Online supplementary information accompanying the regular article:

Dose escalation of antidepressants in unipolar depression: a meta-analysis of double-blind, randomized controlled trials

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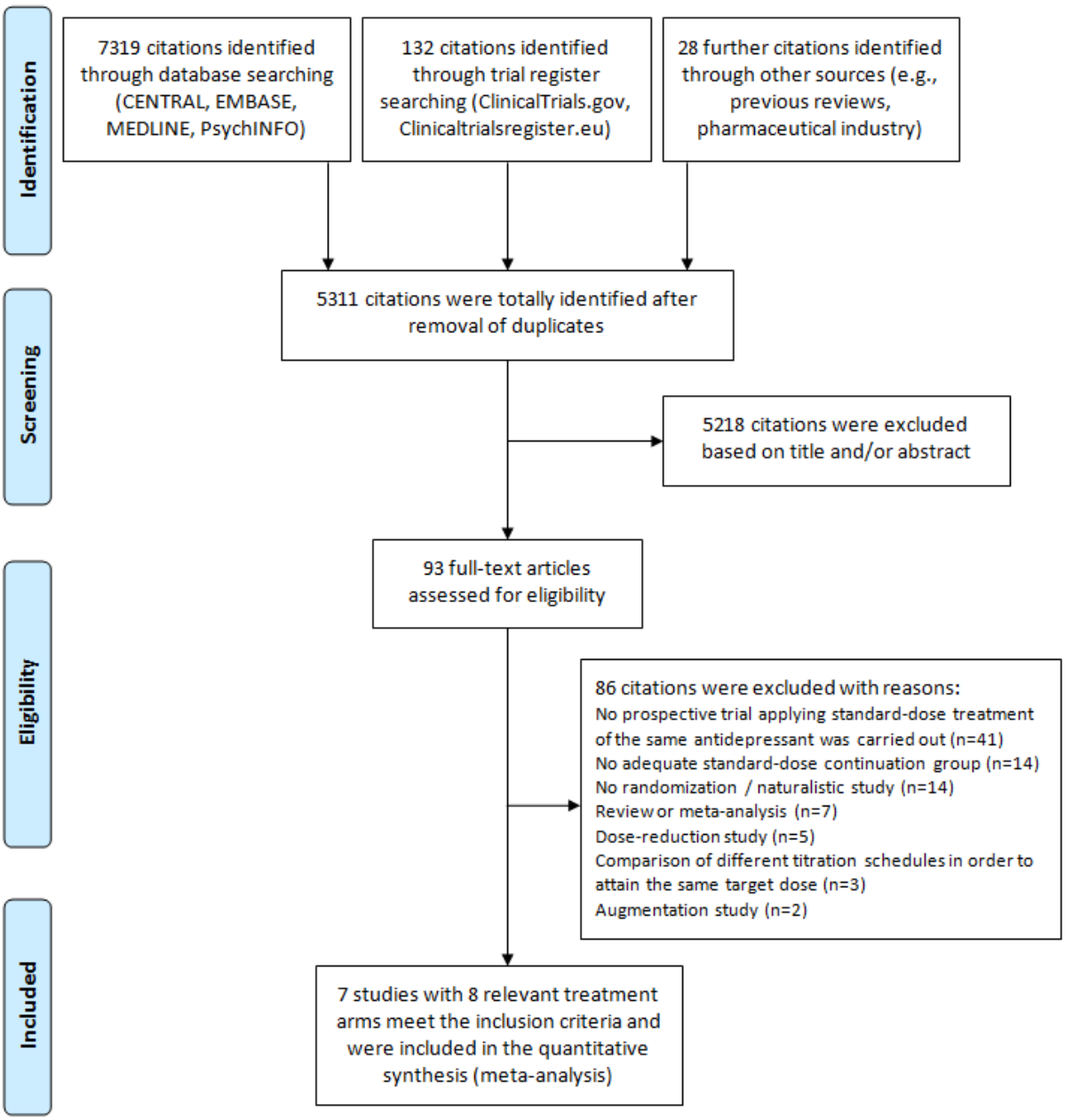
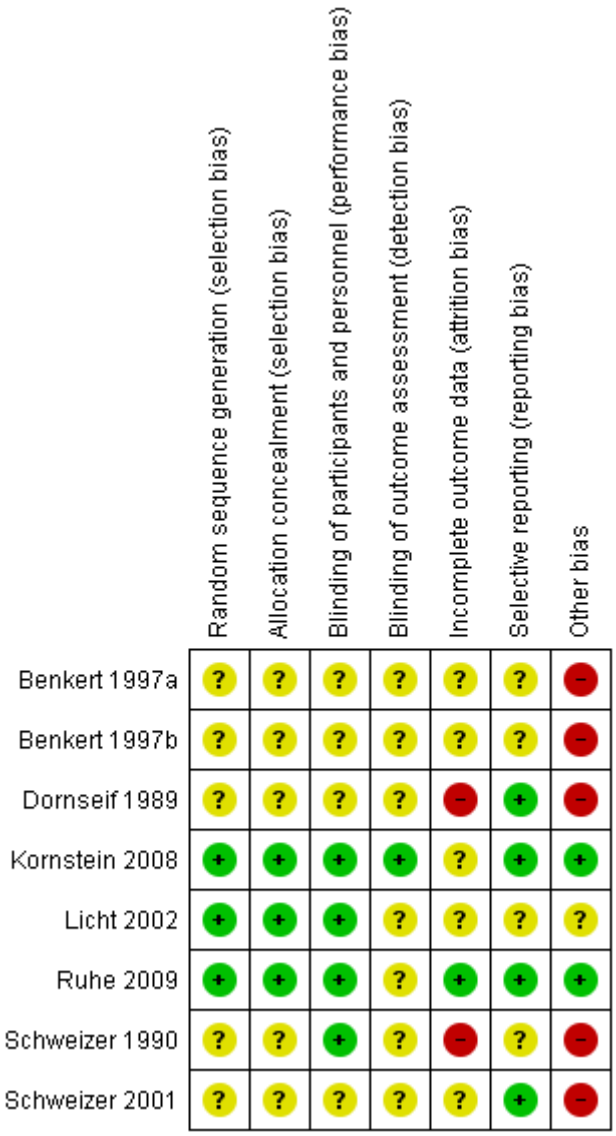
Online suppl. fig. 1. Flowchart of the systematic literature search (according to the PRISMA statement [1]).

