Supplementary Online Content

Mataix-Cols D, Fernández de la Cruz L, Monzani B, et al. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: a systematic review and meta-analysis. *JAMA Psychiatry*. Published online January 25, 2017. doi:10.1001/jamapsychiatry.2016.3955.

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

eMethods 1. Information sources and search

Search strategies for each of the databases searched:

PubMed

("behavior therapy"[Mesh] OR "cognitive therapy"[Mesh] OR "behavior therap*"[tiab] OR "cognitive therap*"[tiab] OR “cognitive behavioral therap*”[tiab]) OR "behaviour therap*"[tiab] OR “cognitive behavioural therap*”[tiab] OR “exposure therap*”[tiab] OR “cue exposure”[tiab]) AND ("D-cycloserine"[tiab] or "DCS"[tiab] or "cycloserine"[tiab]))

EMBASE

'cognitive therapy'/exp OR 'cognitive therapy' OR 'cognitive behavioural therapy'/exp OR 'cognitive behavioural therapy' OR 'cognitive and behavioural therapy' OR 'cognitive and behavioral therapy' OR 'cognitive and behavioral therapy':ab,ti OR 'cognitive and behavioural therapy':ab,ti OR 'cue exposure' OR 'exposure therapy' AND ('D-cycloserine'/exp OR 'D-cycloserine' OR 'D-cycloserine':ab,ti OR 'cycloserine'/exp OR 'cycloserine' OR 'cycloserine':ab,ti OR 'dcs' OR 'dcs':ab,ti)

PsycINFO

(exp cognitive behavior therapy/ or behavior therap*.ti. or cognitive therap*.ti. or behavior therap*.ab. or cognitive therap*.ab. or behaviour* therap*.ti. or behaviour* therap*.ab. or cognitive behavior* therap*.ti. or cognitive behavior* therap*.ab. or cognitive behaviour* therap*.ti. or cognitive behaviour* therap*.ab. or cue exposure.ti or cue exposure.ab or exp exposure therapy/) and (D-cycloserine.ti. or d- cycloserine.ab. or cycloserine.ti. or cycloserine.ab. or DCS.ti. or DCS.ab.)

eMethods 2. Data items

Methods of harmonizing the primary outcome variables within the IPD data sets to ensure common measurements across studies:

Denoted by (y_0, y_1, y_2, y_3) the four measurements of any given patient at time 0 (baseline), 1 (mid-treatment), 2 (post-treatment), and 3 (follow-up). *Within each different type of primary outcome measure*, we first ranked the patients at baseline (time zero). The rank was then normalized between 0 and 100. We defined $R_0(y_0)$ to be the corresponding 'ranking function' returning a value between 0 and 100 for each value of y_0. To compute the final outcome, R_0 was also applied to the other time points (i.e., mid-treatment, post-treatment, and follow-up), such that the outcome of each patient was given by ($R_0(y_0)$, $R_0(y_1)$, $R_0(y_2)$, $R_0(y_3)$). This permitted replacing the original distributions by their rank, using as benchmark the distribution at baseline (time zero).

To ensure that the data transformation did not result in large discrepancies with the original analyses of the raw datasets, we compared the effect sizes obtained from the model used in *primary aim 1*, taking antidepressants into account, in the original and the transformed data. Overall, the transformation resulted in overlapping confidence intervals (**eTable 9**).

eResults. Moderator analyses (secondary aim)

We included study quality (risk of bias) as a post-hoc moderator in our analyses. We used the Cochrane Collaboration's Tool for Assessing Risk of Bias[33] to assess the quality of the individual studies and explore possible bias. Studies were assessed across six domains: adequate sequence generation, allocation concealment, outcome assessment blinding, management of incomplete outcome data, selective reporting, and other sources of bias. Judgements were made according to the instructions in Table 8.5.c *Criteria for judging risk of bias in the 'Risk of Bias' assessment tool.*[34] For each study, each domain was judged as having low, unclear, or high risk. Judgements of "low" risk were assigned a score of 2 points, judgements of "unclear" risk were assigned a score of 1 point, and judgements of "high" risk were assigned a score of 0 points. Scores in all domains were added up to create an overall risk score (possible range 0 – 12). See **eTable 6** and **eTable 7** below. The overall risk score was then included as a post-hoc moderator variable in the analyses. The results of these analyses appear in **Table 2** of the manuscript.

eTable 1. Demographic and clinical characteristics of the individual studies included in the meta-analysis

STUDY (in order of publication within each disorder)	Sample size *n*	Condition DCS/PBO *n/n*	Age *mean (sd)*	Sex *females n (%)*	On antidepressants *n (%)*	Number of CBT sessions *mean (sd), range*	DCS/PBO dose *in mg*	DCS/PBO time of administration *in minutes before/after exposure*	Number of DCS/PBO doses *mean (sd), range*	Primary outcome measure
SP (n = 124)										
Ressler et al., 2004[18]	27	17/10	45.85 (10.15)	16 (59.26)	3 (11.11)	2 (0), 2-2	50 or 500	-120	2 (0), 2-2	SUDS
Nave et al., 2012[35]	20	10/10	36.80 (13.16)	35 (72.92)	6 (30.00)	1 (0), 1-1	50	-60	1 (0), 1-1	SNAQ
Gutner et al., 2012[36]	48	24/24	23.62 (9.61)	12 (60.00)	1 (2.08)	0.98 (0.14), 0-1	50	-60	0.98 (0.14), 0-1	DSR
Tart et al., 2013[37]	29	15/14	33.38 (16.03)	22 (75.86)	0 (0)	1.97 (0.19), 1-2	50	1	1.97 (0.19), 1-2	CGI-Severity
SAD (n = 291)										
Hofmann et al., 2006[19]	32	12/17	33.28 (9.80)	11 (37.93)	11 (37.93)	4.59 (1.15), 0-5	50	-60	3.62 (1.01), 0-4	SPAI
Guastella et al., 2008[38]	56	28/28	35.48 (11.35)	24 (42.86)	5 (8.93)	4.64 (0.80), 2-5	50	-60	4.64 (0.80), 2-5	LSAS
Hofma	169	87/82	32.6	73	0 (0)	10.7	50	-60	4.67	LSA

