7%
Schramm(2014) 150 3	0.20	0.2294	0.20	[−0.25; 0.65]	1.7%	1.7%
Common effect model			**0.05**	**[−0.27; 0.36]**	**3.4%**	**−−**
Random effects model			**0.05**	**[−0.27; 0.36]**	**−−**	**3.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.37						
Substance = Citalopram						
Göder(2011) 18 7	−0.57	0.2774	−0.57	[−1.11; −0.02]	1.1%	1.7%
van Bemmel(1993) 20 1	−0.40	0.2500	−0.40	[−0.89; 0.09]	1.4%	1.7%
van Bemmel(1994) 40 42	−0.19	0.2500	−0.19	[−0.68; 0.30]	1.4%	1.7%
Common effect model			**−0.37**	**[−0.67; −0.08]**	**4.0%**	**−−**
Random effects model			**−0.37**	**[−0.67; −0.08]**	**−−**	**5.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.59						
Substance = Clomipramine						
Kupfer(1994) 200 14	−1.09	0.2500	−1.09	[−1.58; −0.60]	1.4%	1.7%
Substance = Duloxetine						
Kluge(2007) 60 10	−0.39	0.3162	−0.39	[−1.01; 0.23]	0.9%	1.7%
Substance = Escitalopram						
Quera−Salva(2011) 10 14	−0.25	0.1374	−0.25	[−0.52; 0.01]	4.7%	1.7%
Quera−Salva(2011) 20 42	−0.09	0.1443	−0.09	[−0.37; 0.19]	4.2%	1.7%
Quera−Salva(2011) 20 168	−0.05	0.1644	−0.05	[−0.37; 0.27]	3.2%	1.7%
Common effect model			**−0.14**	**[−0.31; 0.02]**	**12.1%**	**−−**
Random effects model			**−0.14**	**[−0.31; 0.02]**	**−−**	**5.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57						
Substance = Fluoxetine						
Hendrickse(1994) 40 84	−0.31	0.3333	−0.31	[−0.96; 0.35]	0.8%	1.7%
Wolf(2001) 20 35	0.02	0.3162	0.02	[−0.60; 0.64]	0.9%	1.7%
Winokur(2003) 20 7	0.04	0.3015	0.04	[−0.55; 0.63]	1.0%	1.7%
Winokur(2003) 20 14	0.23	0.3015	0.23	[−0.36; 0.82]	1.0%	1.7%
Winokur(2003) 40 56	−0.07	0.3015	−0.07	[−0.66; 0.52]	1.0%	1.7%
Trivedi(1999) 20 7	0.13	0.1667	0.13	[−0.20; 0.46]	3.2%	1.7%
Trivedi(1999) 20 35	−0.01	0.1667	−0.01	[−0.34; 0.31]	3.2%	1.7%
Trivedi(1999) 20 70	0.03	0.2774	0.03	[−0.51; 0.57]	1.1%	1.7%
Trivedi(1999) 20 210	0.07	0.2774	0.07	[−0.47; 0.61]	1.1%	1.7%
Dorsey(1996) 40 1	−0.69	0.3333	−0.69	[−1.34; −0.04]	0.8%	1.7%
Gillin(1997) 20 56	−0.41	0.2357	−0.41	[−0.87; 0.05]	1.6%	1.7%
Common effect model			**−0.05**	**[−0.20; 0.10]**	**15.5%**	**−−**
Random effects model			**−0.05**	**[−0.20; 0.10]**	**−−**	**18.6%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52						
Substance = Fluvoxamine						
Hao(2019) 100 14	0.48	0.1961	0.48	[0.09; 0.86]	2.3%	1.7%
Hao(2019) 200 28	0.51	0.2000	0.51	[0.11; 0.90]	2.2%	1.7%
Hao(2019) 200 56	0.46	0.2085	0.46	[0.06; 0.87]	2.0%	1.7%
Common effect model			**0.48**	**[0.25; 0.71]**	**6.5%**	**−−**
Random effects model			**0.48**	**[0.25; 0.71]**	**−−**	**5.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99						
Substance = Imipramine						
Sonntag(1996) 150 2	−0.15	0.3333	−0.15	[−0.80; 0.50]	0.8%	1.7%
Sonntag(1996) 150 28	−0.48	0.3333	−0.48	[−1.14; 0.17]	0.8%	1.7%
Common effect model			**−0.32**	**[−0.78; 0.15]**	**1.6%**	**−−**
Random effects model			**−0.32**	**[−0.78; 0.15]**	**−−**	**3.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.48						
Substance = Mirtazapine						
Winokur(2003) 30 7	0.95	0.3333	0.95	[0.30; 1.61]	0.8%	1.7%
Winokur(2003) 30 14	0.58	0.3333	0.58	[−0.08; 1.23]	0.8%	1.7%
Winokur(2003) 45 56	0.94	0.3333	0.94	[0.28; 1.59]	0.8%	1.7%
Zhang(2018) 30 42	−0.52	0.2132	−0.52	[−0.94; −0.10]	1.9%	1.7%
Mi(2020) 30 7	9.24	0.2582	9.24	[8.73; 9.74]	1.3%	1.7%
Mi(2020) 30 54	2.49	0.2582	2.49	[1.98; 3.00]	1.3%	1.7%
Common effect model			**2.36**	**[2.14; 2.58]**	**6.9%**	**−−**
Random effects model			**2.28**	**[−0.56; 5.12]**	**−−**	**10.1%**
Heterogeneity: I^2 = 99%, τ^2 = 12.4913, p < 0.01						
Substance = Nefazodone						
Argyropoulos(2003d) 500 3	0.30	0.2236	0.30	[−0.14; 0.74]	1.8%	1.7%
Argyropoulos(2003d) 500 10	0.20	0.2236	0.20	[−0.24; 0.64]	1.8%	1.7%
Argyropoulos(2003d) 500 56	0.21	0.2236	0.21	[−0.23; 0.65]	1.8%	1.7%
Armitage(1994) 400 28	0.26	0.3162	0.26	[−0.36; 0.88]	0.9%	1.7%
Gillin(1997) 200 56	0.03	0.2085	0.03	[−0.38; 0.44]	2.0%	1.7%
Common effect model			**0.19**	**[−0.02; 0.39]**	**8.2%**	**−−**
Random effects model			**0.19**	**[−0.02; 0.39]**	**−−**	**8.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.92						
Substance = Nortriptyline						
Reynolds(1991) 150 39	0.22	0.1826	0.22	[−0.14; 0.58]	2.6%	1.7%
Substance = Paroxetine						
Argyropoulos(2003) 30 3	−0.41	0.2236	−0.41	[−0.85; 0.03]	1.8%	1.7%
Argyropoulos(2003b) 30 10	−0.07	0.2236	−0.07	[−0.51; 0.37]	1.8%	1.7%
Argyropoulos(2003c) 30 56	0.00	0.2236	0.00	[−0.44; 0.44]	1.8%	1.7%
Zhang(2018) 75 42	−0.95	0.1857	−0.95	[−1.32; −0.59]	2.5%	1.7%
Common effect model			**−0.42**	**[−0.63; −0.21]**	**7.8%**	**−−**
Random effects model			**−0.37**	**[−0.81; 0.07]**	**−−**	**6.9%**
Heterogeneity: I^2 = 79%, τ^2 = 0.1548, p < 0.01						
Substance = Reboxetine						
Göder(2011) 6 7	0.09	0.2673	0.09	[−0.43; 0.61]	1.2%	1.7%
Substance = Sertraline						
Jindal(2003) 142 84	−0.30	0.2000	−0.30	[−0.69; 0.10]	2.2%	1.7%
Substance = Trazodone						
Scharf(1990) 150 1	0.02	0.4082	0.02	[−0.78; 0.82]	0.5%	1.6%
Scharf(1990) 250 7	0.38	0.4082	0.38	[−0.42; 1.18]	0.5%	1.6%
Scharf(1990) 300 14	0.68	0.4082	0.68	[−0.12; 1.48]	0.5%	1.6%
Scharf(1990) 300 35	0.85	0.4082	0.85	[0.05; 1.65]	0.5%	1.6%
Common effect model			**0.48**	**[0.08; 0.88]**	**2.1%**	**−−**
Random effects model			**0.48**	**[0.08; 0.88]**	**−−**	**6.5%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49						
Substance = Trimipramine						
Wolf(2001) 150 35	0.94	0.3333	0.94	[0.29; 1.59]	0.8%	1.7%
Sonntag(1996) 200 2	0.73	0.3015	0.73	[0.14; 1.32]	1.0%	1.7%
Sonntag(1996) 200 28	0.71	0.3015	0.71	[0.12; 1.30]	1.0%	1.7%
Common effect model			**0.78**	**[0.43; 1.14]**	**2.7%**	**−−**
Random effects model			**0.78**	**[0.43; 1.14]**	**−−**	**5.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86						
Common effect model			**0.25**	**[0.19; 0.31]**	**100.0%**	**−−**
Random effects model			**0.36**	**[0.01; 0.72]**	**−−**	**100.0%**

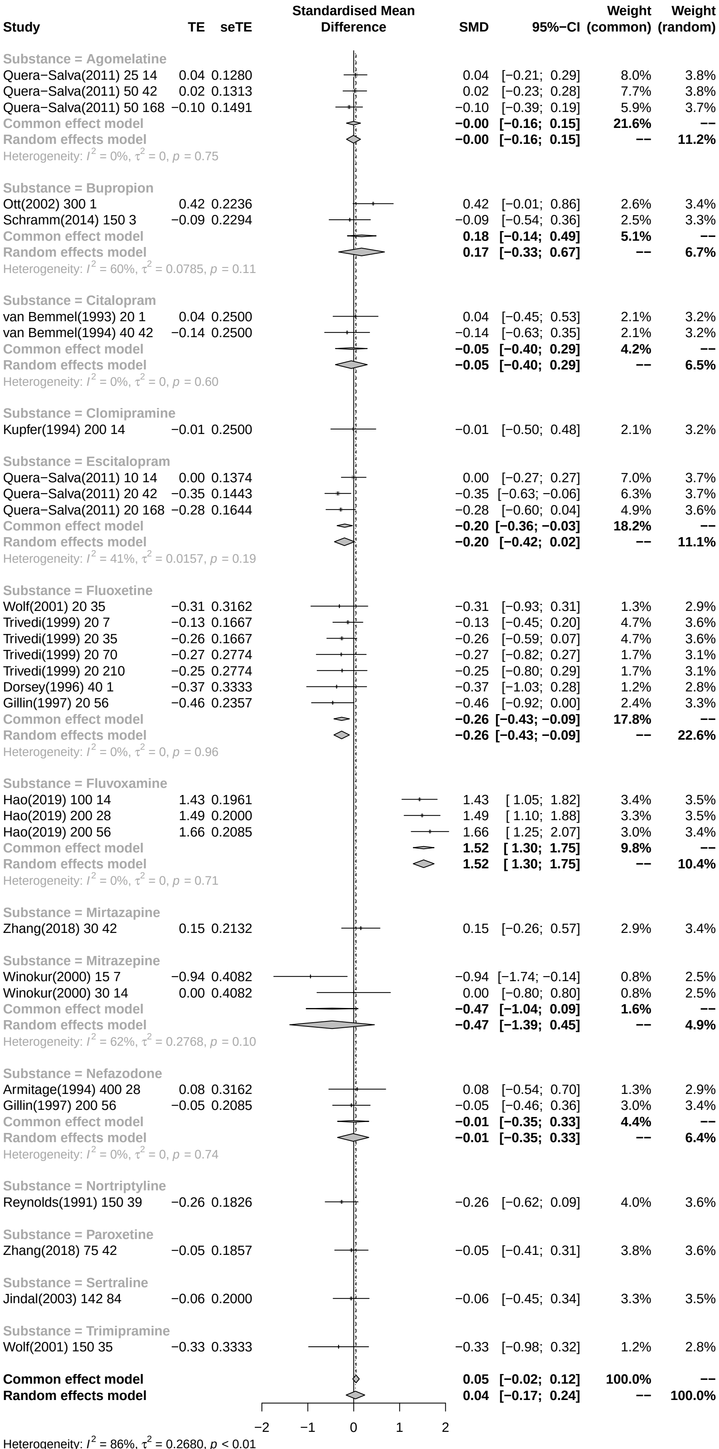
Heterogeneity: I^2 = 97%, τ^2 = 1.8459, p < 0.01
Test for subgroup differences (common effect): χ^2_{16} = 522.84, df = 16 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{16} = 89.96, df = 16 (p < 0.01)