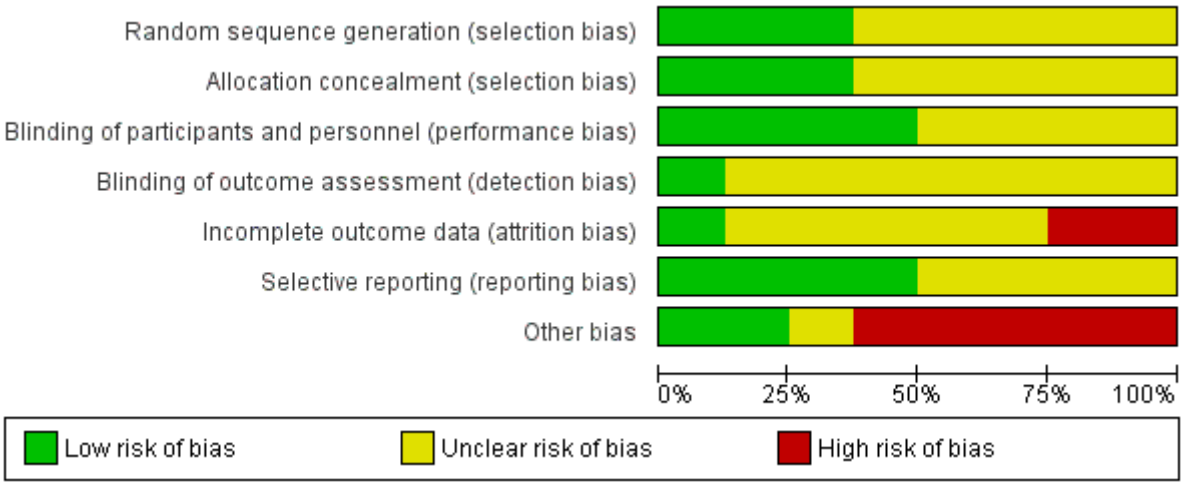


Online suppl. fig. 2. The "risk of bias" ratings for all included trials.