nn et al., 2013[21]			1 (10.36)	(43.20)		3 (2.16), 3-12			(0.75), 1-5	S
Rodebaugh et al., 2013[39]	34	18/16	43.58 (12.50)	25 (73.53)	11 (33.33)	1.88 (0.33), 1-2	250	-5	1 (0), 1-1	SUDS
PD / A (n = 77)										
Otto et al., 2010[40]	33	17/16	35.48 (10.54)	17 (51.52)	19 (61.29)	4.56 (1.32), 0-5	50	-60	2.75 (0.80), 0-3	PDSS
Siegmund et al., 2011[41]	44	22/22	37.57 (12.33)	21 (47.73)	12 (27.27)	10.39 (1.89), 2-11	50	-60	2.77 (0.68), 0-3	PAS
OCD (n = 292)										
Storch et al., 2007[42]	29	14/15	28.72 (9.06)	15 (51.72)	9 (37.50)	12 (0), 12-12	250	-240	12 (0), 12-12	Y-BOCS
Kushner et al., 2007[20]	32	15/17	36.87 (11.48)	20 (62.50)	11 (34.38)	6.84 (2.76), 1-10	125	-120	6.84 (2.76), 1-10	Y-BOCS
Wilhelm et al., 2008[43]	29	12/17	38.18 (12.41)	12 (41.38)	17 (62.96)	9.45 (3.33), 0-11	100	-60	8.52 (3.37), 0-10	Y-BOCS
Storch et al., 2010[44]	30	15/15	12.20 (2.77)	11 (36.67)	10 (33.33)	10 (0), 10-10	25 or 50	-60	7 (0), 7-7	CY-BOCS
Farrell et al., 2013[45]	17	9/8	13.00 (3.35)	10 (58.82)	11 (64.71)	9 (0), 9-9	25 or 50	-60	5 (0), 5-5	CY-BOCS
Matai x-Cols et al.,	27	13/14	15.00 (2.0	13 (48.15)	7 (25.93)	12.15 (3.6	50	15	9.44 (1.31), 5-10	CY-BOCS

2014[46]			4)			4), 0-14				
Andersson et al., 2015[22]	128	64/64	33.75 (12.25)	74 (57.81)	37 (28.91)	12 (0), 12-12	50	-60	4.58 (1.19), 0-5	Y-BOCS
PTSD (n = 289)										
de Kleine et al., 2012[47]	75	36/39	38.87 (11.64)	59 (78.67)	18 (24.00)	6.56 (3.11), 1-10	50	-60	5.41 (3.04), 0-9	CAPS
Litz et al., 2012[48]*	26	13/13	32.19 (9.31)	0 (0%)	7 (26.92)	6	50	-30	4	CAPS
Scheeringa et al., 2014[49]	57	29/28	12.03 (3.29)	33 (57.89)	9 (15.79)	10.98 (2.29), 5-12	50	-60	6.25 (1.80), 1-7	CPSS
Difede et al., 2014[50]	25	13/12	45.84 (10.49)	6 (24.00)	12 (48.00)	12.16 (2.98), 2-15	100	-90	10.20 (2.52), 2-13	CAPS
Rothbaum et al., 2014[51]	106	53/53	34.62 (8.42)	7 (6.60)	66 (68.75)	3.19 (2.08), 0-5	50	-30	3.19 (2.08), 0-5	CAPS

*Information for Litz et al.[48] as reported in the original publication because individual participant data were not available.

Abbreviations: DCS D-cycloserine; PBO placebo; CBT cognitive-behavior therapy; SP specific phobia; SAD social anxiety disorder; PD / A panic disorder with or without agoraphobia; OCD obsessive-compulsive disorder; PTSD posttraumatic stress disorder; SUDS Subjective Units of Distress Scale; SNAQ Snake Questionnaire; DSR Disgust Scale Revised; CGI Clinical Global Impression; SPAI Social Phobia and Anxiety Inventory; LSAS Leibowitz Social Anxiety Scale; PDSS Panic Disorder Severity Scale; PAS Panic and Agoraphobia Scale; Y-BOCS Yale-Brow Obsessive Compulsive Scale; CY-BOCS Children's Yale-Brown Obsessive Compulsive Scale; CAPS Clinician Administered PTSD Scale; CPSS Child PTSD Symptoms Scale.

eTable 2. Antidepressant use for the whole sample for each diagnostic category and for each individual study included in the individual patient data meta-analysis

STUDY	Sample size *n*	On antidepressants *n (%)*	SSRI[a] *n (%)*	SNRI[a] *n (%)*	SARI[a] *n (%)*	TCA[a] *n (%)*	TeCA[a] *n (%)*	Other AD[a] *n (%)*
Total sample	1,047	275 (26.86)[b]	197 (73.23)	31 (11.52)	5 (1.86)	21 (7.81)	16 (5.95)	26 (9.67)
Specific phobia	124	10 (8.06)	2 (33.33)	2 (33.33)	0 (0)	0 (0)	0 (0)	2 (33.33)
Ressler et al., 2004	27	3 (11.11)	NR	NR	NR	NR	NR	NR
Nave et al., 2012	20	6 (30.00)	2 (33.33)	2 (33.33)	0 (0)	0 (0)	0 (0)	2 (33.33)
Gutner et al., 2012	48	1 (2.08)	NR	NR	NR	NR	NR	NR
Tart et al., 2013[c]	29	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Social anxiety disorder	291	27 (9.41)	17 (68.00)	5 (20.00)	2 (8.00)	2 (8.00)	2 (8.00)	4 (16.00)
Hoffman et al., 2006	32	11 (37.93)	7 (70.00)	2 (20.00)	1 (10.00)	0 (0)	0 (0)	3 (30.00)
Guastella et al., 2008	56	5 (8.93)	3 (75.00)	0 (0)	0 (0)	0 (0)	1 (25.00)	0 (0)
Hoffman et al., 2013[c]	169	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rodebaugh et al., 2013	34	11 (33.33)	7 (63.64)	3 (27.27)	1 (9.09)	2 (18.18)	1 (9.09)	1 (9.09)
Panic disorder with or without agoraphobia	77	31 (41.33)	21 (67.74)	2 (6.45)	0 (0)	8 (25.81)	1 (3.23)	0 (0)
Otto et al., 2010	33	19 (61.29)	17 (89.47)	2 (10.5	0 (0)	0 (0)	0 (0)	0 (0)