Depressed Population stage 2 % SPT



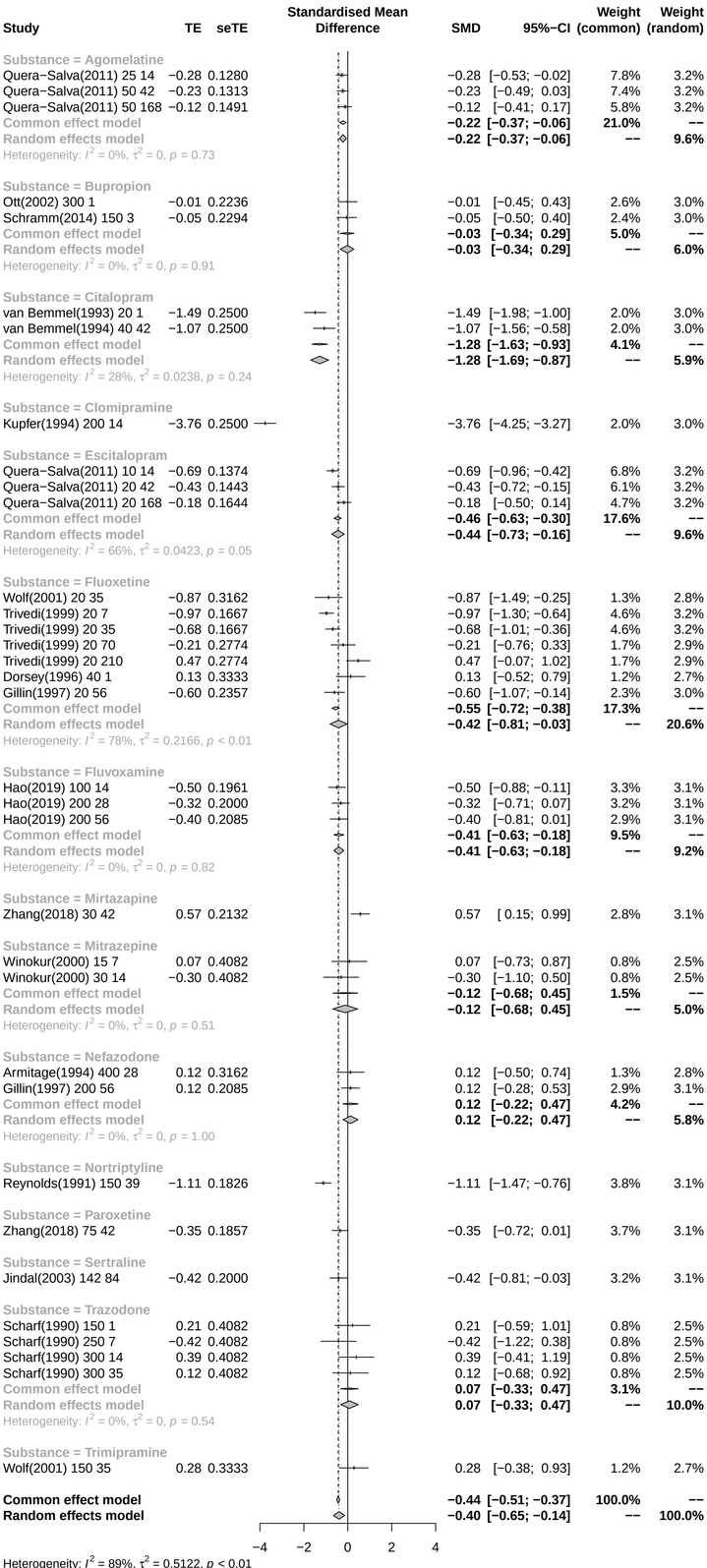
Heterogeneity: I^2 = 67%, τ^2 = 0.0997, p < 0.01
Test for subgroup differences (common effect): χ^2_{13} = 74.68, df = 13 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{13} = 70.96, df = 13 (p < 0.01)

Depressed Population stage SWS % SPT



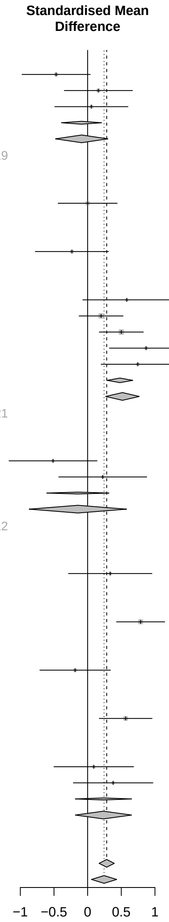
Heterogeneity: I^2 = 86%, τ^2 = 0.2680, p < 0.01
Test for subgroup differences (common effect): χ^2_{13} = 192.10, df = 13 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{13} = 186.05, df = 13 (p < 0.01)

Depressed Population stage REM % SPT



Heterogeneity: I^2 = 89%, τ^2 = 0.5122, p < 0.01
Test for subgroup differences (common effect): χ^2_{14} = 274.91, df = 14 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{14} = 265.43, df = 14 (p < 0.01)

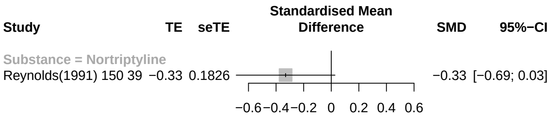
Depressed Population REM density %



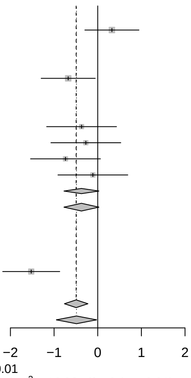
Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine						
Quera(2007) 25 7	−0.47	0.2582	−0.47	[−0.97; 0.04]	5.0%	5.6%
Quera(2007) 25 14	0.16	0.2582	0.16	[−0.35; 0.67]	5.0%	5.6%
Quera(2007) 25 42	0.06	0.2774	0.06	[−0.49; 0.60]	4.3%	5.3%
Common effect model			**−0.09**	**[−0.39; 0.21]**	**14.2%**	**−−**
Random effects model			**−0.09**	**[−0.48; 0.30]**	**−−**	**16.5%**
Heterogeneity: I^2 = 40%, τ^2 = 0.0483, p = 0.19						
Substance = Bupropion						
Ott(2002) 300 1	0.00	0.2236	0.00	[−0.44; 0.44]	6.6%	6.2%
Substance = Citalopram						
Göder(2011) 18 7	−0.23	0.2774	−0.23	[−0.78; 0.31]	4.3%	5.3%
Substance = Fluoxetine						
Hendrickse(1994) 40 84	0.58	0.3333	0.58	[−0.07; 1.23]	3.0%	4.4%
Trivedi(1999) 20 7	0.20	0.1667	0.20	[−0.13; 0.53]	11.9%	7.3%
Trivedi(1999) 20 35	0.50	0.1667	0.50	[0.17; 0.83]	11.9%	7.3%
Trivedi(1999) 20 70	0.87	0.2774	0.87	[0.32; 1.41]	4.3%	5.3%
Trivedi(1999) 20 210	0.74	0.2774	0.74	[0.20; 1.29]	4.3%	5.3%
Common effect model			**0.48**	**[0.29; 0.67]**	**35.4%**	**−−**
Random effects model			**0.52**	**[0.27; 0.77]**	**−−**	**29.6%**
Heterogeneity: I^2 = 31%, τ^2 = 0.0287, p = 0.21						
Substance = Imipramine						
Sonntag(1996) 150 2	−0.51	0.3333	−0.51	[−1.17; 0.14]	3.0%	4.4%
Sonntag(1996) 150 28	0.22	0.3333	0.22	[−0.43; 0.88]	3.0%	4.4%
Common effect model			**−0.14**	**[−0.61; 0.32]**	**6.0%**	**−−**
Random effects model			**−0.14**	**[−0.87; 0.58]**	**−−**	**8.8%**
Heterogeneity: I^2 = 59%, τ^2 = 0.1614, p = 0.12						
Substance = Nefazodone						
Armitage(1994) 400 28	0.34	0.3162	0.34	[−0.28; 0.96]	3.3%	4.7%
Substance = Nortriptyline						
Reynolds(1991) 150 39	0.79	0.1826	0.79	[0.43; 1.14]	9.9%	7.0%
Substance = Reboxetine						
Göder(2011) 6 7	−0.19	0.2673	−0.19	[−0.71; 0.34]	4.6%	5.4%
Substance = Sertraline						
Jindal(2003) 142 84	0.56	0.2000	0.56	[0.17; 0.96]	8.3%	6.7%
Substance = Trimipramine						
Sonntag(1996) 200 2	0.09	0.3015	0.09	[−0.50; 0.68]	3.6%	4.9%
Sonntag(1996) 200 28	0.38	0.3015	0.38	[−0.21; 0.97]	3.6%	4.9%
Common effect model			**0.23**	**[−0.18; 0.65]**	**7.3%**	**−−**
Random effects model			**0.23**	**[−0.18; 0.65]**	**−−**	**9.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.50						
Common effect model			**0.28**	**[0.17; 0.40]**	**100.0%**	**−−**
Random effects model			**0.24**	**[0.06; 0.43]**	**−−**	**100.0%**

Heterogeneity: I^2 = 61%, τ^2 = 0.0970, p < 0.01
Test for subgroup differences (common effect): χ^2_9 = 31.31, df = 9 (p < 0.01)
Test for subgroup differences (random effects): χ^2_9 = 25.97, df = 9 (p < 0.01)

