Supplementary Online Content

Locher C, Koechlin H, Zion SR, et al. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. *JAMA Psychiatry*. Published online August 30, 2017. doi:10.1001/jamapsychiatry.2017.2432

This supplementary material has been provided by the authors to give readers additional information about their work.

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eAppendix 1. Search Terms

PubMed

"Depressive Disorder"[mesh] OR depression*[tiab] OR depressive[tiab] OR dysthymic[tiab] OR dysthymia*[tiab] OR "Anxiety Disorders"[Mesh] OR "Anxiety"[Mesh:noexp] OR anxiety[tiab] OR obsessive-compulsive[tiab] OR ocd[tiab] OR anankastic[tiab] OR phobic[tiab] OR phobia*[tiab] OR panic[tiab] OR stress disorder*[tiab] OR post traumatic stress[tiab] OR posttraumatic stress[tiab] OR post traumatic symptom*[tiab] OR posttraumatic symptom*[tiab] OR ptsd[tiab]

"Serotonin Uptake Inhibitors"[Mesh] OR "Serotonin Uptake Inhibitors"[pa] OR serotonin reuptake inhibitor*[tiab] OR serotonin uptake inhibitor*[tiab] OR SSRI*[tiab] OR SRI*[tiab] OR serotonin norepinephrine reuptake inhibitor*[tiab] OR serotonin norepinephrine uptake inhibitor*[tiab] OR SNRI* OR venlafaxin*[tiab] OR desvenlafaxin*[tiab] OR effexor[tiab] OR pristiq[tiab] OR milnacipran[tiab] OR levomilnacipran[tiab] OR fetzima[tiab] OR savella[tiab] OR duloxetin*[tiab] OR cymbalta[tiab] OR sibutramine[tiab] OR citalopram[tiab] OR celexa[tiab] OR escitalopram[tiab] OR lexapro[tiab] OR fluoxetin*[tiab] OR prozac[tiab] OR sarafem[tiab] OR symbyax[tiab] OR fluvoxamin*[tiab] OR luvox[tiab] OR paroxetin*[tiab] OR paxil[tiab] OR brisdelle[tiab] OR sertralin*[tiab] OR zoloft[tiab]

Child[MeSH Terms] OR Pediatrics[MeSH] OR child*[tiab] OR adolescen*[tiab] OR toddler*[tiab] OR teen*[tiab] OR boy[tiab] OR boys[tiab] OR girl*[tiab] OR pediatric[tiab] OR paediatric[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR schoolchild*[tiab] OR school age*[tiab] OR preschool*[tiab] OR kindergar*[tiab] OR primary school*[tiab] OR secondary school*[tiab] OR elementary school*[tiab] OR high school*[tiab] OR highschool*[tiab] OR youth*[tiab]

random*[tw] OR blind*[tiab] OR placebo*[tiab] OR trial[tiab] OR untreated[tiab] OR "not treated"[tiab] OR sham[tiab]

Embase

'depression'/exp OR depression*:ab,ti OR depressive:ab,ti OR dysthymic:ab,ti OR dysthymia*:ab,ti OR 'anxiety disorder'/exp OR 'anxiety'/de OR anxiety:ab,ti OR obsessive-compulsive:ab,ti OR ocd:ab,ti OR anankastic:ab,ti OR phobic:ab,ti OR phobia*:ab,ti OR panic:ab,ti OR (stress NEXT/1 disorder*):ab,ti OR (('post traumatic' OR posttraumatic) NEXT/1 (stress OR symptom*)):ab,ti OR ptsd:ab,ti

'serotonin uptake inhibitor'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR (('serotonin reuptake' OR 'serotonin uptake' OR 'serotonin norepinephrine reuptake' OR 'serotonin norepinephrine uptake') NEXT/1 inhibitor*):ab,ti OR ssri*:ab,ti OR snri*:ab,ti OR venlafaxin*:ab,ti OR desvenlafaxin*:ab,ti OR effexor:ab,ti OR pristiq:ab,ti OR milnacipran:ab,ti OR levomilnacipran:ab,ti OR fetzima:ab,ti OR savella:ab,ti OR duloxetin*:ab,ti OR cymbalta:ab,ti OR sibutramine:ab,ti OR citalopram:ab,ti OR celexa:ab,ti OR escitalopram:ab,ti OR lexapro:ab,ti OR fluoxetin*:ab,ti OR prozac:ab,ti OR sarafem:ab,ti OR symbyax:ab,ti OR fluvoxamin*:ab,ti OR luvox:ab,ti OR paroxetin*:ab,ti OR paxil:ab,ti OR brisdelle:ab,ti OR sertralin*:ab,ti OR zoloft:ab,ti

'child'/exp AND 'pediatrics'/exp OR child*:ab,ti OR adolescen*:ab,ti OR toddler*:ab,ti OR teen*:ab,ti OR boy:ab,ti OR boys:ab,ti OR girl*:ab,ti OR pediatric:ab,ti OR paediatric:ab,ti OR puber*:ab,ti OR pubescen*:ab,ti OR prepubescen*:ab,ti OR prepuberty*:ab,ti OR schoolchild*:ab,ti OR (school NEXT/1 age*):ab,ti OR preschool*:ab,ti OR kindergar*:ab,ti OR ((primary OR secondary OR elementary OR high) NEXT/1 school*):ab,ti OR highschool*:ab,ti OR youth*:ab,ti

random*:ab,de,ti OR blind*:ab,ti OR placebo*:ab,ti OR trial:ab,ti OR untreated:ab,ti OR 'not treated':ab,ti OR sham:ab,ti