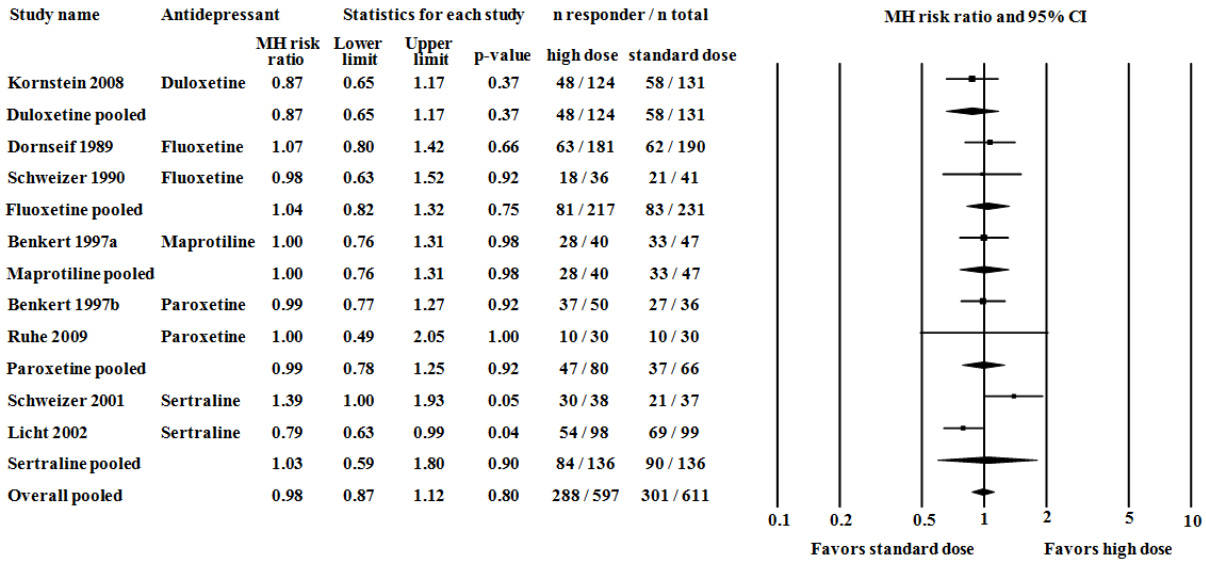
Overview of the single judgments for every item of the "risk of bias" tool of the Cochrane Collaboration [2]. A plus in a green circle displays the rating "low risk of bias", a question mark in a yellow circle illustrates "unclear risk of bias", and a minus in a red circle represents the judgment "high risk of bias".

Online suppl. fig. 3. Overview regarding the "risk of bias" judgments.



The graph illustrates the judgments for each "risk of bias" item presented as percentages across all included studies. The green part of the vertical-bar graph indicates the rating "low risk of bias", whereas the yellow part illustrates the judgment "unclear risk of bias" and the red one "high risk of bias".