				3)				
Siegmund et al., 2011	44	12 (27.27)	4 (33.33)	0 (0)	0 (0)	8 (66.67)	1 (8.33)	0 (0)
Obsessive-compulsive disorder	292	102 (35.79)	88 (86.27)	10 (9.80)	0 (0)	5 (4.90)	2 (1.96)	6 (5.88)
Storch et al., 2007	29	9 (37.50)	8 (88.89)	0 (0)	0 (0)	1 (11.11)	0 (0)	0 (0)
Kushner et al., 2007	32	11 (34.38)	9 (81.82)	2 (18.18)	0 (0)	1 (9.09)	0 (0)	2 (18.18)
Wilhelm et al., 2008	29	17 (62.96)	15 (88.24)	2 (11.76)	0 (0)	0 (0)	1 (5.88)	4 (23.53)
Storch et al., 2010	30	10 (33.33)	8 (80)	1 (10.00)	0 (0)	1 (10.00)	0 (0)	0 (0)
Farrell et al., 2013	17	11 (64.71)	10 (90.91)	0 (0)	0 (0)	2 (18.18)	0 (0)	0 (0)
Mataix-Cols et al., 2014	27	7 (25.93)	7 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Andersson et al., 2015	128	37 (28.91)	31 (83.78)	5 (13.51)	0 (0)	0 (0)	1 (2.70)	0 (0)
Post-traumatic stress disorder	263	105 (41.50)	69 (65.71)	12 (11.43)	3 (2.86)	6 (5.71)	11 (10.48)	14 (13.33)
de Kleine et al., 2012	75	18 (24.00)	10 (55.56)	4 (22.22)	0 (0)	2 (11.11)	1 (5.56)	1 (5.56)
Scheeringa et al., 2014	57	9 (15.79)	7 (77.78)	0 (0)	2 (22.22)	0 (0)	0 (0)	0 (0)
Difede et al., 2014	25	12 (48.00)	8 (66.67)	2 (16.67)	0 (0)	1 (8.33)	1 (8.33)	2 (16.67)
Rothbaum et al., 2014	106	66 (68.75)	44 (66.67)	6 (9.09)	1 (1.52)	3 (4.44)	9 (13.64)	11 (16.67)

[a] Percentage calculated over those patients on antidepressants.

[b] Medication status was missing for 23 individuals. All percentages in the table are calculated over the number of individuals (n=1,024 in the total sample) for which medication status was known.
[c] Participants on medication were excluded from this study.

Abbreviations: SSRI selective serotonin reuptake inhibitors (includes citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline); SNRI serotonin-norepinephrine reuptake inhibitors (includes desvenlafaxine, duloxetine, and venlafaxine); SARI serotonin antagonists and reuptake inhibitors (includes nefazodone and trazodone); TCA tricyclic antidepressants (includes amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, opipramol, and trimipramine); TeCA tetracyclic antidepressants (includes mirtazapine); Other AD other antidepressants (includes bupropion); NR not reported.

eTable 3. Results of individual studies expressed as simple between-group effect sizes (Cohen d) at posttreatment in each of the eligible studies

Results of individual studies, expressed as simple between-group effect sizes (Cohen's *d*) at post-treatment in each one of the eligible studies (based on raw data and not including any moderators). Negative effect sizes indicate that DCS is superior to placebo.

STUDY (in order of publication within each disorder)	Sample size *n*	ES *Cohen's d*	ES 95% Confidence Interval
SP (n = 124)			
Ressler et al., 2004[18]	27	-0.71	-1.59 to 0.17
Nave et al., 2012[35]	20	0.02	-0.97 to 1.11
Gutner et al., 2012[36]	48	0.29	-0.32 to 0.91
Tart et al., 2013[37]	29	0.17	-0.68 to 1.03
SAD (n = 291)			
Hofmann et al., 2006[19]	32	-0.27	-1.12 to 0.58
Guastella et al., 2008[38]	56	-0.37	-0.92 to 0.18
Hofmann et al., 2013[21]	169	-0.15	-0.48 to 0.18
Rodebaugh et al., 2013[39]	34	-0.62	-1.42 to 0.17
PD / A (n = 77)			
Otto et al., 2010[40]	33	-1.01	-1.87 to -0.15
Siegmund et al., 2011[41]	44	-0.63	-1.32 to 0.07
OCD (n = 292)			
Storch et al., 2007[42]	29	0.19	-0.69 to 1.00
Kushner et al., 2007[20]	32	-0.24	-1.24 to 0.71
Wilhelm et al., 2008[43]	29	-0.40	-1.31 to 0.53
Storch et al., 2010[44]	30	-0.64	-1.43 to 0.15
Farrell et al., 2013[45]	17	0.00	-1.10 to 1.11
Mataix-Cols et al., 2014[46]	27	0.07	-0.97 to 1.01
Andersson et al., 2015[22]	128	0.33	-0.02 to 0.69
PTSD (n = 289)			
de Kleine et al., 2012[47]	75	-0.58	-1.17 to 0.02
Litz et al., 2012[48]	26	0.68	-0.15 to 1.51
Scheeringa et al., 2014[49]	57	0.68	0.06 to 1.31
Difede et al., 2014[50]	25	-0.43	-1.39 to 0.53
Rothbaum et al., 2014[51]	106	0.12	-0.39 to 0.64