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PsycInfo

DE ("Major Depression" OR "Dysthymic Disorder" OR "Endogenous Depression" OR "Reactive Depression" OR "Recurrent Depression" OR "Treatment Resistant Depression" OR "Anxiety" OR "AcuteStress Disorder" OR "Generalized Anxiety Disorder" OR "Obsessive Compulsive Disorder" OR "Panic Disorder" OR "Phobias" OR "Posttraumatic Stress Disorder" OR "Panic Disorder" OR "Panic" OR "Panic Attack") OR TI (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive- compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd) OR AB (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive- compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd)

DE ("Serotonin Reuptake Inhibitors" OR "Chlorimipramine" OR "Citalopram" OR "Fluoxetine" OR "Fluvoxamine" OR "Paroxetine" OR "Zimeldine" OR "Serotonin Norepinephrine Reuptake Inhibitors" OR "Venlafaxine") OR TI ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft) OR AB ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft)

AG ("Childhood (birth-12 yrs)") OR TI (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*) OR AB (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*)

DE (random*) OR TI (random* OR placebo* OR trial OR untreated OR sham) OR AB (random* OR placebo* OR trial OR untreated OR sham)
Note: "not treated" is handled as a stop word so all records with treated are retrieved.

Cochrane Central

TI ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft) OR AB ("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft)

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TI (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd) OR AB (depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd)

TI (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*) OR AB (child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*)

Web of Science

TS=("serotonin reuptake inhibitor*" OR "serotonin uptake inhibitor*" OR SSRI* OR SRI* OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin norepinephrine uptake inhibitor*" OR SNRI* OR venlafaxin* OR desvenlafaxin* OR effexor OR pristiq OR milnacipran OR levomilnacipran OR fetzima OR savella OR duloxetin* OR cymbalta OR sibutramine OR citalopram OR celexa OR escitalopram OR lexapro OR fluoxetin* OR prozac OR sarafem OR symbyax OR fluvoxamin* OR luvox OR paroxetin* OR paxil OR brisdelle OR sertralin* OR zoloft)

TS=(depression* OR depressive OR dysthymic OR dysthymia* OR anxiety OR "obsessive-compulsive" OR ocd OR anankastic OR phobic OR phobia* OR panic OR "stress disorder*" OR "post traumatic stress" OR "posttraumatic stress" OR "post traumatic symptom*" OR "posttraumatic symptom*" OR ptsd)

TS=(child* OR adolescen* OR toddler* OR teen* OR boy OR boys OR girl* OR pediatric OR paediatric OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR schoolchild* OR "school age*" OR preschool* OR kindergar* OR "primary school*" OR "secondary school*" OR "elementary school*" OR "high school*" OR highschool* OR youth*)

TS=(random* OR placebo* OR trial OR untreated OR sham)

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eAppendix 2. Moderator Analyses

Methods and Results for the Univariate Analyses – Continuous Variables

Methods: Moderator analyses were conducted for six continuous moderators (treatment duration, publication year, illness duration, age of onset, number of sites, and baseline severity) for both the combined disorders group and individual disorders groups. We examined whether specific characteristics of the studies were related to the effect sizes (i.e., drug-placebo differences) in univariate analyses. Continuous variables were analyzed with a meta-regression analysis using method-of-moments analyses in a random- effects model. The Z-statistic was used to test the significance of the slope. As various scales were used to assess baseline severity, we standardized the baseline and outcome values by dividing the mean values by the SD.

Results: The relationship between effect size and publication year was significant in the combined analyses (Z=-2.36, p=.02), as well as in the DD subgroup analyses (Z=-2.26, p=.02), with recently published studies yielding smaller antidepressant-placebo differences. Further, the relationship between effect size and illness duration was significant in the combined analyses (Z=2.89, p=.004), indicating that children with a longer duration of illness exhibit greater response to antidepressants compared to placebo. Finally, number of sites was found to be significantly correlated to effect size in the combined analyses (Z=-2.98, p=.003), as well as in the DD subgroup analyses (Z=-2.16, p<.03), and the OCD subgroup analyses (Z=-2.16, p=.03), with number of study sites negatively associated with magnitude of differences between antidepressants and placebo. See eTable 4 for all calculations.

Methods and Results for the Univariate Analyses – Categorical Variables

Methods: Moderator analyses were conducted for four categorical moderators (placebo lead-in, comorbidity, region, and primary funding source) for both the combined disorders group and individual disorders groups. Categorical variables were analyzed using a mixed-effects model We examined whether specific characteristics of the studies were related to the effect sizes (i.e., drug-placebo differences) in univariate analyses.

Results: The relationship between effect size and primary funding source was significant in the combined analyses (p = .02), as well as in the DD subgroup analyses (p = .02). In both cases, studies that were funded by industry yielded significantly smaller effect sizes than those that reported public sources of funding only (e.g., NIMH). See eTable 5 for further details.

Methods and Results for the Multivariate Metaregression Analysis

Methods: Given the relatively large number of moderator analyses, we decided to conduct a multivariate meta-regression. Effect sizes (i.e., dependent variable) were weighted by the sample size divided by s2 (i.e., n/var)[1]. Multivariate regression analyses were conducted in SPSS (Version 21.0.0.2).

This approach is in line with the methods adopted by Cuijpers[2-5]. The model indicates the significance of each potential moderator while controlling for the others. To avoid collinearity among the predictors of the regression model, we first tested whether high correlations (i.e., correlations higher than 0.60) were found among the moderators that could be entered into the model. Three variables were found to have correlations higher than 0.60: the funding source correlated high with the number of sites (r = .698), treatment duration correlated high with illness duration (r = 0.62), and comorbidity correlated high with the number of sites (r = -0.75). We decided to use the number of sites (not funding source or comorbidity) and illness duration (not treatment duration) as predictors in the model. All remaining variables (i.e., illness duration, publication year, baseline severity, number of sites, age of onset, placebo lead-in, and study location) were included as predictors in the model.