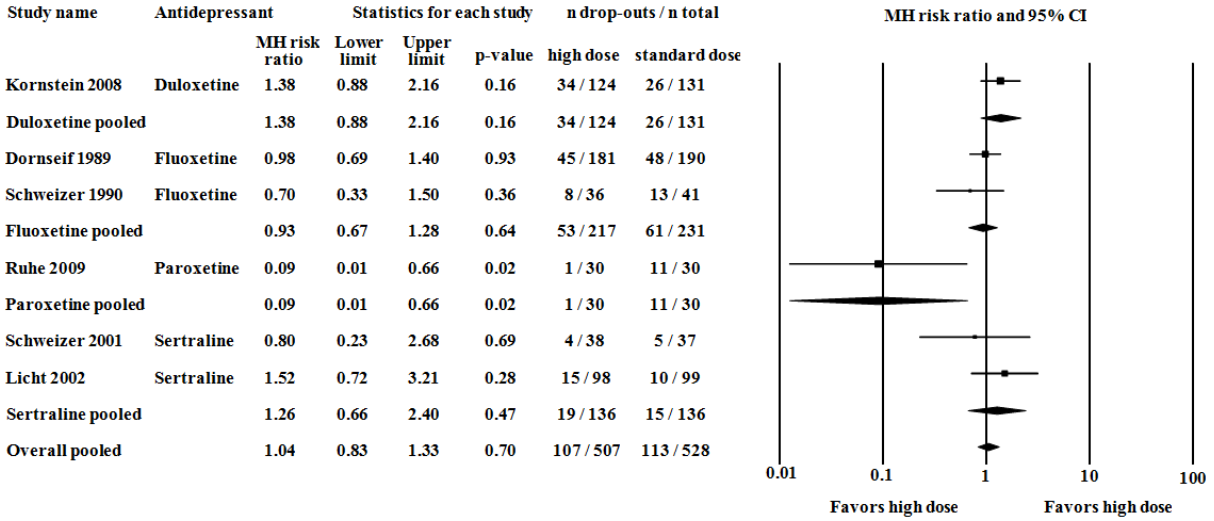
Online suppl. fig. 4. Effect sizes for the number of participants with treatment response (response rates).



Study name	Antidepressant	Statistics for each study				n responder / n total	
		MH risk ratio	Lower limit	Upper limit	p-value	high dose	standard dose
Kornstein 2008	Duloxetine	0.87	0.65	1.17	0.37	48 / 124	58 / 131
Duloxetine pooled		0.87	0.65	1.17	0.37	48 / 124	58 / 131
Dornseif 1989	Fluoxetine	1.07	0.80	1.42	0.66	63 / 181	62 / 190
Schweizer 1990	Fluoxetine	0.98	0.63	1.52	0.92	18 / 36	21 / 41
Fluoxetine pooled		1.04	0.82	1.32	0.75	81 / 217	83 / 231
Benkert 1997a	Maprotiline	1.00	0.76	1.31	0.98	28 / 40	33 / 47
Maprotiline pooled		1.00	0.76	1.31	0.98	28 / 40	33 / 47
Benkert 1997b	Paroxetine	0.99	0.77	1.27	0.92	37 / 50	27 / 36
Ruhe 2009	Paroxetine	1.00	0.49	2.05	1.00	10 / 30	10 / 30
Paroxetine pooled		0.99	0.78	1.25	0.92	47 / 80	37 / 66
Schweizer 2001	Sertraline	1.39	1.00	1.93	0.05	30 / 38	21 / 37
Licht 2002	Sertraline	0.79	0.63	0.99	0.04	54 / 98	69 / 99
Sertraline pooled		1.03	0.59	1.80	0.90	84 / 136	90 / 136
Overall pooled		0.98	0.87	1.12	0.80	288 / 597	301 / 611

Comparison: high-dose treatment versus standard-dose treatment with antidepressants. The forest plot illustrates the Mantel-Haenszel risk ratios with the associated 95% confidence intervals (CIs). Numerical values greater than 1 indicate a higher rate of responders in the high-dose study group than in the control group receiving the standard-dose treatment. Statistical significance is present if the 95% CI does not include the numerical value of 1, and/or if the p-value of the comparison is <.05. Overall heterogeneity: I^2=22%, p=.26. Abbreviations: CI = confidence interval; MH = Mantel-Haenszel; n = number of participants.