Abbreviations: ES effect size; SP specific phobia; SAD social anxiety disorder; PD / A panic disorder with or without agoraphobia; OCD obsessive-compulsive disorder; PTSD posttraumatic stress disorder.

eTable 4. Predicted means for D-cycloserine and placebo groups at each time point (no moderators included)

	Baseline	Mid-treatment	Post-treatment*	Follow-up*
D-cycloserine	50.9	25.3	13.8	12.5
Placebo	50.3	26.4	17.1	15.2

Note: * indicates that the mean for the DCS treatment condition is significantly lower than the mean for the Placebo condition at that time-point.

eTable 5. Multilevel model coefficients for the effect of D-cycloserine (DCS) vs placebo (PBO) in the augmentation of cognitive-behavior therapy in each specific disorder, including antidepressants in the model as an a priori moderator

	SP (Studies=4) (n=124)	SAD (Studies=4) (n=291)	PD/A (Studies=2) (n=77)	OCD (Studies=7) (n=292)	PTSD (Studies=4) (n=263)
	Regression Coefficient	Regression Coefficient	Regression Coefficient	Regression Coefficient	Regression Coefficient
Intercept	45.74	51.35***	49.60[a]	53.00***	48.89***
Group (DCS/PBO)[a]	2.43	0.49	0.42	1.08	1.31
Antidepressants	-4.62	0.62	5.25	2.11	3.48
Baseline Severity	0.59*	0.75***	0.48[a]	0.44***	0.72**
Time pre-to-mid-treatment	-15.46*	-14.99*	-35.38[a]	-43.08***	-17.14**
Time pre-to-post-treatment	-25.50	-21.15**	-37.59[a]	-51.37***	-26.32*
Time pre-to-follow-up	-29.46*	-26.79**	-39.29[a]	-49.95***	-28.66**
Group × Antidepressants	22.96*	-0.63	-15.08	2.06	0.08
Group × Time pre-to-mid-treatment	2.64	-11.07*	-8.04	-0.73	-0.25
Group × Time pre-to-post-treatment	-5.87	-7.56*	-8.91	-0.99	-3.10
Group × Time pre-to-follow-up	-6.08	-10.86**	-1.79	-2.64	-0.09
Antidepressants × Time pre-to-mid-treatment	-	9.79	-8.30	-1.99	5.56
Antidepressants × Time pre-to-post-treatment	11.07	1.02	-3.53	-1.76	-7.46*
Antidepressants × Time pre-to-follow-up	8.05	-1.37	-4.06	-3.71	-9.72**
Group × Time pre-to-mid-treatment × Antidepressants	-	-31.76	36.06*	-8.19	1.86
Group × Time pre-to-post-treatment × Antidepressants	-23.60	-10.54	24.42*	-6.77	-7.99
Group × Time pre-to-follow-up × Antidepressants	-27.09	-17.62	28.33*	0.43	-5.63

Abbreviations: DCS D-cycloserine; PBO placebo; SP specific phobia; SAD social anxiety disorder; PD / A panic disorder with or without agoraphobia; OCD obsessive-compulsive disorder; PTSD posttraumatic stress disorder.

Significance codes: ≤0.001 '***'; ≤0.01 '**'; ≤0.05 '*'

[a]Group was coded PBO=0, DCS=1.

- Cannot be computed.

eTable 6. Risk of bias scores according to the items from the Cochrane Collaboration Tool for Assessing Risk of Bias

Risk of bias scores according to the items from The Cochrane Collaboration's Tool for Assessing Risk of Bias (judgements of low, unclear, or high risk made according to the instructions in Table 8.5.c *Criteria for judging risk of bias in the 'Risk of Bias' assessment tool*[a]).

Study (in order of publication within each disorder)	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS	INCOMPLETE OUTCOME DATA	SELECTIVE OUTCOME REPORTING	OTHER POTENTIAL THREATS TO VALIDITY	Overall risk score[b]
SP							
Ressler et al., 2004	**unclear**	**unclear**	**low**	**unclear**	**low**	**unclear**	8
Nave et al., 2012	**unclear**	**low**	**low**	**low**	**low**	**unclear**	10
Gutner et al., 2012	**unclear**	**unclear**	**low**	**high**	**low**	**unclear**	7
Tart et al., 2013	**low**	**low**	**low**	**low**	**low**	**unclear**	11
SAD							
Hofmann et al., 2006	**unclear**	**low**	**low**	**high**	**low**	**unclear**	8
Guastella et al., 2008	**unclear**	**low**	**low**	**low**	**low**	**unclear**	10
Hofmann et al., 2013	**low**	**low**	**low**	**low**	**unclear**	**unclear**	10

Rodebaugh et al., 2013	**unclear**	**low**	**low**	**high**	**low**	**unclear**	8
PD / A							
Otto et al., 2010	**unclear**	**unclear**	**low**	**high**	**unclear**	**unclear**	6
Siegmund et al., 2011	**unclear**	**unclear**	**low**	**high**	**low**	**unclear**	7
OCD							
Storch et al., 2007	**unclear**	**low**	**low**	**high**	**low**	**unclear**	8
Kushner et al., 2007	**unclear**	**low**	**low**	**unclear**	**low**	**unclear**	9
Wilhelm et al., 2008	**unclear**	**low**	**low**	**high**	**low**	**unclear**	8
Storch et al., 2010	**low**	**low**	**low**	**low**	**high**	**unclear**	9
Farrell et al., 2013	**low**	**low**	**low**	**low**	**unclear**	**unclear**	10
Mataix-Cols et al., 2014	**low**	**low**	**low**	**low**	**high**	**unclear**	9
Andersson et al., 2015	**unclear**	**low**	**low**	**low**	**high**	**unclear**	8
PTSD							
de Kleine et al., 2012	**low**	**low**	**low**	**high**	**high**	**unclear**	7
Scheeringa et al.,	**low**	**unclear**	**low**	**high**	**high**	**unclear**	6

2014							
Difede et al., 2014	**unclear**	**low**	**low**	**low**	**unclear**	**unclear**	9
Rothbaum et al., 2014	**unclear**	**low**	**low**	**unclear**	**high**	**unclear**	8

[a] Higgins, J.P.T. & Altman, D.G. on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group (2008). *Assessing risk of bias in included studies.* In: Cochrane Handbook of Systematic Reviews of Interventions, Higgins, J. & Green, S. (Eds.). The Cochrane Collaboration and John Wiley & Sons Ltd.: West Sussex, England.