Results: None of the moderators were found to be significant in the multivariate meta-regression with weighted effect sizes. All results can be found in eTable 6.

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eAppendix 3. Study Heterogeneity Stratified by Disorder

OCD: The eight studies exhibited no heterogeneity (Q=2.28, p=.07, I^2=0.00 r^{-2}=0.00). There was no evidence of asymmetry in a funnel plot. Neither the Begg's test nor the Egger's test yielded a significant result. The fail-safe N indicated that 43 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method lead to a very slight adjustment of Hedges' g (g=0.41, CI=0.26-0.55).

DD: The seventeen studies exhibited moderate heterogeneity (Q=20.28, p=.38, I^2=6.31, r^{-2}=0.00). There was some evidence of asymmetry in a funnel plot. Neither the Begg's test nor the Egger's test yielded a significant result. The fail-safe N indicated that 165 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method did not lead to an adjustment of Hedges' g.

AD: The ten studies exhibited moderate heterogeneity (Q=22.93, p=.01, I^2=56.40, r^{-2}=0.04). There was evidence of asymmetry in a funnel plot. Both the Begg's test and the Egger's test yielded a non-significant result (2-tailed p > .05). The fail-safe N indicated that 308 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method lead to a slight adjustment of the standard mean difference (g=0.53, CI=0.36- 0.70).

Across all studies: The combined analysis yielded low to moderate heterogeneity (Q=76.62, p<.001, I^2=47.79, r^{-2}=0.03).

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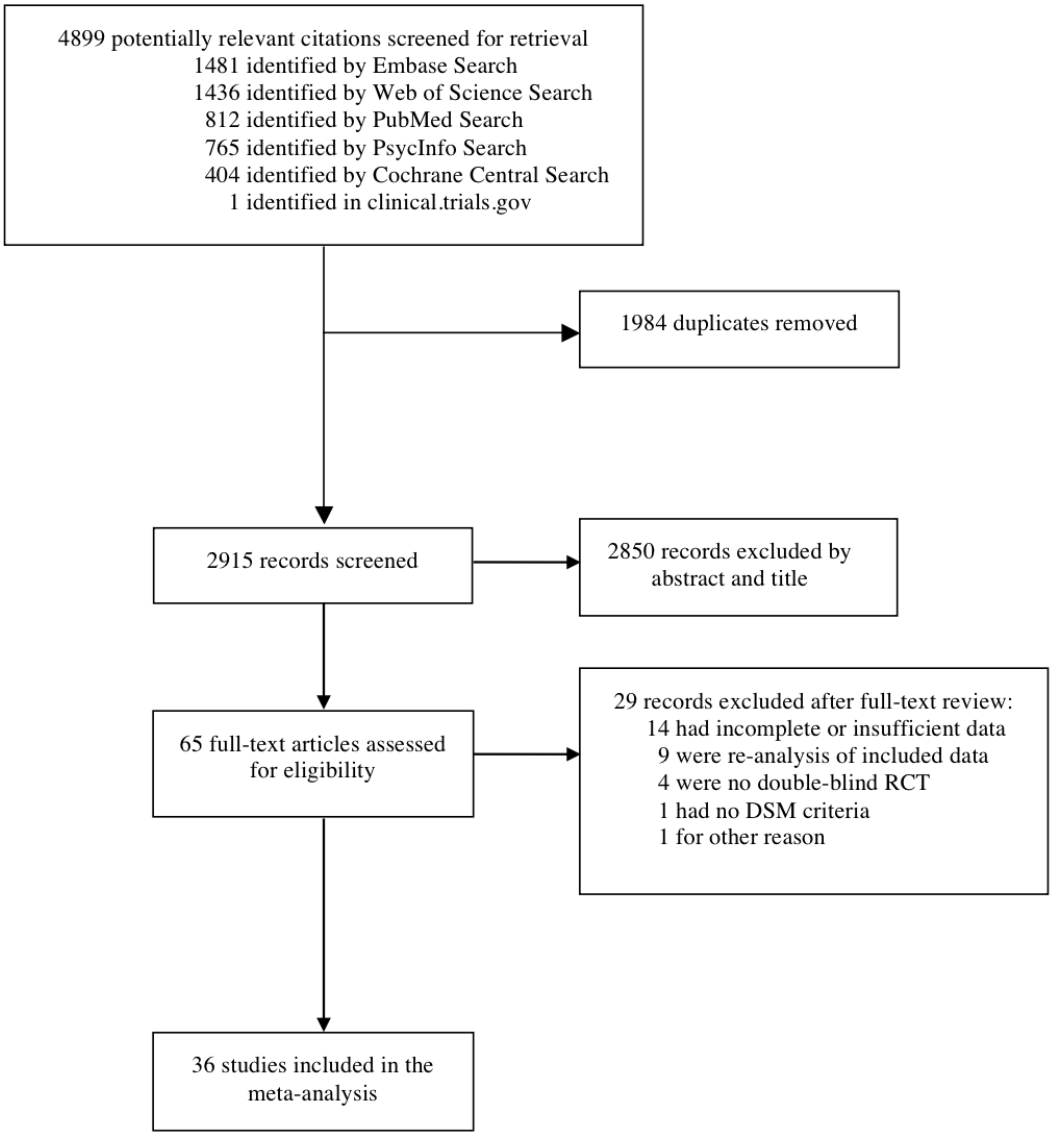
eFigure 1. Flow Chart