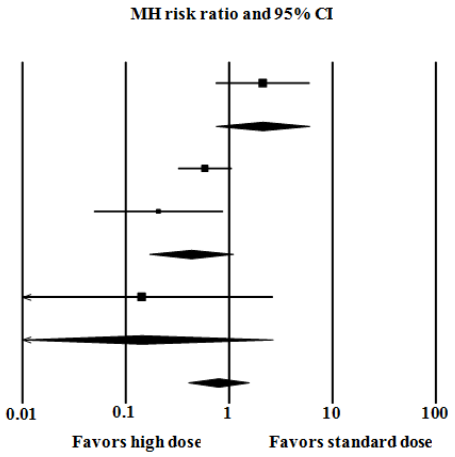
Online suppl. fig. 5. Effect sizes for the number of drop-outs due to any reason (all-cause discontinuation).



Comparison: high-dose treatment versus standard-dose antidepressant treatment. The forest plot illustrates the Mantel-Haenszel risk ratios with the associated 95% confidence intervals (CIs). Numerical values greater than 1 indicate a higher drop-out rate in the high-dose study group than in the control group. Overall heterogeneity: I^2=48%, p=.08. Abbreviations: CI = confidence interval; MH = Mantel-Haenszel; n = number of participants.

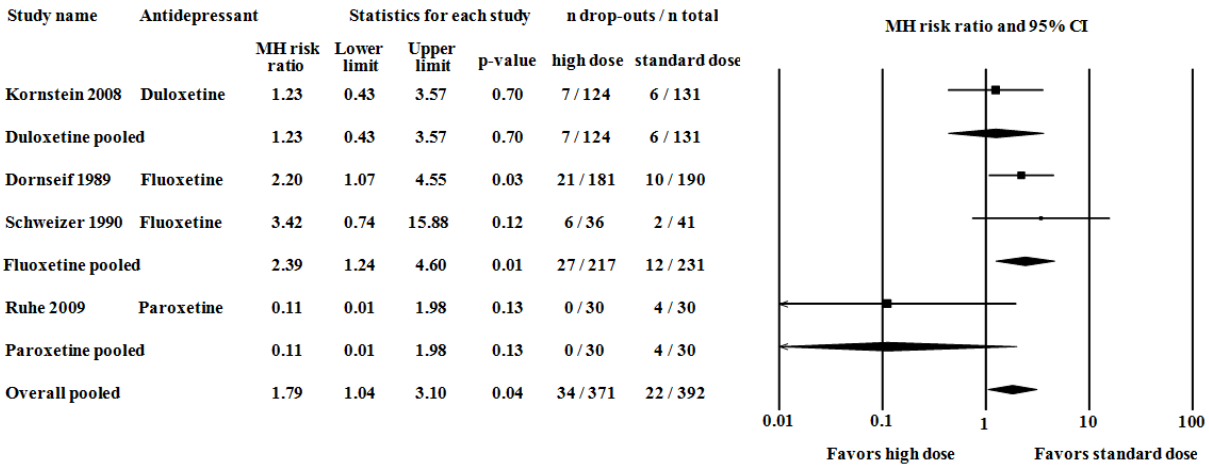
Online suppl. fig. 6. Effect sizes for drop-outs due to inefficacy of treatment.

Study name	Antidepressant	Statistics for each study				n drop-outs / n total	
		MH risk ratio	Lower limit	Upper limit	p-value	high dose	standard dose
Kornstein 2008	Duloxetine	2.11	0.74	6.01	0.16	10 / 124	5 / 131
Duloxetine pooled		2.11	0.74	6.01	0.16	10 / 124	5 / 131
Dornseif 1989	Fluoxetine	0.58	0.32	1.06	0.08	15 / 181	27 / 190
Schweizer 1990	Fluoxetine	0.21	0.05	0.87	0.03	2 / 36	11 / 41
Fluoxetine pooled		0.43	0.17	1.09	0.08	17 / 217	38 / 231
Ruhe 2009	Paroxetine	0.14	0.01	2.65	0.19	0 / 30	3 / 30
Paroxetine pooled		0.14	0.01	2.65	0.19	0 / 30	3 / 30
Overall pooled		0.79	0.40	1.56	0.50	27 / 371	46 / 392