[b] Judgements of "low" risk have been assigned a score of 2 points, judgements of "unclear" risk have been assigned a score of 1 point, judgements of "high" risk have been assigned a score of 0 points. Scores in all domains have been added up to create an overall risk score (possible range 0 – 12).

Abbreviations: SP social phobia; SAD social anxiety disorder; PD / A panic disorder with or without agoraphobia; OCD obsessive-compulsive disorder; PTSD posttraumatic stress disorder.

eTable 7. Risk of bias scores and support for judgement according to the items from the Cochrane Collaboration Tool for Assessing Risk of Bias

Risk of bias scores and support for judgement according to the items from The Cochrane Collaboration's Tool for Assessing Risk of Bias (judgements of low, unclear, or high risk made according to the instructions in Table 8.5.c *Criteria for judging risk of bias in the 'Risk of Bias' assessment tool*[a]).

Study (in order of publication within each disorder)	**SEQUENCE GENERATION Was the allocation sequence adequately generated?**	**ALLOCATION CONCEALMENT Was allocation adequately concealed?**	**BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS Was knowledge of the allocated interventions adequately prevented during the study?**	**INCOMPLETE OUTCOME DATA Were incomplete outcome data adequately addressed?**	**SELECTIVE OUTCOME REPORTING Are reports of the study free of suggestion of selective outcome reporting?**	**OTHER POTENTIAL THREATS TO VALIDITY Was the study apparently free of other problems that could put it at a risk of bias?**
SP						
Ressler et al., 2004	**unclear**	**unclear**	**low**	**unclear**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "27 were randomly assigned, via a	Method of concealment is not described.	"Treatment condition was double-blinded, such that the subjects, therapists, and assessors were not	There were no drop-outs at post-treatment but 6 patients did not return for follow-up. Unclear whether the follow-up analyses were intention-to-treat.	All outcomes stated in the trial registration (available at clinicaltrials.gov) were reported.	Difficult to judge whether the study is free of other sources of bias.

	predetermined and blinded order of treatment assignment."		aware of the assigned study medication condition. The blind was maintained throughout the study."	"Twenty-seven participants (11 men, 16 women) completed pretreatment, both therapy sessions, and the 3-month follow-up assessment. Twenty-one of the 27 completing participants returned for follow-up assessment (8 placebo [80% of enrolled], 13 DCS [77% of enrolled]). Analysis of the pretreatment data and the 1-week posttreatment assessments showed that there were no significant pretreatment or posttreatment differences on anxiety or fear measures between those who returned for follow-up and the 6 who did not."		
Nave et al.,	**unclear**	**low**	**low**	**low**	**low**	**unclear**

2012						
Support for judgement	Random component in the sequence generation process not described. "20 patients, right-handed males and females aged 20-63 years, were randomized."	"Subjects received DCS or an identically packaged placebo capsule."	"The study used a double-blind, placebo-controlled design (…)."	All randomized subjects seem to have been included in the analyses.	All outcomes stated in the trial registration (available at clinicaltrials.gov) were reported.	Difficult to judge whether the study is free of other sources of bias.
Gutner et al., 2012	**unclear**	**unclear**	**low**	**high**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "Participants were randomly assigned to one or two conditions."	Method of concealment is not described.	"Neither the experimenter, nor the participant were aware of the condition."	Analyses were not intention-to-treat as not all randomized participants were analyzed. "Analyses were completed only for individuals who attended both days of the study. Therefore, results were based on 24 individuals randomized to the DCS	Study protocol not available but all expected outcomes seem to be reported.	Difficult to judge whether the study is free of other sources of bias.

				group and 21 individuals randomized to the placebo group". "Although the number of dropouts was small (n=3), all dropouts were in the placebo group."		
Tart et al., 2013	**low**	**low**	**low**	**low**	**low**	**unclear**
Support for judgement	"Randomization was done by research staff not involved in the trial using minimization procedures (Scott et al., 2002) and stratifying on gender, therapist, and time of day of treatment sessions."	"All capsules were identical in appearance to maintain the blind."	"Blind to the condition, therapists were advanced doctoral-student level therapists trained and supervised by the senior author (JAJS). In order to obtain CGI ratings, the therapists (blind to study condition) interviewed the participant (…)."	Intention-to-treat analysis according to CONSORT diagram. "Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data in groups; n = 15 assigned to DCS and cognitive and behavioral therapies arm and n = 14 to placebo and cognitive and behavioral therapies arm, with n = 3 withdrawing from placebo arm by post-	All outcomes stated in the trial registration (available at clinicaltrials.gov) were reported.	Difficult to judge whether the study is free of other sources of bias.

				treatment, n = 3 withdrawing from DCS arm at follow-up and n = 1 withdrawing from follow-up in placebo arm"		
SAD						
Hofmann et al., 2006	**unclear**	**low**	**low**	**high**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "Patients were randomized to either adjunctive DCS or pill placebo administered as a 50-mg pill on each of 4 occasions."	"The random allocation sequence was generated by numbering containers with the medication. The sequence was generated prior to allocating participants and was concealed until the end of the study. Matching d-cycloserine or placebo was given."	"All of the individuals involved inpatient care, evaluation, or study supervision were blind to group assignment until the end of the study."	Analyses were not intention-to-treat as not all randomized participants were analyzed. Of the 32 participants who were randomized, only 27 were analyzed (according to CONSORT diagram).	Study protocol not available but all expected outcomes seem to be reported.	Difficult to judge whether the study is free of other sources of bias.
Guastella et al.,	**unclear**	**low**	**low**	**low**	**low**	**unclear**