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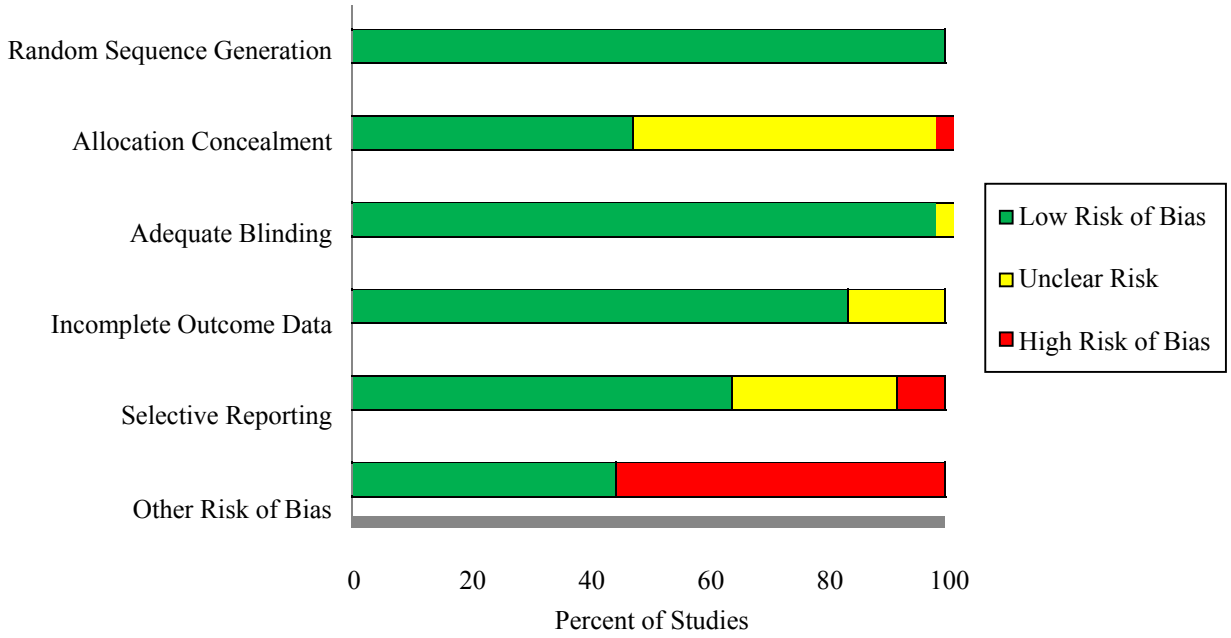
eFigure 2. Risk of Bias Assessment



Note: The large amount of high risk in the "other risk of bias" category was mainly due to per protocol analysis rather than intent-to-treat analysis.

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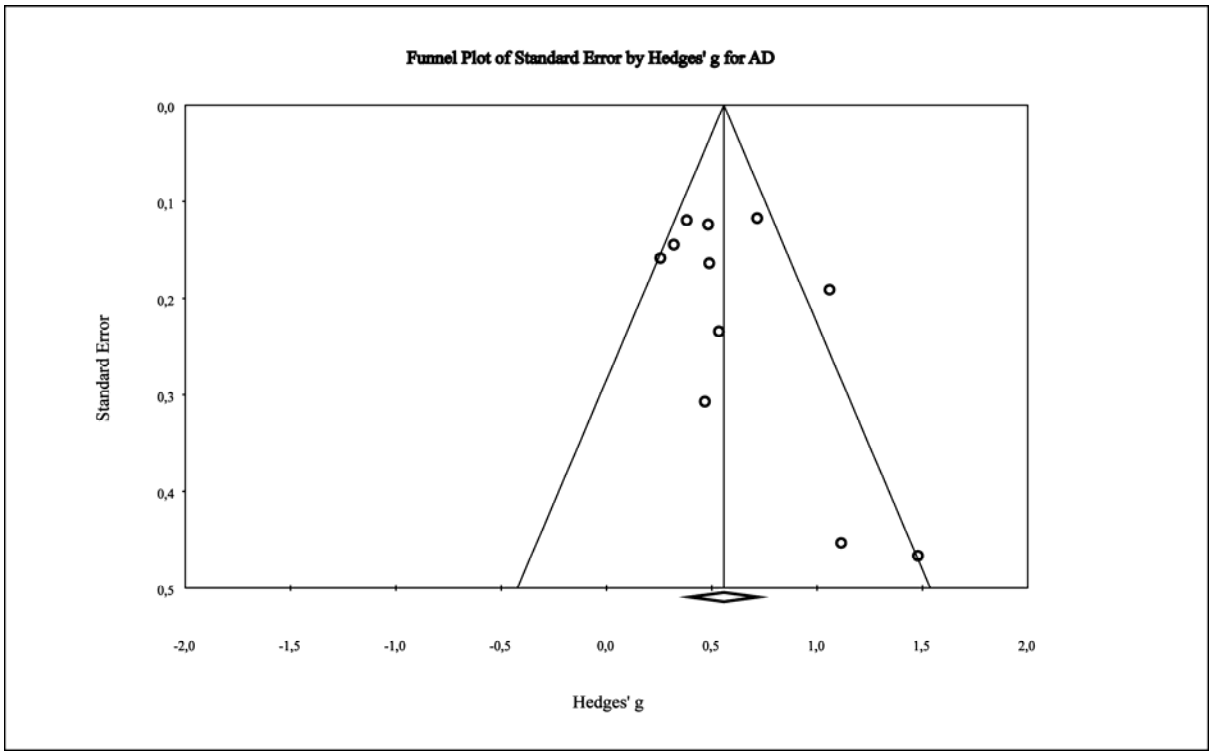
eFigure 3. Funnel Plots Stratified by Disorder