Depressed Population apnea/hypopnea index



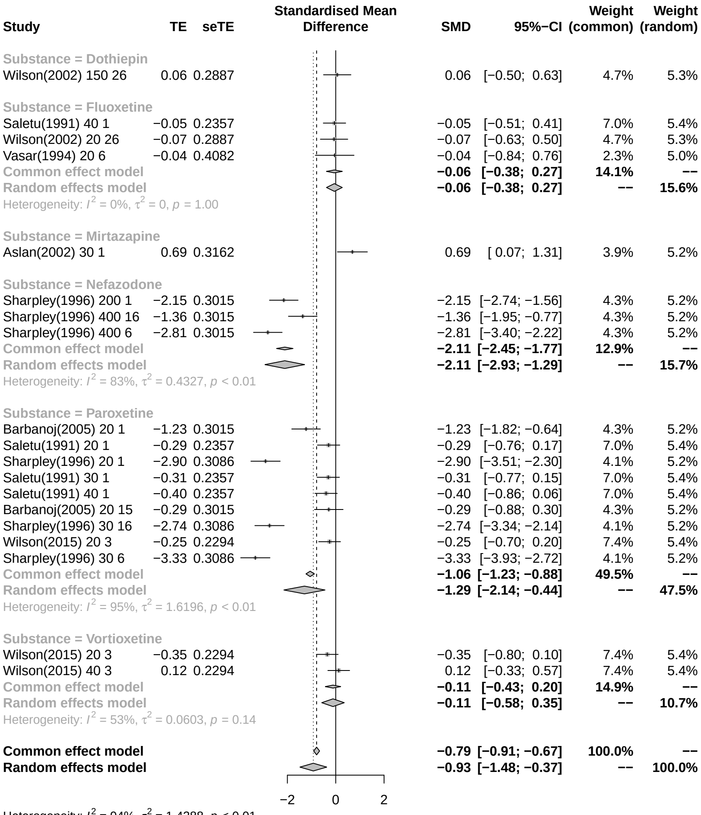
Depressed Population stage wake % SPT



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Fluoxetine						
Wolf(2001) 20 35	0.32	0.3162	0.32	[−0.29; 0.94]	18.9%	15.8%
Substance = Nefazodone						
Armitage(1994) 400 28	−0.68	0.3162	−0.68	[−1.30; −0.06]	18.9%	15.8%
Substance = Trazodone						
Scharf(1990) 150 1	−0.37	0.4082	−0.37	[−1.17; 0.43]	11.3%	13.3%
Scharf(1990) 250 7	−0.27	0.4082	−0.27	[−1.07; 0.53]	11.3%	13.3%
Scharf(1990) 300 14	−0.74	0.4082	−0.74	[−1.54; 0.06]	11.3%	13.3%
Scharf(1990) 300 35	−0.11	0.4082	−0.11	[−0.91; 0.69]	11.3%	13.3%
Common effect model			**−0.37**	**[−0.77; 0.03]**	**45.3%**	**––**
Random effects model			**−0.37**	**[−0.77; 0.03]**	**––**	**53.1%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73						
Substance = Trimipramine						
Wolf(2001) 150 35	−1.52	0.3333	−1.52	[−2.18; −0.87]	17.0%	15.3%
Common effect model			**−0.49**	**[−0.76; −0.22]**	**100.0%**	**––**
Random effects model			**−0.49**	**[−0.95; −0.03]**	**––**	**100.0%**

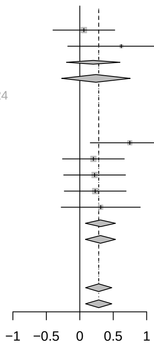
Heterogeneity: I^2 = 67%, τ^2 = 0.2490, p < 0.01
Test for subgroup differences (common effect): χ^2_3 = 16.93, df = 3 (p < 0.01)
Test for subgroup differences (random effects): χ^2_3 = 16.93, df = 3 (p < 0.01)

Healthy Population continuity vs Placebo



Heterogeneity: I^2 = 94%, τ^2 = 1.4288, p < 0.01
Test for subgroup differences (common effect): χ^2_5 = 133.72, df = 5 (p < 0.01)
Test for subgroup differences (random effects): χ^2_5 = 36.76, df = 5 (p < 0.01)

Healthy Population depth vs Placebo



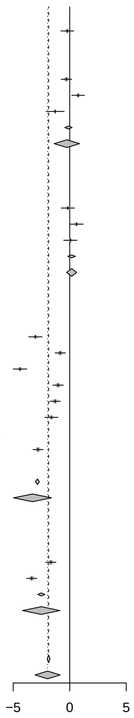
Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Fluoxetine							
Saletu(1991) 40 1	0.06	0.2357		0.06	[−0.40; 0.52]	18.0%	18.0%
Vasar(1994) 20 6	0.62	0.4082		0.62	[−0.18; 1.42]	6.0%	6.0%
Common effect model				**0.20**	**[−0.20; 0.60]**	**24.0%**	**––**
Random effects model				**0.24**	**[−0.27; 0.75]**	**––**	**24.0%**
Heterogeneity: I^2 = 29%, τ^2 = 0.0453, p = 0.24							
Substance = Paroxetine							
Barbanoj(2005) 20 1	0.75	0.3015		0.75	[0.16; 1.34]	11.0%	11.0%
Saletu(1991) 20 1	0.20	0.2357		0.20	[−0.26; 0.67]	18.0%	18.0%
Saletu(1991) 30 1	0.22	0.2357		0.22	[−0.24; 0.68]	18.0%	18.0%
Saletu(1991) 40 1	0.23	0.2357		0.23	[−0.23; 0.69]	18.0%	18.0%
Barbanoj(2005) 20 15	0.31	0.3015		0.31	[−0.28; 0.90]	11.0%	11.0%
Common effect model				**0.31**	**[0.08; 0.53]**	**76.0%**	**––**
Random effects model				**0.31**	**[0.08; 0.53]**	**––**	**76.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.63							
Common effect model				**0.28**	**[0.09; 0.48]**	**100.0%**	**––**
Random effects model				**0.28**	**[0.09; 0.48]**	**––**	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.65

Test for subgroup differences (common effect): χ^2_1 = 0.21, df = 1 (p = 0.65)

Test for subgroup differences (random effects): χ^2_1 = 0.06, df = 1 (p = 0.81)

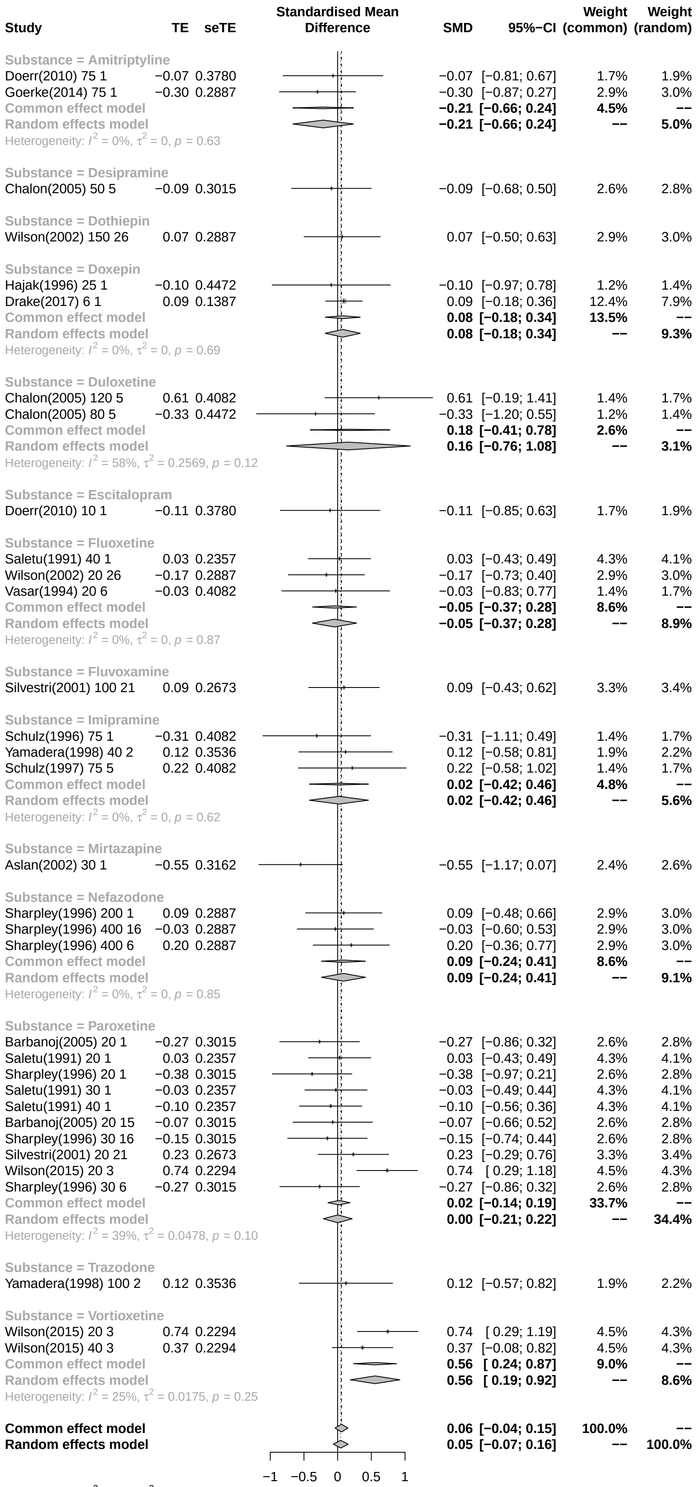
Healthy Population REMpressure vs Placebo