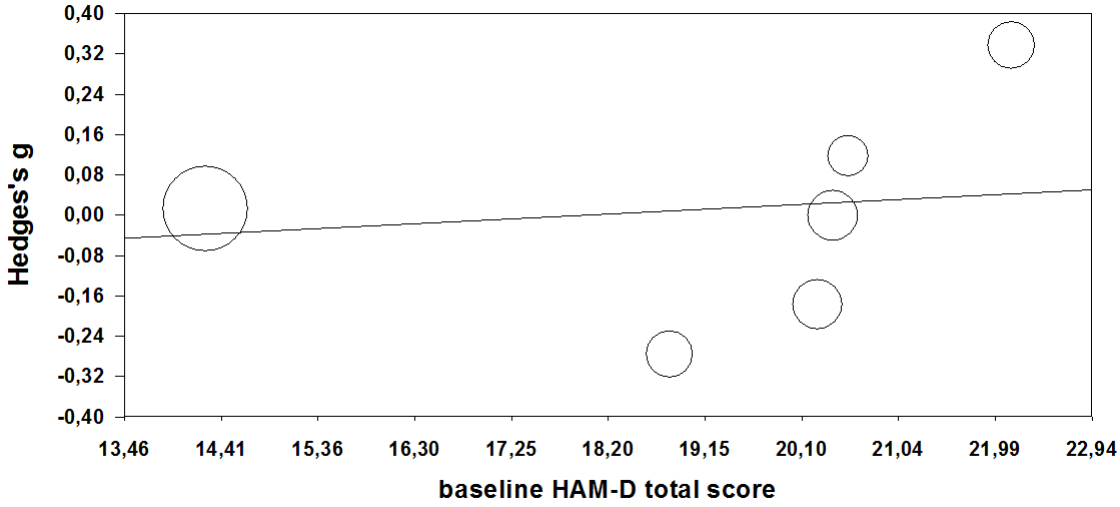
Outcome: Number of drop-outs due to inefficacy of treatment. Comparison: high-dose versus standard-dose treatment with antidepressants. The forest plot illustrates the Mantel-Haenszel risk ratios with the associated 95% confidence intervals (CIs). Numerical values >1 indicate a higher drop-out rate in the high-dose study group than in the control group receiving the standard dose treatment. Abbreviations: CI = confidence interval; MH = Mantel-Haenszel; n = number of participants.

Online suppl. fig. 7. Effect sizes for drop-outs due to adverse effects.



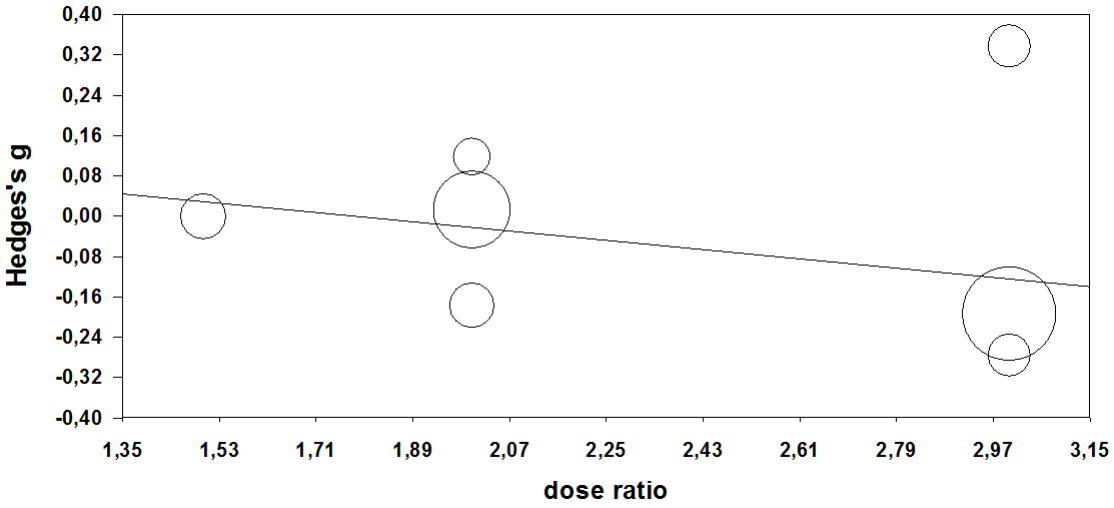
Outcome: Number of drop-outs due to adverse effects. Comparison: high-dose versus standard-dose treatment with antidepressants. The forest plot illustrates the Mantel-Haenszel risk ratios with the associated 95% confidence intervals (CIs). Numerical values >1 indicate a higher drop-out rate in the high-dose study group than in the control group. Abbreviations: CI = confidence interval; MH = Mantel-Haenszel; n = number of participants.