Anxiety Disorders



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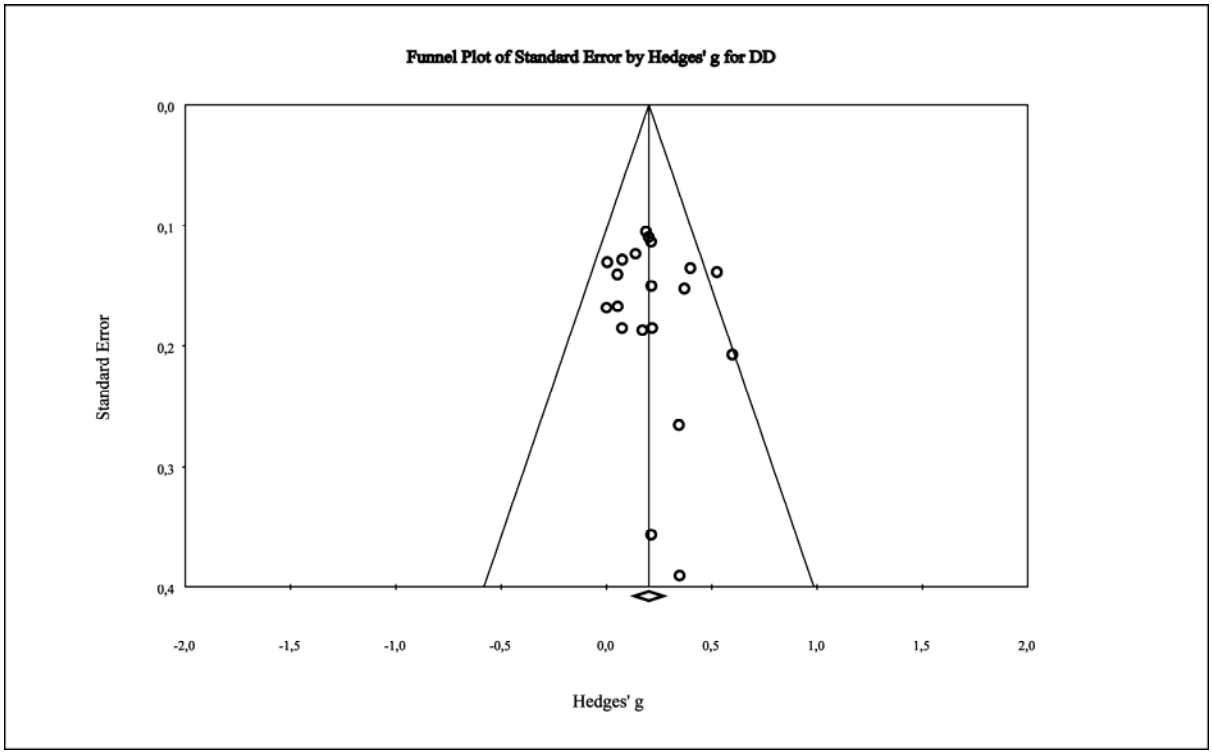
Depressive Disorder



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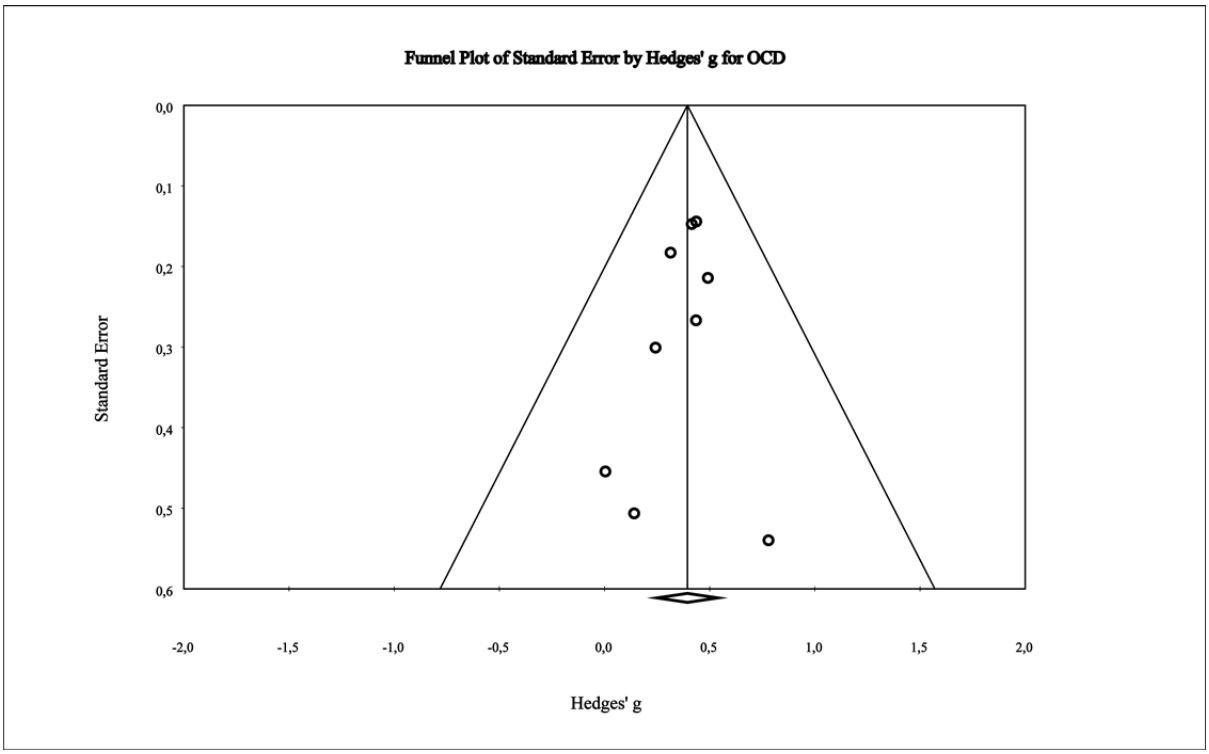
Obsessive-Compulsive Disorder



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eTable 1. Characteristics of Included Studies