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Dothiepin						
Wilson(2002) 150 26	−0.21	0.2887	−0.21	[−0.78; 0.35]	4.9%	5.6%
Substance = Fluoxetine						
Saletu(1991) 40 1	−0.30	0.2357	−0.30	[−0.76; 0.17]	7.3%	5.6%
Wilson(2002) 20 26	0.75	0.2887	0.75	[0.18; 1.31]	4.9%	5.6%
Vasar(1994) 20 6	−1.29	0.4082	−1.29	[−2.09; −0.49]	2.4%	5.5%
Common effect model			**−0.11**	**[−0.44; 0.21]**	**14.7%**	**––**
Random effects model			**−0.25**	**[−1.38; 0.87]**	**––**	**16.6%**
Heterogeneity: I^2 = 89%, τ^2 = 0.8899, p < 0.01						
Substance = Nefazodone						
Sharpley(1996) 200 1	−0.16	0.3015	−0.16	[−0.75; 0.43]	4.5%	5.5%
Sharpley(1996) 400 16	0.60	0.3015	0.60	[0.01; 1.19]	4.5%	5.5%
Sharpley(1996) 400 6	0.06	0.3015	0.06	[−0.53; 0.65]	4.5%	5.5%
Common effect model			**0.17**	**[−0.17; 0.51]**	**13.4%**	**––**
Random effects model			**0.17**	**[−0.28; 0.61]**	**––**	**16.6%**
Heterogeneity: I^2 = 41%, τ^2 = 0.0626, p = 0.18						
Substance = Paroxetine						
Barbanoj(2005) 20 1	−3.04	0.3015	−3.04	[−3.63; −2.45]	4.5%	5.5%
Saletu(1991) 20 1	−0.84	0.2357	−0.84	[−1.30; −0.37]	7.3%	5.6%
Sharpley(1996) 20 1	−4.40	0.3086	−4.40	[−5.00; −3.79]	4.3%	5.5%
Saletu(1991) 30 1	−1.03	0.2357	−1.03	[−1.49; −0.57]	7.3%	5.6%
Saletu(1991) 40 1	−1.29	0.2357	−1.29	[−1.75; −0.82]	7.3%	5.6%
Barbanoj(2005) 20 15	−1.62	0.3015	−1.62	[−2.21; −1.03]	4.5%	5.5%
Sharpley(1996) 30 16	−6.88	0.3086	−6.88	[−7.48; −6.27]	4.3%	5.5%
Wilson(2015) 20 3	−2.80	0.2294	−2.80	[−3.25; −2.35]	7.7%	5.6%
Sharpley(1996) 30 6	−7.80	0.3086	−7.80	[−8.41; −7.20]	4.3%	5.5%
Common effect model			**−2.86**	**[−3.03; −2.68]**	**51.5%**	**––**
Random effects model			**−3.29**	**[−4.97; −1.62]**	**––**	**50.0%**
Heterogeneity: I^2 = 99%, τ^2 = 6.4951, p < 0.01						
Substance = Vortioxetine						
Wilson(2015) 20 3	−1.67	0.2294	−1.67	[−2.12; −1.22]	7.7%	5.6%
Wilson(2015) 40 3	−3.36	0.2294	−3.36	[−3.81; −2.91]	7.7%	5.6%
Common effect model			**−2.52**	**[−2.83; −2.20]**	**15.5%**	**––**
Random effects model			**−2.52**	**[−4.17; −0.86]**	**––**	**11.2%**
Heterogeneity: I^2 = 96%, τ^2 = 1.3775, p < 0.01						
Common effect model			**−1.87**	**[−1.99; −1.74]**	**100.0%**	**––**
Random effects model			**−1.96**	**[−3.07; −0.85]**	**––**	**100.0%**

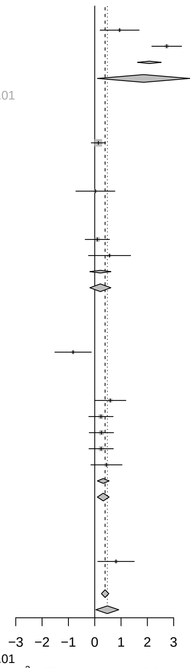
Heterogeneity: I^2 = 98%, τ^2 = 5.6860, p < 0.01
Test for subgroup differences (common effect): χ^2_4 = 420.45, df = 4 (p < 0.01)
Test for subgroup differences (random effects): χ^2_4 = 23.25, df = 4 (p < 0.01)

Healthy Population continuity



Heterogeneity: I^2 = 12%, τ^2 = 0.0211, p = 0.28
Test for subgroup differences (common effect): χ^2_{13} = 15.90, df = 13 (p = 0.25)
Test for subgroup differences (random effects): χ^2_{13} = 13.39, df = 13 (p = 0.42)

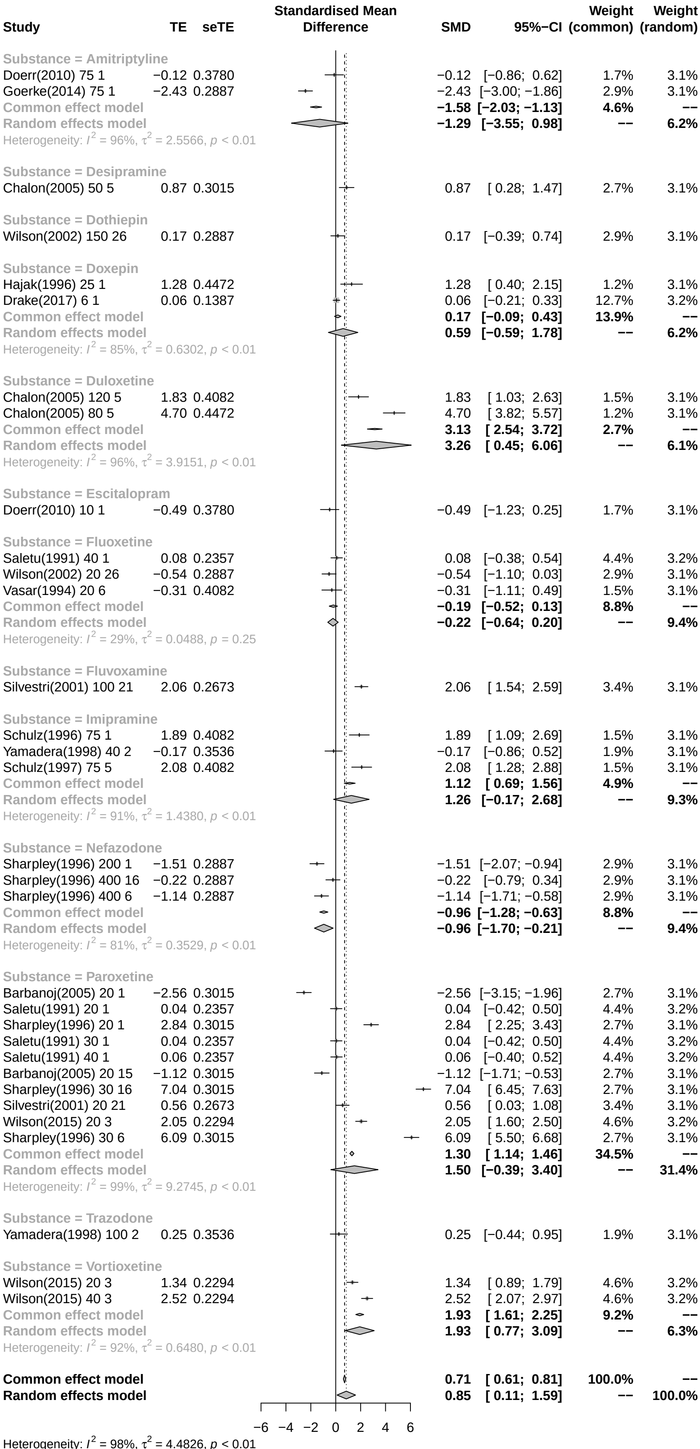
Healthy Population depth



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Amitriptyline							
Doerr(2010) 75 1	0.95	0.3780		0.95	[0.20; 1.69]	3.6%	7.1%
Goerke(2014) 75 1	2.73	0.2887		2.73	[2.17; 3.30]	6.2%	7.8%
Common effect model				**2.08**	**[1.63; 2.53]**	**9.8%**	**––**
Random effects model				**1.86**	**[0.10; 3.61]**	**––**	**14.9%**
Heterogeneity: I^2 = 93%, τ^2 = 1.4881, p < 0.01							
Substance = Doxepin							
Drake(2017) 6 1	0.14	0.1387		0.14	[−0.13; 0.41]	26.8%	8.6%
Substance = Escitalopram							
Doerr(2010) 10 1	0.02	0.3780		0.02	[−0.72; 0.77]	3.6%	7.1%
Substance = Fluoxetine							
Saletu(1991) 40 1	0.10	0.2357		0.10	[−0.36; 0.56]	9.3%	8.1%
Vasar(1994) 20 6	0.56	0.4082		0.56	[−0.24; 1.36]	3.1%	6.9%
Common effect model				**0.21**	**[−0.19; 0.61]**	**12.4%**	**––**
Random effects model				**0.21**	**[−0.19; 0.61]**	**––**	**15.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.33							
Substance = Imipramine							
Yamadera(1998) 40 2	−0.82	0.3536		−0.82	[−1.51; −0.13]	4.1%	7.3%
Substance = Paroxetine							
Barbanoj(2005) 20 1	0.59	0.3015		0.59	[0.00; 1.18]	5.7%	7.7%
Saletu(1991) 20 1	0.24	0.2357		0.24	[−0.22; 0.70]	9.3%	8.1%
Saletu(1991) 30 1	0.25	0.2357		0.25	[−0.21; 0.72]	9.3%	8.1%
Saletu(1991) 40 1	0.24	0.2357		0.24	[−0.22; 0.71]	9.3%	8.1%
Barbanoj(2005) 20 15	0.45	0.3015		0.45	[−0.15; 1.04]	5.7%	7.7%
Common effect model				**0.32**	**[0.10; 0.55]**	**39.2%**	**––**
Random effects model				**0.32**	**[0.10; 0.55]**	**––**	**39.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86							
Substance = Trazodone							
Yamadera(1998) 100 2	0.81	0.3536		0.81	[0.12; 1.50]	4.1%	7.3%
Common effect model				**0.39**	**[0.25; 0.53]**	**100.0%**	**––**
Random effects model				**0.48**	**[0.04; 0.91]**	**––**	**100.0%**

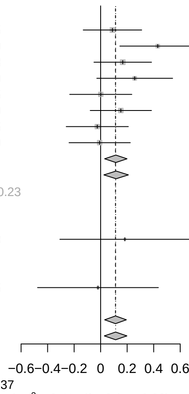
Heterogeneity: I^2 = 86%, τ^2 = 0.5512, p < 0.01
Test for subgroup differences (common effect): χ^2_6 = 72.44, df = 6 (p < 0.01)
Test for subgroup differences (random effects): χ^2_6 = 16.24, df = 6 (p = 0.01)

Healthy Population REMpressure



Heterogeneity: I^2 = 98%, τ^2 = 4.4826, p < 0.01
Test for subgroup differences (common effect): χ^2_{12} = 460.78, df = 12 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{12} = 83.93, df = 12 (p < 0.01)