Online suppl. fig. 8. Meta-regression examining the impact of the mean baseline HAM-D-17 total score on effect sizes.



This figure displays the unrestricted maximum-likelihood meta-regression with mean baseline HAM-D-17 total scores as continuous moderator variable. Hedges g refers to the effect sizes of the primary outcome (mean HAM-D total score change). The circle size reflects the weight a study obtained in this meta-regression. Slope=0.01, 95% CI: -0.04 to 0.06; p=.69.

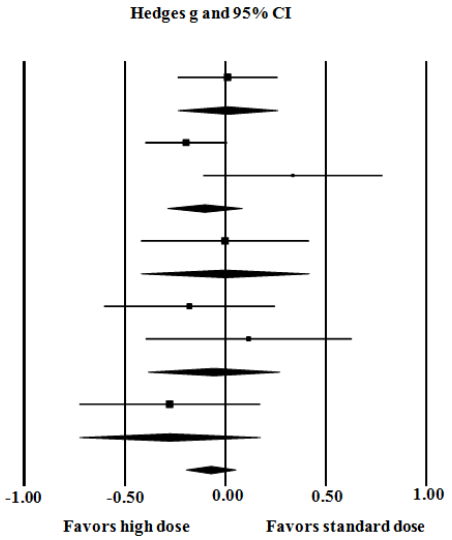
Online suppl. fig. 9. Meta-regression investigating the influence of dose ratios of the antidepressant drugs on effect sizes.



This figure illustrates the unrestricted maximum-likelihood meta-regression with the dose ratios of the antidepressant drugs (high dose in the intervention group / dose in the control group) as continuous moderator variable. Hedges g refers to the effect sizes of the primary outcome (mean HAM-D total score change). The circle size reflects the weight a study obtained in this meta-regression. Slope=-0.10, 95% CI: -0.32 to 0.12; p=.36.