Study	Dx	Tx Dur, Wk	Study N[c]	Primary Outcome	Intervention, mg/d	Mean Age, Y (SD)	%F	Length of Illness, M	Age of Onset, Y (SD)	Quality[k]	Funding	Location
Depressive Disorder												
Simeon et al,[6] 1990	MDD[a]	7	40	HAM-D	Fluoxetine 20 - 60	16	55	NR	NR	0.33	Industry	North America
Emslie et al,[7] 1997	MDD[a,b]	8	96	CDRS-R	Fluoxetine 20	12.35 (2.65)	46	18.40	10.80 (2.65)	0.78	Public	North America
Keller et al,[8] 2001[d]	MDD	8	180	HAM-D	Paroxetine 20 - 40	14.95 (1.60)	64	13.52	13.29 (2.56)	0.89	Industry	North America
Emslie et al,[9] 2002	MDD[b]	9	219	CDRS-R	Fluoxetine 20	12.70 (2.57)	49	14	10.33 (3.02)	0.89	Industry	North America
Wagner et al,[10] 2003	MDD	10	376	CDRS-R	Sertraline 50 - 200	6-17[e]	51	23.07	10.04	0.78	Industry	Inter-national
March et al,[11] 2004[d,h]	MDD	12	328	CDRS-R	Fluoxetine 10 - 40	14.60 (1.5)	55	40	NR	1.00	Public[i]	North America
Wagner et al,[12] 2004a	MDD	8	178	CDRS-R	Citalopram 20 - 40	12.10 (2.95)	63	27	9.80 (3.15)	0.78	Industry	North America
Berard et al,[13] 2006	MDD	12	286	MADRS	Paroxetine 20 - 40	15.60 (1.60)	67	NR	NR	0.89	Industry	Inter-national
Emslie et al,[14] 2006	MDD[a]	8	206	CDRS-R	Paroxetine 10 - 50	12.00 (2.97)	47	25.90	9.80 (3.30)	0.78	Industry	North America
von Knorring et al,[15] 2006	MDD	12	244	K-SADS-P	Citalopram 10 - 40	16 (1.00)	NR	NR	NR	0.44	Industry	Europe

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eTable 1. Characteristics of Included Studies (cont.)

Study	Dx	Tx Dur, Wk	Study N[c]	Primary Outcome	Intervention, mg/d	Mean Age, Y (SD)	%F	Length of Illness, M	Age of Onset, Y (SD)	Quality[k]	Funding	Location
Wagner et al,[16] 2006	MDD	8	268	CDRS-R	Escitalopram 10 - 20	12.30 (3.00)	52	25.80	10.15 (3.25)	0.67	Industry	North America
Emslie et al,[17] 2007	MDD	8	367	CDRS-R	Venlafaxine ER 37.50 - 225	12.25 (2.60)	46	21.13	NR	0.78	Industry	North America
Emslie et al,[18] 2009	MDD	8	316	CDRS-R	Escitalopram 10 - 20	14.60 (1.55)	59	16.10	12.35 (2.55)	0.67	Industry	North America
Findling et al,[19] 2009	MDD, Dys-thymia, DDNOS, SUD	8	34	CDRS-R	Fluoxetine 10 - 20	16.46 (1.08)	15	49.04	11.41 (2.50)	0.89	Industry	North America
PIR-112487,[20] 2011[j]	MDD[b]	8	56	CDRS-R	Paroxetine 10 - 40	14.59 (2.33)	61	NR	NR	0.56	Industry	Asia
Atkinson et al,[21] 2014	MDD[a, b]	10	337	CDRS-R	Duloxetine 60 - 120 Fluoxetine 20 - 40	13.20 (3.14)	52	NR	11.60	0.89	Industry	Inter-national
Emslie et al,[22] 2014	MDD[a, b]	10	463	CDRS-R	Duloxetine 60 Duloxetine 30 Fluoxetine 20	12.98 (2.98)	51	NR	NR	0.78	Industry	Inter-national

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eTable 1. Characteristics of Included Studies (cont.)

Study	Dx	Tx Dur, Wk	Study N[c]	Primary Outcome	Intervention, mg/d	Mean Age, Y (SD)	%F	Length of Illness, M	Age of Onset, Y (SD)	Quality[k]	Funding	Location
Anxiety Disorder												
RUPP,[23] 2001	SP, SAD, GAD	8	128	PARS	Fluvoxamine 50 - 300	10.30 (2.95)	49	NR	NR	0.67	Public / Industry	North America
Rynn et al,[24] 2001	GAD	9	22	HAM-A	Sertraline 25 - 50	11.70 (3.90)	23	>12	NR	0.67	Public	North America
Birmaher et al,[25] 2003	SAD, SP, GAD, SM PH, PD	12	74	PARS[f]	Fluoxetine 10 - 20	11.80 (2.80)	54	62.70	NR	0.78	Public[i]	North America
Wagner et al,[26] 2004b	SP	16	322	LSAS-CA[f]	Paroxetine 10 - 50	13.10 (2.77)	49	NR	NR	0.89	Industry	Inter-national
March et al,[27] 2007	SP	16	293	SAS-CA	Venlafaxine ER 37.50 - 225	13.60 (2.55)	57	58	NR	1.00	Industry	North America
Rynn et al,[28] 2007[g]	GAD	8	323	K-SADS-GA	Venlafaxine 37.50 - 225	11.30 (2.86)	41	39.12	NR	0.78	Industry	North America
Walkup et al,[29] 2008[d, h]	SAD, GAD, SP	12	349	PARS	Sertraline 25 - 200	10.70 (2.80)	50	NR	NR	1.00	Public[i]	North America
da Costa et al,[30] 2013[d]	GAD, SAD, SP	12	21	MASC[f]	Fluoxetine 10 - 60	11.50	48	NR	NR	0.56	Public	South America
Strawn et al,[31] 2015	GAD	10	272	PARS	Duloxetine 30 - 120	12.40 (2.95)	53	52.20	NR	1.00	Public / Industry	Inter-national
Melvin et al,[32] 2016	SP, PH, GAD, SAD, PD	10	42	RCMAS[f]	Fluoxetine + CBT 10 - 60	13.60 (1)	45	NR	NR	0.89	Public[i]	Australia

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eTable 1. Characteristics of Included Studies (cont.)