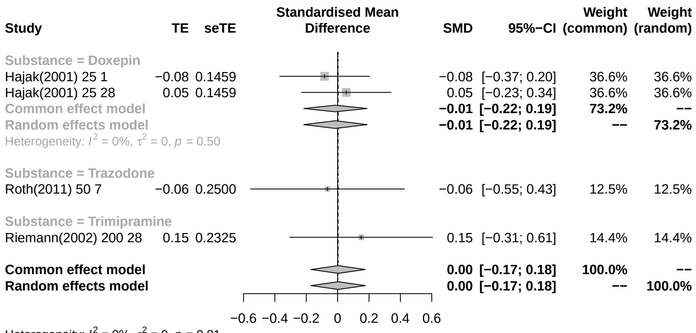
Insomnia Population continuity vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Krystal(2010) 1 1	0.09	0.1125		0.09	[−0.13; 0.31]	13.8%	13.6%
Hajak(2001) 25 1	0.43	0.1459		0.43	[0.14; 0.72]	8.2%	8.4%
Krystal(2010) 3 1	0.17	0.1108		0.17	[−0.05; 0.38]	14.2%	14.0%
Hajak(2001) 25 28	0.26	0.1459		0.26	[−0.03; 0.54]	8.2%	8.4%
Krystal(2010) 1 29	0.00	0.1195		0.00	[−0.23; 0.24]	12.2%	12.2%
Krystal(2010) 3 29	0.15	0.1179		0.15	[−0.08; 0.38]	12.6%	12.5%
Krystal(2010) 1 85	−0.03	0.1195		−0.03	[−0.26; 0.21]	12.2%	12.2%
Krystal(2010) 3 85	−0.01	0.1179		−0.01	[−0.24; 0.22]	12.6%	12.5%
Common effect model				**0.11**	**[0.03; 0.20]**	**94.0%**	**––**
Random effects model				**0.12**	**[0.02; 0.21]**	**––**	**93.6%**
Heterogeneity: I^2 = 25%, τ^2 = 0.0028, p = 0.23							
Substance = Trazodone							
Roth(2011) 50 7	0.18	0.2500		0.18	[−0.31; 0.67]	2.8%	3.0%
Substance = Trimipramine							
Riemann(2002) 200 28	−0.02	0.2325		−0.02	[−0.48; 0.44]	3.2%	3.4%
Common effect model				**0.11**	**[0.03; 0.19]**	**100.0%**	**––**
Random effects model				**0.11**	**[0.03; 0.20]**	**––**	**100.0%**

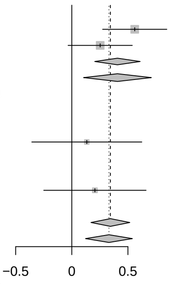
Heterogeneity: I^2 = 8%, τ^2 = 0.0012, p = 0.37
Test for subgroup differences (common effect): χ^2_2 = 0.41, df = 2 (p = 0.82)
Test for subgroup differences (random effects): χ^2_2 = 0.41, df = 2 (p = 0.81)

Insomnia Population REMpressure vs Placebo



Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.81
Test for subgroup differences (common effect): χ^2_2 = 0.50, df = 2 (p = 0.78)
Test for subgroup differences (random effects): χ^2_2 = 0.50, df = 2 (p = 0.78)

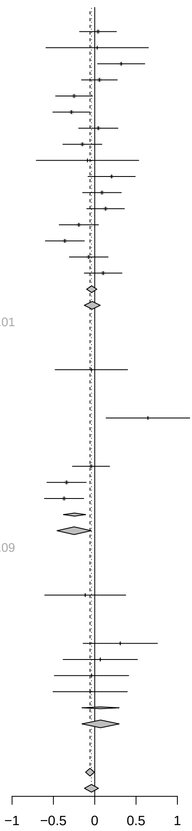
Insomnia Population depth vs Placebo



Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	0.56	0.1459		0.56	[0.27; 0.85]	36.6%	33.9%
Hajak(2001) 25 28	0.25	0.1459		0.25	[−0.03; 0.54]	36.6%	33.9%
Common effect model				**0.41**	**[0.20; 0.61]**	**73.2%**	**––**
Random effects model				**0.41**	**[0.11; 0.71]**	**––**	**67.8%**
Heterogeneity: I^2 = 55%, τ^2 = 0.0261, p = 0.14							
Substance = Trazodone							
Roth(2011) 50 7	0.13	0.2500		0.13	[−0.36; 0.62]	12.5%	15.1%
Substance = Trimipramine							
Riemann(2002) 200 28	0.21	0.2325		0.21	[−0.25; 0.66]	14.4%	17.1%
Common effect model				**0.34**	**[0.17; 0.52]**	**100.0%**	**––**
Random effects model				**0.33**	**[0.12; 0.54]**	**––**	**100.0%**

Heterogeneity: I^2 = 18%, τ^2 = 0.0120, p = 0.30
Test for subgroup differences (common effect): χ^2_2 = 1.43, df = 2 (p = 0.49)
Test for subgroup differences (random effects): χ^2_2 = 1.09, df = 2 (p = 0.58)

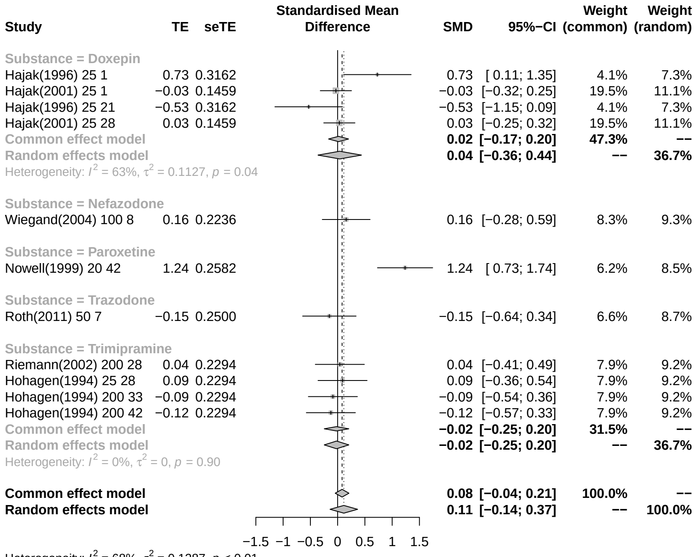
Insomnia Population continuity



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin						
Krystal(2010) 1 1	0.04	0.1140	0.04	[−0.18; 0.26]	5.8%	4.9%
Hajak(1996) 25 1	0.03	0.3162	0.03	[−0.59; 0.65]	0.8%	1.5%
Hajak(2001) 25 1	0.32	0.1459	0.32	[0.03; 0.61]	3.5%	4.1%
Krystal(2010) 3 1	0.06	0.1104	0.06	[−0.16; 0.27]	6.2%	5.0%
Krystal(2011) 3 1	−0.25	0.1140	−0.25	[−0.47; −0.03]	5.8%	4.9%
Krystal(2011) 6 1	−0.28	0.1147	−0.28	[−0.51; −0.06]	5.7%	4.9%
Krystal(2011) 3 15	0.04	0.1213	0.04	[−0.19; 0.28]	5.1%	4.7%
Krystal(2011) 6 15	−0.15	0.1204	−0.15	[−0.39; 0.09]	5.2%	4.7%
Hajak(1996) 25 21	−0.09	0.3162	−0.09	[−0.71; 0.53]	0.8%	1.5%
Hajak(2001) 25 28	0.20	0.1459	0.20	[−0.08; 0.49]	3.5%	4.1%
Krystal(2010) 1 29	0.09	0.1195	0.09	[−0.15; 0.32]	5.3%	4.8%
Krystal(2010) 3 29	0.13	0.1162	0.13	[−0.10; 0.36]	5.6%	4.9%
Krystal(2011) 3 29	−0.19	0.1213	−0.19	[−0.43; 0.05]	5.1%	4.7%
Krystal(2011) 6 29	−0.36	0.1204	−0.36	[−0.60; −0.13]	5.2%	4.7%
Krystal(2010) 1 85	−0.07	0.1195	−0.07	[−0.31; 0.16]	5.3%	4.8%
Krystal(2010) 3 85	0.10	0.1162	0.10	[−0.13; 0.33]	5.6%	4.9%
Common effect model			**−0.04**	**[−0.10; 0.03]**	**74.5%**	**––**
Random effects model			**−0.03**	**[−0.13; 0.07]**	**––**	**69.2%**
Heterogeneity: I^2 = 54%, τ^2 = 0.0208, p < 0.01						
Substance = Nefazodone						
Wiegand(2004) 100 8	−0.04	0.2236	−0.04	[−0.48; 0.40]	1.5%	2.5%
Substance = Paroxetine						
Nowell(1999) 20 42	0.64	0.2582	0.64	[0.14; 1.15]	1.1%	2.1%
Substance = placebo						
Krystal(2011) 1	−0.04	0.1147	−0.04	[−0.27; 0.18]	5.7%	4.9%
Krystal(2011) 15	−0.34	0.1213	−0.34	[−0.58; −0.10]	5.1%	4.7%
Krystal(2011) 29	−0.37	0.1213	−0.37	[−0.61; −0.13]	5.1%	4.7%
Common effect model			**−0.24**	**[−0.38; −0.11]**	**16.0%**	**––**
Random effects model			**−0.25**	**[−0.46; −0.04]**	**––**	**14.4%**
Heterogeneity: I^2 = 58%, τ^2 = 0.0193, p = 0.09						
Substance = Trazodone						
Roth(2011) 50 7	−0.11	0.2500	−0.11	[−0.60; 0.38]	1.2%	2.2%
Substance = Trimipramine						
Riemann(2002) 200 28	0.31	0.2294	0.31	[−0.14; 0.76]	1.4%	2.4%
Hohagen(1994) 25 28	0.07	0.2294	0.07	[−0.38; 0.52]	1.4%	2.4%
Hohagen(1994) 200 33	−0.04	0.2294	−0.04	[−0.49; 0.41]	1.4%	2.4%
Hohagen(1994) 200 42	−0.06	0.2294	−0.06	[−0.50; 0.39]	1.4%	2.4%
Common effect model			**0.07**	**[−0.15; 0.30]**	**5.7%**	**––**
Random effects model			**0.07**	**[−0.15; 0.30]**	**––**	**9.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.66						
Common effect model			**−0.06**	**[−0.11; −0.00]**	**100.0%**	**––**
Random effects model			**−0.04**	**[−0.12; 0.05]**	**––**	**100.0%**

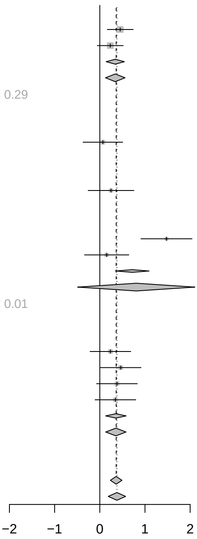
Heterogeneity: I^2 = 55%, τ^2 = 0.0254, p < 0.01
Test for subgroup differences (common effect): χ^2_5 = 16.52, df = 5 (p < 0.01)
Test for subgroup differences (random effects): χ^2_5 = 11.97, df = 5 (p = 0.04)

Insomnia Population REMpressure



Heterogeneity: I^2 = 68%, τ^2 = 0.1287, p < 0.01
Test for subgroup differences (common effect): χ^2_4 = 22.26, df = 4 (p < 0.01)
Test for subgroup differences (random effects): χ^2_4 = 21.57, df = 4 (p < 0.01)