2008						
Support for judgement	Random component in the sequence generation process not described. "A random allocation sequence was generated by numbering containers with the medication."	"A random allocation sequence was generated by numbering containers with the medication. This randomization sequence was developed by the compounding chemist before the trial and concealed from all individuals involved in patient care, evaluation, or supervision until follow-up assessments were completed. The compounding chemist purchased DCS to make 50 mg DCS capsules, along with identical placebo"	"Participants and assessor were blinded until follow-up assessments were completed."	"After drug assignment, 6 participants (n = 1 DCS; n = 5 placebo) failed to attend at least three group exposure sessions between session 2 and 5 and dropped out of treatment. The χ^2 analysis showed the difference between the two groups in dropout rates after drug assignment approached significance (P = 0.08). No dropouts occurred over the 1-month follow-up assessment period. LOCF used, with ITT principle."	Study protocol not available but all expected outcomes seem to be reported.	Difficult to judge whether the study is free of other sources of bias.

Hofmann et al., 2013	**low**	**low**	**low**	**Low**	**unclear**	**unclear**
Support for judgement	"Assignment to treatment condition was determined by a computer-generated allocation schedule with stratification by baseline severity of social anxiety disorder."	"All capsules were identical in appearance to maintain the blind."	"Patients were asked to indicate whether they believed the pill contained d-cycloserine or placebo or whether they were unable to guess (…)." "The blinded assessments were conducted by a master's-level or doctoral-level clinician trained in these assessments."	Intent-to-treat analysis according to CONSORT diagram. "Attrition rates during the 12-week treatment phase were low and did not differ significantly between groups (10.3% for the DCS group and 15.9% for the placebo group)." "Attrition was low during the follow-up phase (11.5% and 11.)% for the DCS and placebo groups, respectively)."	The Social Phobic Disorders Change score is reported in the paper but is not pre-specified as outcome in the trial registration (available at clinicaltrials.gov).	Difficult to judge whether the study is free of other sources of bias.
Rodebaugh et al., 2013	**unclear**	**low**	**low**	**high**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process	"Participants were randomly assigned to 250 mg of DCS or	"Adequacy of the blind was assessed by having both	Analyses were not intention-to-treat as not all randomized participants	Study protocol not available but all expected	Difficult to judge whether the study is free of

	not described. "Participants were randomly assigned to 250 mg of DCS or placebo"	placebo in identical-appearing capsules by a data manager who had no interaction with participants ."	participants and experimenters guess treatment assignment based on Visit 1 of the study; neither participants nor experimenters were able to discern assignment ."	were analyzed (based on completers). "Only those participants completing visit 2 are analyzed because the intent is to assess the sensitivity of the clinical assay, not evaluate the real-world effectiveness of an intervention package." 4 dropouts reported, 2 in each group.	outcomes seem to be reported.	other sources of bias.
PD / A						
Otto et al., 2010	**unclear**	**unclear**	**low**	**high**	**unclear**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "Participants were randomized."	Insufficient information to permit judgement.	"Blinding occurred for both participant and personnel." "Doses of study drug (50 mg of DCS or matching placebo) were administered by study personnel in a double-blind	Analyses were not intent-to-treat. "Only those patients who completed the 1-month follow-up assessment were included in the analyses." Unclear if the 3 patients that dropped-out after randomization were included.	The trial registration (available at clinicaltrials.gov) lists as primary outcome "significant reduction in panic symptoms". The paper reports as primary outcome	Difficult to judge whether the study is free of other sources of bias.

			fashion."	Dropout rates: Five patients discontinued participation (two before randomization at week 3 of the protocol, three after randomization). Reasons for discontinuation and which group they belonged to were not reported.	the Panic Disorder Severity Scale (PDSS).	
Siegmund et al., 2011	**unclear**	**unclear**	**low**	**high**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "Randomization was performed by pharmacy which prepared the study medication using the method of randomly permuted blocks of pairs."	Insufficient information to permit judgement (use of sequentially numbered drug containers is described, but it remains unclear if they were of identical appearance; use of assignment envelopes is described, but it remains unclear	"All study staff (including those who did recruitment, assessments and therapy) and all participants were blind to the random allocation sequence."	No intent-to-treat analysis according to CONSORT diagram (44 randomized, 39 analyzed). "Data of patients who finished treatment and who were assessed at post-therapy and at least at one of the follow-up assessments were included into analyses. Missing data of single follow-up assessments or single	All outcomes stated in the trial registry (ISRCTN Registry) were reported.	Difficult to judge whether the study is free of other sources of bias.

		whether envelopes were sequentially numbered, opaque and sealed): "The study medication was handed out by the study staff in consecutive numbers, according to the individual time arrangements for exposure therapy (next exposure received next container). The randomization sequence was kept in the pharmacy inaccessible to study staff until the last follow-up data had been assessed and monitored. For reasons		scales were extrapolated by method of last-observation-carried-forward."		