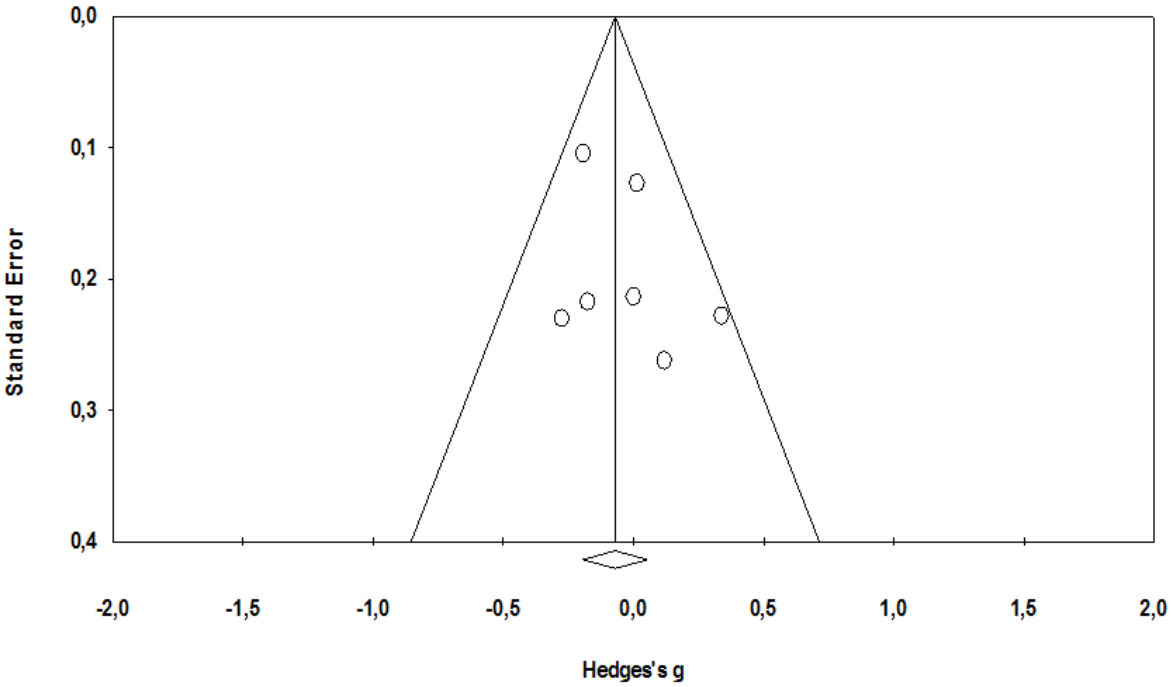
Online suppl. fig. 10. Sensitivity analysis with application of a fixed-effects model.

Study name	Antidepressant	Statistics for each study				
		Hedges g	Lower limit	Upper limit	p-value	n
Kornstein 2008	Duloxetine	0.01	-0.24	0.26	0.92	248
Duloxetine pooled		0.01	-0.24	0.26	0.92	248
Dornseif 1989	Fluoxetine	-0.19	-0.40	0.01	0.06	369
Schweizer 1990	Fluoxetine	0.34	-0.11	0.78	0.14	77
Fluoxetine pooled		-0.10	-0.29	0.08	0.29	446
Benkert 1997a	Maprotiline	0.00	-0.42	0.42	1.00	87
Maprotiline pooled		0.00	-0.42	0.42	1.00	87
Benkert 1997b	Paroxetine	-0.18	-0.60	0.25	0.42	86
Ruhe 2009	Paroxetine	0.12	-0.39	0.63	0.65	57
Paroxetine pooled		-0.06	-0.38	0.27	0.74	143
Schweizer 2001	Sertraline	-0.28	-0.73	0.17	0.23	75
Sertraline pooled		-0.28	-0.73	0.17	0.23	75
Overall pooled		-0.07	-0.19	0.05	0.26	999



The forest plot displays the effect sizes for the sensitivity analysis of the primary outcome (mean HAM-D total score change): Application of a fixed effects model instead of the random effects model for the pooling of the individual trials. Comparison: high-dose versus standard-dose treatment with antidepressants. The forest plot illustrates the standardized mean differences based on Hedges g with the corresponding 95% confidence intervals (CI). Numerical values <0 indicate a larger HAM-D reduction in the high-dose group than in the control group. Abbreviations: CI = confidence interval; n = number of participants.

Online suppl. fig. 11. Funnel-plot visualization.



In the funnel plot, the effects sizes (Hedges g) for the primary outcome (mean HAM-D change) are plotted against the standard errors (referring to the primary outcome of mean HAM-D change). Based on the largely symmetrical arrangement of the single trials around the pooled effect size as equivalence line, there is no evidence for the presence of publication bias. Additionally, the non-significant Egger's regression intercept test (p=.36) indicates absence of a publication bias.

References

1 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. BMJ 2009;339:b2535.

2 Higgins J, Green S: Cochrane handbook for systematic reviews of interventions, version 5.0.1 [updated online march 2011]. Chichester, Wiley & Sons, 2011.