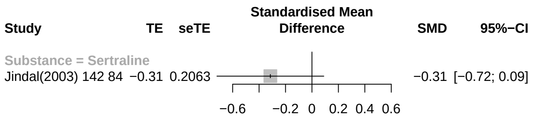
Insomnia Population depth



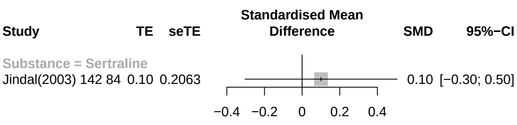
Study	TE	seTE	Standardised Mean Difference	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Doxepin							
Hajak(2001) 25 1	0.45	0.1459		0.45	[0.17; 0.74]	20.2%	13.8%
Hajak(2001) 25 28	0.23	0.1459		0.23	[−0.05; 0.52]	20.2%	13.8%
Common effect model				**0.34**	**[0.14; 0.54]**	**40.3%**	**––**
Random effects model				**0.34**	**[0.13; 0.56]**	**––**	**27.6%**
Heterogeneity: I^2 = 12%, τ^2 = 0.0030, p = 0.29							
Substance = Nefazodone							
Wiegand(2004) 100 8	0.07	0.2236		0.07	[−0.37; 0.51]	8.6%	9.8%
Substance = Paroxetine							
Nowell(1999) 20 42	0.25	0.2582		0.25	[−0.26; 0.75]	6.4%	8.4%
Substance = Trazodone							
Paterson(2009) 100 56	1.48	0.2887		1.48	[0.91; 2.04]	5.2%	7.3%
Roth(2011) 50 7	0.15	0.2500		0.15	[−0.34; 0.64]	6.9%	8.7%
Common effect model				**0.72**	**[0.35; 1.09]**	**12.0%**	**––**
Random effects model				**0.81**	**[−0.49; 2.10]**	**––**	**16.0%**
Heterogeneity: I^2 = 92%, τ^2 = 0.8026, p < 0.01							
Substance = Trimipramine							
Riemann(2002) 200 28	0.24	0.2294		0.24	[−0.21; 0.68]	8.2%	9.5%
Hohagen(1994) 25 28	0.46	0.2294		0.46	[0.01; 0.91]	8.2%	9.5%
Hohagen(1994) 200 33	0.38	0.2294		0.38	[−0.07; 0.83]	8.2%	9.5%
Hohagen(1994) 200 42	0.35	0.2294		0.35	[−0.10; 0.80]	8.2%	9.5%
Common effect model				**0.36**	**[0.13; 0.58]**	**32.6%**	**––**
Random effects model				**0.36**	**[0.13; 0.58]**	**––**	**38.2%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.92							
Common effect model				**0.36**	**[0.23; 0.49]**	**100.0%**	**––**
Random effects model				**0.38**	**[0.19; 0.57]**	**––**	**100.0%**

Heterogeneity: I^2 = 53%, τ^2 = 0.0488, p = 0.02
Test for subgroup differences (common effect): χ^2_4 = 5.54, df = 4 (p = 0.24)
Test for subgroup differences (random effects): χ^2_4 = 2.02, df = 4 (p = 0.73)

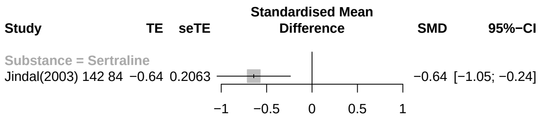
Depressed Population continuity vs Placebo