		of safety, closed envelopes including the individual allocation of each patient were kept in a place accessible to all staff, to allow fast individual deblinding in case of a severe adverse event."				
OCD						
Storch et al., 2007	**unclear**	**low**	**low**	**high**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "Participants were randomized to receive DCS or placebo."	"The rater, the treatment teams, the patients and their families were unaware of and unable to determine, the study drug assignment by appearance or otherwise."	"The rater, the treatment teams, the patients and their families were unaware of and unable to determine, the study drug assignment by appearance or otherwise."	No intent-to-treat analysis according to CONSORT diagram (34 randomized, 24 analyzed). Missing data balanced in numbers across intervention groups with similar reasons for missing data across groups (detailed in CONSORT diagram).	Study protocol not available but all expected outcomes seem to be reported.	Difficult to judge whether the study is free of other sources of bias.
Kushn	**unclear**	**low**	**low**	**unclear**	**low**	**unclear**

er et al., 2007						
Support for judgement	Random component in the sequence generation process not described. "We dispensed to each subject 10 doses of 125 mg DCS or 10 identical-looking placebo doses in a random double-blind fashion."	"We dispensed to each subject 10 doses of 125 mg DCS or 10 identical-looking placebo doses in a random double-blind fashion."	"Double-blind fashion." "Psychiatrist and raters reported to be blind to treatment condition."	Unbalanced drop-out rates between groups, which may have introduced a bias. "Seventy-eight percent of the entire sample completed the EX/RP therapy. However, this was true for 93.3% of DCS subjects versus 64.7% of placebo subjects [$\chi^2(1) = 3.82$, $p = .05$; Fisher exact test, $p = .09$]." Different endpoints used for each individual: "Because subjects potentially completed the therapy at different rates, comparing the groups at subjects' last session (vs. at session 10) provided a	Study protocol not available but all expected outcomes seem to be reported.	Difficult to judge whether the study is free of other sources of bias.

				more sensible and inclusive endpoint. An alternative we considered was to carry the last observation forward to the 10th session for those completing the therapy in less than 10 sessions; however, we rejected this approach because it was more speculative than the approach we adopted."		
Wilhelm et al., 2008	**unclear**	**low**	**low**	**high**	**low**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "The research pharmacies at Massachusetts General Hospital and the Institute	"The research pharmacies at Massachusetts General Hospital and the Institute of Living prepared and dispensed the study medication (100 mg D-cycloserine or placebo)	"Double-blind design." "Masking: Double Blind (Subject, Investigator)" (from trial registration at clinicaltrials.gov).	CONSORT diagram not provided but seems that at least the six patients who discontinued treatment before mid-treatment were randomized but not included in intent-to-treat analyses (despite stated otherwise in	All outcomes stated in the trial registration (available at clinicaltrials.gov) were reported – although the trial registration does not mention specific	Difficult to judge whether the study is free of other sources of bias.

	of Living prepared and dispensed the study medication (100 mg D-cycloserine or placebo) and maintained the coded random assignment schedule for the double-blind design."	and maintained the coded random assignment schedule for the double-blind design."		the text). "Data were analyzed both as intent-to-treat (with last observation carried forward) and completer-only analyses." "Thirty-three OCD patients signed informed consent. Of those 33 patients, three did not meet inclusion criteria, one refused the treatment because he reported that he was "not ready for change," and six discontinued treatment before the mid-treatment evaluation. Twenty-two patients completed the treatment and were included in the statistical analysis. One patient dropped out after the mid-treatment	outcome measures but "reduction in symptoms."	

				evaluation; his data were carried forward."		
Storch et al., 2010	**low**	**low**	**low**	**Low**	**high**	**unclear**
Support for judgement	"Participants were randomized by a computer-generated program maintained in the site research pharmacy in a double-blinded fashion to CBT + DCS or CBT + Placebo."	"D-cycloserine (Seromycin, 250 mg; Eli Lilly and Co, Indianapolis, Indiana) will be capsulated into 25mg with identical placebo capsules" (from trial registration at clinicaltrials.gov).	"Double-blinded fashion." "Assessments were conducted by trained blinded raters at pretreatment, after Session 6, and within 1 week posttreatment."	"There were no missing data."	Data from questionnaires that were not pre-specified as outcome measures in the trial registration (available at clinicaltrials.gov) were reported in the paper (MASC, CDI, ADIS-CSR for OCD). Additionally, one measure (Adverse Symptom Checklist) was listed in the trial registration but not in the paper.	Difficult to judge whether the study is free of other sources of bias.
Farrell et al.,	**low**	**low**	**low**	**Low**	**unclear**	**unclear**

2013						
Support for judgement	"Children were randomized using a computer-generated list of randomly permuted blocks of pairs, with an allocation of 1:1 to either ERP + DCS (n = 9) or ERP + PBO (n = 8)."	"Pills were compounded to be identical in size and color, and were dispensed by the study pharmacist corresponding to randomization, prior to session 5."	"Blinding managed by the study pharmacy investigator (Laetitia Hattingh, Ph.D.). All other investigators were blind, as were assessors, therapists, and all participants (…)."	"All children enrolled in the trial completed treatment."	The ADIS-CSR for OCD, GOCS, CGI, and MASC were reported in the paper but are not pre-specified as outcomes in the trial registration (at ANZCTR).	Difficult to judge whether the study is free of other sources of bias.
Mataix-Cols et al., 2014	**low**	**low**	**low**	**low**	**high**	**unclear**
Support for judgement	"Participants were randomly allocated via an external computer allocation system to receive either 50 mg D-cycloserine or placebo in a double-blind design."	"The D-cycloserine and identical placebo capsules were manufactured for the study at Guy's and St Thomas's Hospital production pharmacy (London, UK)."	"Double-blind design." "A masked rater administered the CY-BOCS at the beginning of each session, providing session-by-session data. Double-blind follow-up	Intention-to-treat analyses according to CONSORT diagram. Drop-outs and missing data detailed in CONSORT.	Several of the secondary outcomes pre-specified in the trial registration (at clinicaltrials.gov) were not reported in the paper (ADIS, SDQ, DASS, FAS, RCMAS,	Difficult to judge whether the study is free of other sources of bias.