Study	Dx	Tx Dur, Wk	Study N[c]	Primary Outcome	Intervention, mg/d	Mean Age, Y (SD)	%F	Length of Illness, M	Age of Onset, Y (SD)	Quality[k]	Funding	Location
Obsessive-Compulsive Disorder												
Riddle et al,[33] 1992	OCD	8	14	CY-BOCS[f]	Fluoxetine 20	11.80 (2.30)	57	NR	NR	0.44	Public[i]	North America
March et al,[34] 1998	OCD	12	189	CY-BOCS[f]	Sertraline 25 - 200	12.60 (6-17)[e]	NR	45.60	NR	0.78	Industry	North America
Geller et al,[35] 2001	OCD	13	103	CY-BOCS	Fluoxetine 20 - 60	11.40 (2.90)	37	>6	NR	0.89	Industry	North America
Riddle et al,[36] 2001[d]	OCD	10	120	CY-BOCS	Fluvoxamine 50 - 200	13.03	47	43.20	NR	0.67	Industry	North America
Liebowitz et al,[37] 2002[d]	OCD	8	43	CY-BOCS	Fluoxetine 20 - 80	12.65 (2.19)	42	≥12	NR	1.00	Public / Industry	North America
POTS,[38] 2004[h]	OCD	12	84	CY-BOCS	Sertraline 25-200	12 (2.70)	45	NR	NR	1.00	Public[i]	North America
Geller et al,[39] 2004	OCD	10	207	CY-BOCS	Paroxetine 10 - 50	11.30 (3.00)	42	50.40	7.50 (3.09)	1.00	Industry	North America
Storch et al,[40] 2013	OCD	18	47	CY-BOCS	Sertraline (Reg) + CBT Sertraline (Slow) + CBT 25 - 200	11.90 (3.47)	38	NR	NR	0.67	Public[i]	North America

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eTable 1. Characteristics of Included Studies (cont.)

Study	Dx	Tx Dur, Wk	Study N[c]	Primary Outcome	Intervention, mg/d	Mean Age, Y (SD)	Female %	Length of Illness, M	Age of Onset, Y (SD)	Quality[k]	Funding	Location
Posttraumatic Stress Disorder												
Robb et al,[41] 2010	PTSD	10	131	UCLA-PTSD	Sertraline 50 - 200	10.98 (1.75)	60	29.40	NR	0.78	Industry	North America

Abbreviations: DDNOS, Depressive Disorder Not Otherwise Specified; Dx, diagnosis; GAD, Generalized Anxiety Disorder; M, months; MDD, Major Depressive Disorder; NR, not reported, OCD, Obsessive Compulsive Disorder; PD, Panic Disorder; PH, Specific Phobia; SAD, Separation Anxiety Disorder; SD, Standard Deviation; SM, Selective Mutism; SP, Social Phobia; SUD, Substance Use Disorder; Tx Dur, treatment duration; Wk, weeks; Y, years.

[a] Without psychotic features.

[b] Single episode or recurrent.

[c] N included in our analysis. Some studies included additional arms (i.e., tricyclic antidepressant, CBT alone, etc.) that were not extracted.

[d] Only SSRI or SNRI treatment arms from acute treatment phase / pre-crossover phase extracted as per protocol.

[e] Range. Mean (SD) not available.

[f] Primary outcome not specified or data not usable; most common measure for which data was available was chosen.

[g] Two trials. Analyses broken down by study.

[h] Additional arm (antidepressant + CBT) was not extracted.

[i] Study medication and matching placebo provided by the drug manufacturer.

[j] Unpublished Study.

[k] Based on adequacy of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, usage of observer-rated outcomes, completeness of outcome data, specification of main outcomes a priori, reporting on all outcomes, and conduction of ITT-analyses. Individual items were summed and divided by the total number of applicable items to produce a total score ranging from 0 to 1, where higher scores denote greater methodological quality.

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eTable 2. Study Heterogeneity

Drug	Treatment Arms	Hedges g	95% CI	SE	p-Value	Q-value	p-Value	I^2	Ta
Stratified Between Drug									
Citalopram	2	0.18	-0.18 - 0.54	0.18	.33	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Escitalopram	2	0.18	0.01 - 0.34	0.08	.03	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Fluoxetine	13	0.38	0.26 - 0.51	0.06	<0.001	13.17	.36	8.90	0.01
Fluvoxamine	2	0.68	-0.05 - 1.41	0.37	.07	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Paroxetine	6	0.31	0.07 - 0.54	0.12	.01	19.83	.001	74.78	0.06
Sertraline	8	0.31	0.15 - 0.47	0.08	<.001	9.38	.23	25.37	0.01
Venlafaxine	4	0.31	0.18 - 0.44	0.07	<.001	2.66	.45	0.00	0.00
Duloxetine	4	0.24	0.06 - 0.46	0.16	.04	5.91	.12	49.20	0.03
Stratified Within Drug									
Citalopram	2	1.78	1.56 - 2.04	0.12	<.001	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Escitalopram	2	1.68	1.48 - 1.87	0.10	<.001	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Fluoxetine	13	1.73	1.32 - 2.13	0.21	<.001	100.36	<.001	88.05	0.45
Fluvoxamine	2	1.22	0.41 - 2.02	0.41	.003	N/A[a]	N/A[a]	N/A[a]	N/A[a]
Paroxetine	6	1.46	1.31 - 1.61	0.08	<.001	7.19	.21	30.45	0.01
Sertraline	8	1.38	1.02-1.73	0.18	<.001	37.54	<.001	81.35	0.18
Venlafaxine	4	1.77	1.59-1.95	0.09	<.001	3.71	.29	19.15	0.01
Duloxetine	4	1.95	1.73-2.18	0.11	<.001	5.17	.16	41.97	0.02

[a]Heterogeneity was not assessed due to the low number of studies.