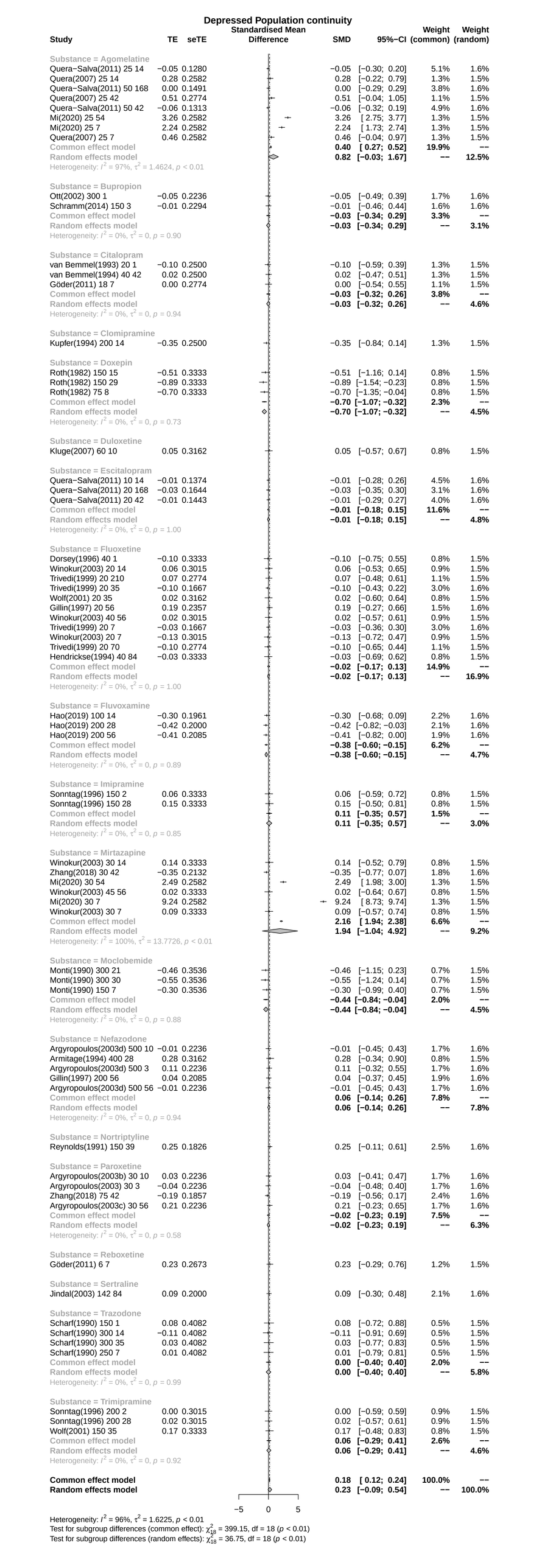


Depressed Population depth vs Placebo

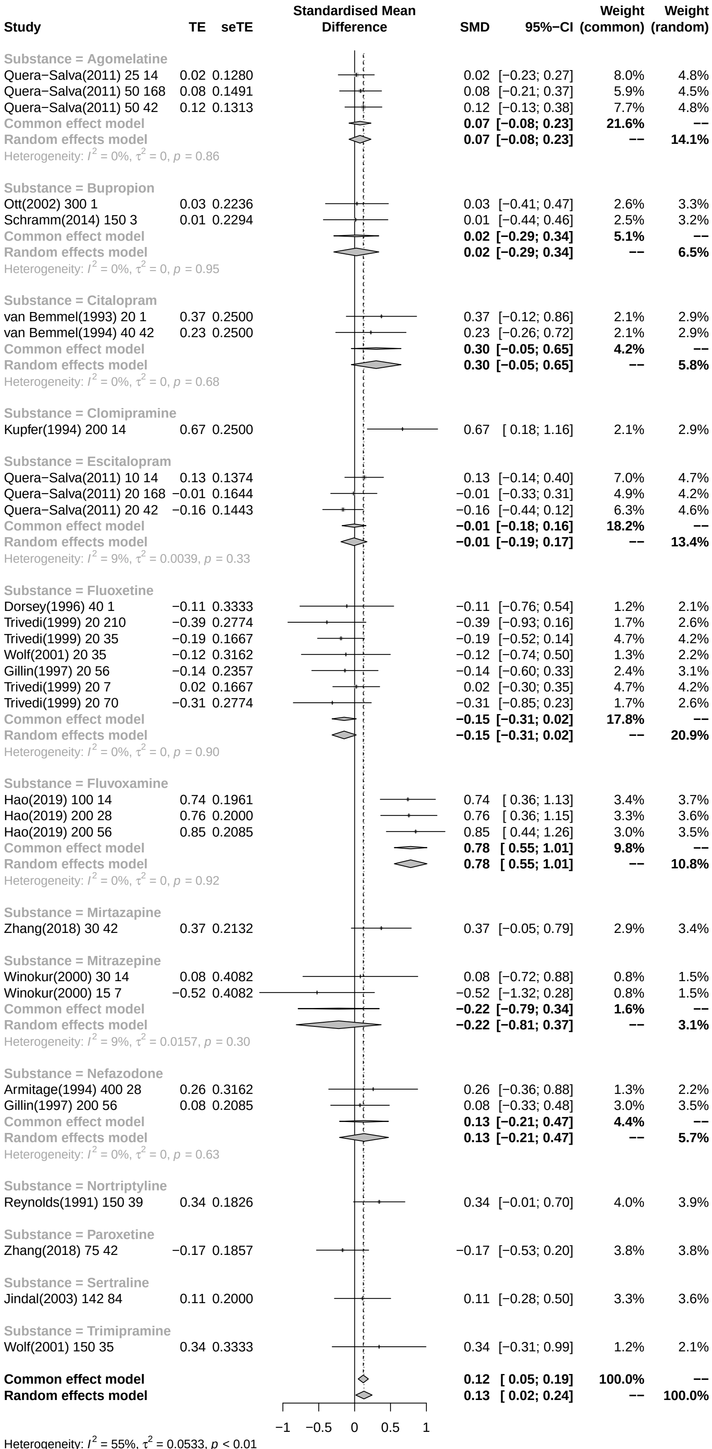


Depressed Population REMpressure vs Placebo



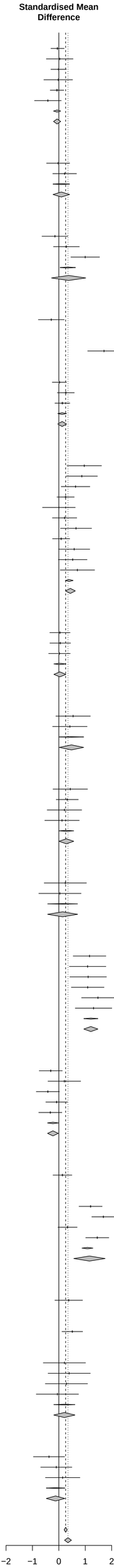

Depressed Population continuity
Standardised Mean Difference
Study
TE
seTE
SMD
95%−CI
Weight (common)
Weight (random)
Substance = Agomelatine
Quera−Salva(2011) 25 14 −0.05 0.1280 −0.05 [−0.30; 0.20] 5.1% 1.6%
Quera(2007) 25 14 0.28 0.2582 0.28 [−0.22; 0.79] 1.3% 1.5%
Quera−Salva(2011) 50 168 0.00 0.1491 0.00 [−0.29; 0.29] 3.8% 1.6%
Quera(2007) 25 42 0.51 0.2774 0.51 [−0.04; 1.05] 1.1% 1.5%
Quera−Salva(2011) 50 42 −0.06 0.1313 −0.06 [−0.32; 0.19] 4.9% 1.6%
Mi(2020) 25 54 3.26 0.2582 3.26 [2.75; 3.77] 1.3% 1.5%
Mi(2020) 25 7 2.24 0.2582 2.24 [1.73; 2.74] 1.3% 1.5%
Quera(2007) 25 7 0.46 0.2582 0.46 [−0.04; 0.97] 1.3% 1.5%
Common effect model 0.40 [0.27; 0.52] 19.9% −−
Random effects model 0.82 [−0.03; 1.67] −− 12.5%
Heterogeneity: I^2 = 97%, τ^2 = 1.4624, p < 0.01
Substance = Bupropion
Ott(2002) 300 1 −0.05 0.2236 −0.05 [−0.49; 0.39] 1.7% 1.6%
Schramm(2014) 150 3 −0.01 0.2294 −0.01 [−0.46; 0.44] 1.6% 1.6%
Common effect model −0.03 [−0.34; 0.29] 3.3% −−
Random effects model −0.03 [−0.34; 0.29] −− 3.1%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.90
Substance = Citalopram
van Bemmel(1993) 20 1 −0.10 0.2500 −0.10 [−0.59; 0.39] 1.3% 1.5%
van Bemmel(1994) 40 42 0.02 0.2500 0.02 [−0.47; 0.51] 1.3% 1.5%
Göder(2011) 18 7 0.00 0.2774 0.00 [−0.54; 0.55] 1.1% 1.5%
Common effect model −0.03 [−0.32; 0.26] 3.8% −−
Random effects model −0.03 [−0.32; 0.26] −− 4.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94
Substance = Clomipramine
Kupfer(1994) 200 14 −0.35 0.2500 −0.35 [−0.84; 0.14] 1.3% 1.5%
Substance = Doxepin
Roth(1982) 150 15 −0.51 0.3333 −0.51 [−1.16; 0.14] 0.8% 1.5%
Roth(1982) 150 29 −0.89 0.3333 −0.89 [−1.54; −0.23] 0.8% 1.5%
Roth(1982) 75 8 −0.70 0.3333 −0.70 [−1.35; −0.04] 0.8% 1.5%
Common effect model −0.70 [−1.07; −0.32] 2.3% −−
Random effects model −0.70 [−1.07; −0.32] −− 4.5%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73
Substance = Duloxetine
Kluge(2007) 60 10 0.05 0.3162 0.05 [−0.57; 0.67] 0.8% 1.5%
Substance = Escitalopram
Quera−Salva(2011) 10 14 −0.01 0.1374 −0.01 [−0.28; 0.26] 4.5% 1.6%
Quera−Salva(2011) 20 168 −0.03 0.1644 −0.03 [−0.35; 0.30] 3.1% 1.6%
Quera−Salva(2011) 20 42 −0.01 0.1443 −0.01 [−0.29; 0.27] 4.0% 1.6%
Common effect model −0.01 [−0.18; 0.15] 11.6% −−
Random effects model −0.01 [−0.18; 0.15] −− 4.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00
Substance = Fluoxetine
Dorsey(1996) 40 1 −0.10 0.3333 −0.10 [−0.75; 0.55] 0.8% 1.5%
Winokur(2003) 20 14 0.06 0.3015 0.06 [−0.53; 0.65] 0.9% 1.5%
Trivedi(1999) 20 210 0.07 0.2774 0.07 [−0.48; 0.61] 1.1% 1.5%
Trivedi(1999) 20 35 −0.10 0.1667 −0.10 [−0.43; 0.22] 3.0% 1.6%
Wolf(2001) 20 35 0.02 0.3162 0.02 [−0.60; 0.64] 0.8% 1.5%
Gillin(1997) 20 56 0.19 0.2357 0.19 [−0.27; 0.66] 1.5% 1.6%
Winokur(2003) 40 56 0.02 0.3015 0.02 [−0.57; 0.61] 0.9% 1.5%
Trivedi(1999) 20 7 −0.03 0.1667 −0.03 [−0.36; 0.30] 3.0% 1.6%
Winokur(2003) 20 7 −0.13 0.3015 −0.13 [−0.72; 0.47] 0.9% 1.5%
Trivedi(1999) 20 70 −0.10 0.2774 −0.10 [−0.65; 0.44] 1.1% 1.5%
Hendrickse(1994) 40 84 −0.03 0.3333 −0.03 [−0.69; 0.62] 0.8% 1.5%
Common effect model −0.02 [−0.17; 0.13] 14.9% −−
Random effects model −0.02 [−0.17; 0.13] −− 16.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00
Substance = Fluvoxamine
Hao(2019) 100 14 −0.30 0.1961 −0.30 [−0.68; 0.09] 2.2% 1.6%
Hao(2019) 200 28 −0.42 0.2000 −0.42 [−0.82; −0.03] 2.1% 1.6%
Hao(2019) 200 56 −0.41 0.2085 −0.41 [−0.82; 0.00] 1.9% 1.6%
Common effect model −0.38 [−0.60; −0.15] 6.2% −−
Random effects model −0.38 [−0.60; −0.15] −− 4.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.89
Substance = Imipramine
Sonntag(1996) 150 2 0.06 0.3333 0.06 [−0.59; 0.72] 0.8% 1.5%
Sonntag(1996) 150 28 0.15 0.3333 0.15 [−0.50; 0.81] 0.8% 1.5%
Common effect model 0.11 [−0.35; 0.57] 1.5% −−
Random effects model 0.11 [−0.35; 0.57] −− 3.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.85
Substance = Mirtazapine
Winokur(2003) 30 14 0.14 0.3333 0.14 [−0.52; 0.79] 0.8% 1.5%
Zhang(2018) 30 42 −0.35 0.2132 −0.35 [−0.77; 0.07] 1.8% 1.6%
Mi(2020) 30 54 2.49 0.2582 2.49 [1.98; 3.00] 1.3% 1.5%
Winokur(2003) 45 56 0.02 0.3333 0.02 [−0.64; 0.67] 0.8% 1.5%
Mi(2020) 30 7 9.24 0.2582 9.24 [8.73; 9.74] 1.3% 1.5%
Winokur(2003) 30 7 0.09 0.3333 0.09 [−0.57; 0.74] 0.8% 1.5%
Common effect model 2.16 [1.94; 2.38] 6.6% −−
Random effects model 1.94 [−1.04; 4.92] −− 9.2%
Heterogeneity: I^2 = 100%, τ^2 = 13.7726, p < 0.01
Substance = Moclobemide
Monti(1990) 300 21 −0.46 0.3536 −0.46 [−1.15; 0.23] 0.7% 1.5%
Monti(1990) 300 30 −0.55 0.3536 −0.55 [−1.24; 0.14] 0.7% 1.5%
Monti(1990) 150 7 −0.30 0.3536 −0.30 [−0.99; 0.40] 0.7% 1.5%
Common effect model −0.44 [−0.84; −0.04] 2.0% −−
Random effects model −0.44 [−0.84; −0.04] −− 4.5%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.88
Substance = Nefazodone
Argyropoulos(2003d) 500 10 −0.01 0.2236 −0.01 [−0.45; 0.43] 1.7% 1.6%
Armitage(1994) 400 28 0.28 0.3162 0.28 [−0.34; 0.90] 0.8% 1.5%
Argyropoulos(2003d) 500 3 0.11 0.2236 0.11 [−0.32; 0.55] 1.7% 1.6%
Gillin(1997) 200 56 0.04 0.2085 0.04 [−0.37; 0.45] 1.9% 1.6%
Argyropoulos(2003d) 500 56 −0.01 0.2236 −0.01 [−0.45; 0.43] 1.7% 1.6%
Common effect model 0.06 [−0.14; 0.26] 7.8% −−
Random effects model 0.06 [−0.14; 0.26] −− 7.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94
Substance = Nortriptyline
Reynolds(1991) 150 39 0.25 0.1826 0.25 [−0.11; 0.61] 2.5% 1.6%
Substance = Paroxetine
Argyropoulos(2003b) 30 10 0.03 0.2236 0.03 [−0.41; 0.47] 1.7% 1.6%
Argyropoulos(2003) 30 3 −0.04 0.2236 −0.04 [−0.48; 0.40] 1.7% 1.6%
Zhang(2018) 75 42 −0.19 0.1857 −0.19 [−0.56; 0.17] 2.4% 1.6%
Argyropoulos(2003c) 30 56 0.21 0.2236 0.21 [−0.23; 0.65] 1.7% 1.6%
Common effect model −0.02 [−0.23; 0.19] 7.5% −−
Random effects model −0.02 [−0.23; 0.19] −− 6.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.58
Substance = Reboxetine
Göder(2011) 6 7 0.23 0.2673 0.23 [−0.29; 0.76] 1.2% 1.5%
Substance = Sertraline
Jindal(2003) 142 84 0.09 0.2000 0.09 [−0.30; 0.48] 2.1% 1.6%
Substance = Trazodone
Scharf(1990) 150 1 0.08 0.4082 0.08 [−0.72; 0.88] 0.5% 1.5%
Scharf(1990) 300 14 −0.11 0.4082 −0.11 [−0.91; 0.69] 0.5% 1.5%
Scharf(1990) 300 35 0.03 0.4082 0.03 [−0.77; 0.83] 0.5% 1.5%
Scharf(1990) 250 7 0.01 0.4082 0.01 [−0.79; 0.81] 0.5% 1.5%
Common effect model 0.00 [−0.40; 0.40] 2.0% −−
Random effects model 0.00 [−0.40; 0.40] −− 5.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99
Substance = Trimipramine
Sonntag(1996) 200 2 0.00 0.3015 0.00 [−0.59; 0.59] 0.9% 1.5%
Sonntag(1996) 200 28 0.02 0.3015 0.02 [−0.57; 0.61] 0.9% 1.5%
Wolf(2001) 150 35 0.17 0.3333 0.17 [−0.48; 0.83] 0.8% 1.5%
Common effect model 0.06 [−0.29; 0.41] 2.6% −−
Random effects model 0.06 [−0.29; 0.41] −− 4.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.92
Common effect model 0.18 [0.12; 0.24] 100.0% −−
Random effects model 0.23 [−0.09; 0.54] −− 100.0%
−5
0
5
Heterogeneity: I^2 = 96%, τ^2 = 1.6225, p < 0.01
Test for subgroup differences (common effect): χ^2_{18} = 399.15, df = 18 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{18} = 36.75, df = 18 (p < 0.01)

Depressed Population depth



Heterogeneity: I^2 = 55%, τ^2 = 0.0533, p < 0.01
Test for subgroup differences (common effect): χ^2_{13} = 57.78, df = 13 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{13} = 57.32, df = 13 (p < 0.01)

Depressed Population REMpressure



Study	TE	seTE	SMD	95%−CI	Weight (common)	Weight (random)
Substance = Agomelatine						
Quera−Salva(2011) 25 14	−0.05	0.1280	−0.05	[−0.30; 0.20]	5.3%	2.0%
Quera(2007) 25 14	0.03	0.2582	0.03	[−0.47; 0.54]	1.3%	1.6%
Quera−Salva(2011) 50 168	−0.01	0.1491	−0.01	[−0.30; 0.28]	3.9%	1.9%
Quera(2007) 25 42	−0.02	0.2774	−0.02	[−0.57; 0.52]	1.1%	1.6%
Quera−Salva(2011) 50 42	−0.07	0.1313	−0.07	[−0.33; 0.19]	5.1%	2.0%
Quera(2007) 25 7	−0.42	0.2582	−0.42	[−0.92; 0.09]	1.3%	1.6%
Common effect model			**−0.07**	**[−0.20; 0.07]**	**18.1%**	**−−**
Random effects model			**−0.07**	**[−0.20; 0.07]**	**−−**	**10.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.83						
Substance = Bupropion						
Ott(2002) 300 1	−0.03	0.2236	−0.03	[−0.47; 0.41]	1.7%	1.7%
Schramm(2014) 150 3	0.22	0.2294	0.22	[−0.23; 0.67]	1.7%	1.7%
Common effect model			**0.09**	**[−0.22; 0.41]**	**3.4%**	**−−**
Random effects model			**0.09**	**[−0.22; 0.41]**	**−−**	**3.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.44						
Substance = Citalopram						
van Bemmel(1993) 20 1	−0.15	0.2500	−0.15	[−0.64; 0.34]	1.4%	1.7%
van Bemmel(1994) 40 42	0.29	0.2500	0.29	[−0.20; 0.78]	1.4%	1.7%
Göder(2011) 18 7	1.00	0.2774	1.00	[0.45; 1.54]	1.1%	1.6%
Common effect model			**0.34**	**[0.05; 0.63]**	**3.9%**	**−−**
Random effects model			**0.37**	**[−0.28; 1.02]**	**−−**	**4.9%**
Heterogeneity: I^2 = 79%, τ^2 = 0.2605, p < 0.01						
Substance = Clomipramine						
Kupfer(1994) 200 14	−0.29	0.2500	−0.29	[−0.78; 0.20]	1.4%	1.7%
Substance = Duloxetine						
Kluge(2007) 60 10	1.71	0.3162	1.71	[1.09; 2.33]	0.9%	1.4%
Substance = Escitalopram						
Quera−Salva(2011) 10 14	0.02	0.1374	0.02	[−0.25; 0.29]	4.6%	2.0%
Quera−Salva(2011) 20 168	0.26	0.1644	0.26	[−0.06; 0.59]	3.2%	1.9%
Quera−Salva(2011) 20 42	0.13	0.1443	0.13	[−0.15; 0.42]	4.2%	2.0%
Common effect model			**0.13**	**[−0.04; 0.29]**	**12.1%**	**−−**
Random effects model			**0.13**	**[−0.04; 0.29]**	**−−**	**5.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52						
Substance = Fluoxetine						
Dorsey(1996) 40 1	0.96	0.3333	0.96	[0.31; 1.62]	0.8%	1.4%
Winokur(2003) 20 14	0.87	0.3015	0.87	[0.28; 1.46]	1.0%	1.5%
Trivedi(1999) 20 210	0.63	0.2774	0.63	[0.09; 1.18]	1.1%	1.6%
Trivedi(1999) 20 35	0.26	0.1667	0.26	[−0.07; 0.58]	3.1%	1.9%
Wolf(2001) 20 35	0.00	0.3162	0.00	[−0.62; 0.62]	0.9%	1.4%
Gillin(1997) 20 56	0.22	0.2357	0.22	[−0.24; 0.68]	1.6%	1.7%
Winokur(2003) 40 56	0.65	0.3015	0.65	[0.06; 1.24]	1.0%	1.5%
Trivedi(1999) 20 7	0.09	0.1667	0.09	[−0.24; 0.41]	3.1%	1.9%
Winokur(2003) 20 7	0.58	0.3015	0.58	[−0.01; 1.17]	1.0%	1.5%
Trivedi(1999) 20 70	0.52	0.2774	0.52	[−0.02; 1.07]	1.1%	1.6%
Hendrickse(1994) 40 84	0.70	0.3333	0.70	[0.05; 1.35]	0.8%	1.4%
Common effect model			**0.39**	**[0.24; 0.54]**	**15.5%**	**−−**
Random effects model			**0.44**	**[0.25; 0.62]**	**−−**	**17.3%**
Heterogeneity: I^2 = 31%, τ^2 = 0.0317, p = 0.15						
Substance = Fluvoxamine						
Hao(2019) 100 14	0.04	0.1961	0.04	[−0.34; 0.43]	2.3%	1.8%
Hao(2019) 200 28	0.05	0.2000	0.05	[−0.34; 0.44]	2.2%	1.8%
Hao(2019) 200 56	0.02	0.2085	0.02	[−0.39; 0.43]	2.0%	1.8%
Common effect model			**0.04**	**[−0.19; 0.27]**	**6.5%**	**−−**
Random effects model			**0.04**	**[−0.19; 0.27]**	**−−**	**5.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99						
Substance = Imipramine						
Sonntag(1996) 150 2	0.54	0.3333	0.54	[−0.11; 1.19]	0.8%	1.4%
Sonntag(1996) 150 28	0.42	0.3333	0.42	[−0.24; 1.07]	0.8%	1.4%
Common effect model			**0.48**	**[0.02; 0.94]**	**1.6%**	**−−**
Random effects model			**0.48**	**[0.02; 0.94]**	**−−**	**2.8%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.79						
Substance = Mirtazapine						
Winokur(2003) 30 14	0.43	0.3333	0.43	[−0.22; 1.09]	0.8%	1.4%
Zhang(2018) 30 42	0.32	0.2132	0.32	[−0.10; 0.74]	1.9%	1.8%
Winokur(2003) 45 56	0.21	0.3333	0.21	[−0.44; 0.86]	0.8%	1.4%
Winokur(2003) 30 7	0.12	0.3333	0.12	[−0.53; 0.77]	0.8%	1.4%
Common effect model			**0.28**	**[0.00; 0.56]**	**4.3%**	**−−**
Random effects model			**0.28**	**[0.00; 0.56]**	**−−**	**5.9%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.92						
Substance = Mitrazepine						
Winokur(2000) 30 14	0.24	0.4082	0.24	[−0.56; 1.04]	0.5%	1.2%
Winokur(2000) 15 7	0.04	0.4082	0.04	[−0.76; 0.84]	0.5%	1.2%
Common effect model			**0.14**	**[−0.42; 0.71]**	**1.0%**	**−−**
Random effects model			**0.14**	**[−0.42; 0.71]**	**−−**	**2.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.72						
Substance = Moclobemide						
Monti(1989) 300 19	1.16	0.3162	1.16	[0.54; 1.78]	0.9%	1.4%
Monti(1990) 300 21	1.09	0.3536	1.09	[0.40; 1.78]	0.7%	1.3%
Monti(1990) 300 30	1.11	0.3536	1.11	[0.42; 1.80]	0.7%	1.3%
Monti(1989) 300 31	1.09	0.3162	1.09	[0.47; 1.71]	0.9%	1.4%
Monti(1989) 150 4	1.48	0.3162	1.48	[0.86; 2.10]	0.9%	1.4%
Monti(1990) 150 7	1.31	0.3536	1.31	[0.62; 2.01]	0.7%	1.3%
Common effect model			**1.21**	**[0.94; 1.48]**	**4.7%**	**−−**
Random effects model			**1.21**	**[0.94; 1.48]**	**−−**	**8.3%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.95						
Substance = Nefazodone						
Argyropoulos(2003d) 500 10	−0.31	0.2236	−0.31	[−0.75; 0.13]	1.7%	1.7%
Armitage(1994) 400 28	0.21	0.3162	0.21	[−0.41; 0.83]	0.9%	1.4%
Argyropoulos(2003d) 500 3	−0.42	0.2236	−0.42	[−0.85; 0.02]	1.7%	1.7%
Gillin(1997) 200 56	−0.08	0.2085	−0.08	[−0.49; 0.32]	2.0%	1.8%
Argyropoulos(2003d) 500 56	−0.32	0.2236	−0.32	[−0.76; 0.12]	1.7%	1.7%
Common effect model			**−0.22**	**[−0.43; −0.02]**	**8.1%**	**−−**
Random effects model			**−0.22**	**[−0.43; −0.02]**	**−−**	**8.4%**
Heterogeneity: I^2 = 0%, τ^2 = < 0.0001, p = 0.50						
Substance = Nortriptyline						
Reynolds(1991) 150 39	0.14	0.1826	0.14	[−0.22; 0.49]	2.6%	1.9%
Substance = Paroxetine						
Argyropoulos(2003b) 30 10	1.20	0.2236	1.20	[0.76; 1.64]	1.7%	1.7%
Argyropoulos(2003) 30 3	1.69	0.2236	1.69	[1.25; 2.12]	1.7%	1.7%
Zhang(2018) 75 42	0.33	0.1857	0.33	[−0.04; 0.69]	2.5%	1.8%
Argyropoulos(2003c) 30 56	1.45	0.2236	1.45	[1.02; 1.89]	1.7%	1.7%
Common effect model			**1.08**	**[0.87; 1.29]**	**7.8%**	**−−**
Random effects model			**1.16**	**[0.57; 1.75]**	**−−**	**7.0%**
Heterogeneity: I^2 = 89%, τ^2 = 0.3185, p < 0.01						
Substance = Reboxetine						
Göder(2011) 6 7	0.37	0.2673	0.37	[−0.15; 0.90]	1.2%	1.6%
Substance = Sertraline						
Jindal(2003) 142 84	0.51	0.2000	0.51	[0.12; 0.90]	2.2%	1.8%
Substance = Trazodone						
Scharf(1990) 150 1	0.21	0.4082	0.21	[−0.59; 1.01]	0.5%	1.2%
Scharf(1990) 300 14	0.39	0.4082	0.39	[−0.41; 1.19]	0.5%	1.2%
Scharf(1990) 300 35	0.29	0.4082	0.29	[−0.51; 1.09]	0.5%	1.2%
Scharf(1990) 250 7	−0.06	0.4082	−0.06	[−0.86; 0.74]	0.5%	1.2%
Common effect model			**0.21**	**[−0.19; 0.61]**	**2.1%**	**−−**
Random effects model			**0.21**	**[−0.19; 0.61]**	**−−**	**4.7%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.88						
Substance = Trimipramine						
Sonntag(1996) 200 2	−0.37	0.3015	−0.37	[−0.96; 0.22]	1.0%	1.5%
Sonntag(1996) 200 28	−0.10	0.3015	−0.10	[−0.69; 0.49]	1.0%	1.5%
Wolf(2001) 150 35	0.14	0.3333	0.14	[−0.51; 0.80]	0.8%	1.4%
Common effect model			**−0.12**	**[−0.48; 0.23]**	**2.7%**	**−−**
Random effects model			**−0.12**	**[−0.48; 0.23]**	**−−**	**4.4%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.51						
Common effect model			**0.26**	**[0.20; 0.32]**	**100.0%**	**−−**
Random effects model			**0.35**	**[0.22; 0.48]**	**−−**	**100.0%**

Heterogeneity: I^2 = 76%, τ^2 = 0.2030, p < 0.01
Test for subgroup differences (common effect): χ^2_{18} = 197.15, df = 18 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{18} = 140.51, df = 18 (p < 0.01)