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eTable 3. Adverse Events

eTable 3a. Mean Percentages and Numbers of TEAEs

	Reporting Method 1[a]			Reporting Method 2[b]		
Intervention	No. Trials	Mean Percentage Drug	Mean Percentage Placebo	No. Trials	Mean Number Drug	Mean Number Placebo
SSRI vs. Placebo	19	66.89%	56.84%	24	0.14	0.09
SNRI vs. Placebo	7	62.09%	57.99%	2	0.13	0.09

[a]Percent of patients reporting TEAEs.
[b]Mean number of TEAEs per patient across all reported symptoms.

eTable 3b. Mean Percentages of Discontinuation of Study due to TEAEs and SAEs and Mean Percentages of SAEs

	Discontinuation[c]			SAEs[d]		
Intervention	No. Trials	Mean Percentage Drug	Mean Percentage Placebo	No. Trials	Mean Percentage Drug	Mean Percentage Placebo
SSRI vs. Placebo	27	6.83%	3.46%	17	6.24%	3.42%
SNRI vs. Placebo	6	6.80%	3.62%	7	4.75%	2.17%

[c]Percent of patients who discontinued the study due to TEAEs and SAEs.
[d]Percent of patients reporting SAEs.

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eTable 4. Continuous Univariate Moderator Analyses

Moderator	Z-Value	p-Value
	Overall	
Treatment Duration	0.57	.57
Publication Year	-2.36	.02
Baseline Severity	0.20	.84
Number of Sites	-2.98	.003
Illness Duration	2.89	.004
Age of Onset	-1.11	.27
	Depressive Disorders	
Treatment Duration	-1.12	.26
Publication Year	-2.26	.02
Baseline Severity	1.21	.23
Number of Sites	-2.16	.03
Illness Duration	-0.01	1.00
Age of Onset	-0.31	.76
	Obsessive-Compulsive Disorder	
Treatment Duration	-0.47	.64
Publication Year	-0.88	.38
Baseline Severity	-0.33	.74
Number of Sites	-0.50	.62
Illness Duration	0.45	.65
Age of Onset	*N/A*[a]	
	Anxiety Disorders	
Treatment Duration	-0.55	.58
Publication Year	-1.90	.06
Baseline Severity	-1.18	.24
Number of Sites	-1.84	.07
Illness Duration	1.62	.11
Age of Onset	*N/A*[b]	

[a]Only 1 Study
[b]No Studies

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eTable 5. Categorical Univariate Moderator Analyses

Moderator	Number of included studies	Hedges g	95% CI	Q-value	I^2	p-Value
Overall						
Placebo lead-in				0.23		.63
No	28	0.35	0.25 - 0.46		64.30	
Yes	13	0.31	0.17 - 0.45		8.66	
Comorbidity				2.47		.12
No	6	0.24	0.04 - 0.43		29.90	
Yes	28	0.41	0.31 - 0.51		60.61	
Study location				1.94		.16
US only	27	0.38	0.28 - 0.48		50.10	
Not US only	14	0.26	0.13 - 0.39		62.97	
Primary funding source				5.42		.02[a]
Industry only	27	0.26	0.19 - 0.33		37.91	
Public only	11	0.48	0.31 - 0.64		2.97	
Depressive Disorders						
Placebo lead-in				2.71		.10
No	11	0.15	0.06 - 0.24		0.00	
Yes	9	0.26	0.16 - 0.35		23.51	
Comorbidity				1.98		.16
No	3	0.12	-0.04 - 0.28		0.00	
Yes	11	0.25	0.16 - 0.35		27.54	
Study location				2.61		.11
US only	10	0.25	0.16 - 0.35		15.15	
Not US only	10	0.15	0.05 - 0.24		0.00	
Primary funding source				5.64		.02[a]
Industry only	18	0.18	0.11 - 0.25		0.00	
Public only	2	0.46	0.24 - 0.68		0.00	
Obsessive-Compulsive Disorder						
Placebo lead-in				0.05		.83
No	7	0.41	0.22 - 0.60		0.00	
Yes	2	0.38	0.15 - 0.60		0.00	
Comorbidity	*N/A*[b]					
Study location	*N/A*[b]					
Primary funding source				0.07		.79
Industry only	4	0.41	0.25 - 0.58		0.00	
Public only	4	0.36	-0.03 - 0.74		0.00	
Anxiety Disorders						
Placebo lead-in				1.69		.19
No	9	0.69	0.47 - 0.91		71.87	
Yes	2	0.37	-0.06 - 0.80		4.13	
Comorbidity				3.32		0.07
No	3	0.37	0.06 - 0.69		0.00	
Yes	8	0.74	0.51 - 0.97		71.38	
Study location				0.00		0.96
US only	7	0.62	0.37 - 0.88		78.68	
Not US only	4	0.63	0.28 - 0.99		9.85	
Primary funding source				0.31		0.58
Industry only	4	0.47	0.24 - 0.70		55.44	
Public only	5	0.57	0.28 - 0.87		48.85	

[a]Significant at $p<0.05$ level
[b]Not enough variance

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eTable 6. Multivariate Meta-regression Analyses

	Standardized Beta	p-Value
Placebo lead-in	-1.02	.90
Study location	0.63	.59
Illness Duration	-1.23	.52
Publication Year	0.47	.73
Age of Onset	-1.07	.50
Number of Sites	-0.58	.70
Baseline Severity	0.14	.85

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