			assessments were completed at 3, 6 and12 months post-treatment. Unmasking took place after the last patient had completed the 12-month follow-.up."		CARBQ-C/P, SUDS, BAT, PEAS, and heath rate variability). Additionally, the ChOCI and the CGAS were reported in the paper but are not listed as outcomes in the trial registration.	
Andersson et al., 2015	**unclear**	**low**	**low**	**low**	**high**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "The randomization sequence was generated by an independent party before the first inclusion"	"Masked randomization was conducted in block of eight patients (…) by an independent party (Apoteket Production and Laboratories). Sealed envelopes with information on treatment	"Both patients and clinicians were blinded to treatment allocation."	Intention-to-treat analyses according to CONSORT diagram. "The main analysis was conducted according to intention-to-treat-principles. We had no data loss on the clinician-administered outcomes at post-treatment and only 2% missing data	One of the secondary outcomes pre-specified in the protocol (available as supplemental material) was not reported on the paper (TIC-P: Trimbos and Institute of	Difficult to judge whether the study is free of other sources of bias.

		allocation were stored in a secure locker in case of emergency unblinding" (from supplemental material).		points at follow-up. The corresponding proportion of data loss on the self-rated assessments was 8% at post-treatment and 5% at 3-month follow-up."	Medical Technology Assessment Cost Questionnaire for Psychiatry).	
PTSD						
de Kleine et al., 2012	**low**	**low**	**low**	**high**	**high**	**unclear**
Support for judgement	"Using standard software, an independent statistician generated a randomization list using random blocks with a maximum of 10numbers each."	"The active and placebo capsules were dispensed by the pharmacist in numbered containers in accordance with the randomization list." "The compounding chemist purchased DCS from Duchefa Farma (Haarlem, The Netherlands) to make the 50 mg DCS	"All assessments were conducted by trained, independent assessors who were blind to the treatment condition." "Everyone involved in the study (i.e., researchers, participants, therapists, and assessors) were blind to the treatment condition until all follow-up assessment	Analyses were not intention-to-treat as not all randomized participants were analyzed. "For administrative reasons, participants were randomized before the baseline assessments. Consequently, 16 patients received a randomization number but never entered the study because they were excluded or withdrew	Two outcomes pre-specified in the trial registration (at Nederlands Trial Register) were not reported in the paper (posttraumatic cognitions and avoidance behavior). Additionally, the SCL-90 was reported in the paper but is not pre-specified	Difficult to judge whether the study is free of other sources of bias.

		capsules along with the identical-looking placebo."	s were completed. "	before completion of the baseline assessment." Large number of dropouts and reasons for dropping out not detailed: "Of the 75 eligible participants randomly assigned in double-blind fashion to the treatment conditions, 8 dropped out before the first exposure session, leaving 67 participants receiving the allocated intervention. The treatment protocol was completed by 45participants , 24 receiving exposure plus DCS and 21 receiving exposure plus placebo, whereas 40 completers and 5 dropouts completed the 3-month follow-up assessment. No significant	as an outcome in the trial registratio n.	

				differences between completers and dropouts were found for any sample characteristic or baseline symptom severity measures."		
Scheeringa et al., 2014	**low**	**unclear**	**low**	**high**	**high**	**unclear**
Support for judgement	"We created a list of randomized numbers using the Microsoft Excel 2007 random number generator. Block randomization in sets of four was used. Within the first set of four numbers, two were randomly assigned to CBT and DCS and two to CBT	Method of concealment is not described.	"All research personnel were blinded except the pharmacist, who had no contact with subjects." "The study was triple-blind as the Board, the participants, and the investigators were blind to allocation status."	Analyses are reported as intention-to-treat but according to CONSORT diagram, the analysis of the 3-month follow-up only includes 47 individuals that completed treatment, instead of the 57 randomized.	The trial registration (at clinicaltrials.gov) reports the following outcomes: Number of PTSD symptoms (diagnostic interview) and Number of anxiety symptoms (self- and parent-reports). However, the paper reports data on a larger number of non-pre-specified measures (modules	Difficult to judge whether the study is free of other sources of bias.

	and placebo. This procedure was repeated for the second set of four numbers, and so on. This was used to prevent long runs of unequal assignment.”				for PTSD of the DISC-IV, CDI, SCARED, SNAP and AEC – all children-reported).	
Difede et al., 2014	**unclear**	**low**	**low**	**low**	**unclear**	**unclear**
Support for judgement	Random component in the sequence generation process not described. “25 participants were randomized to receive VRE therapy combined with either 100 mg DCS (n=13; VRE-DCS group)	“The research pharmacy oversaw randomization.”	“Medication was administered double-blind.” “A psychologist who was blind to the medication condition conducted assessments at six time points.”	Intention-to-treat analyses according to CONSORT diagram. “All analyses adhered to intent-to-treat principle, with the last available observation used as the outcome data (ITT/LOCF).” “All three dropouts were in the VRE-placebo group and the observed differences in group mean were minimal	The BDI-II, the STAXI-2, and the PCL were reported in the paper but are not pre-specified as outcomes in the trial registration (at clinicaltrials.gov).	Difficult to judge whether the study is free of other sources of bias.

	or placebo (n=12; VRE-placebo group)."			for all measures (eg, VRE-placebo group CAPS scores at post-treatment: intent-to-treat analysis: M=42.17, SD=20.75 vs completer analysis M=43.11, SD=18.56; at 6-month follow-up: Intent-to-treat analysis M=45.92, SD=22.66 vs completer analysis M=48.11, SD=25.31)."		
Rothbaum et al., 2014	**unclear**	**low**	**low**	**unclear**	**high**	**unclear**
Support for judgement	Random component in the sequence generation process not described. "The participants were randomly assigned in a 1:1:1 ratio to the three treatment conditions	"The compounding pharmacy randomly assigned patients to the medications in blocks of 30."	"This double-blind, placebo-controlled study consisted of a base-line screening assessment, six treatment visits, and follow-up assessments at 3, 6, and 12	"Outcomes were analyzed on the basis of the intent-to-treat group of all randomly assigned participants." Large number of drop-outs. "There were no significant differences in dropout rate across conditions at posttreatment	Several outcomes pre-specified in the trial registration (at clinicaltrials.gov) were not reported in the paper (Cognitive Global Impression, Quality of Life Inventory,	Difficult to judge whether the study is free of other sources of bias.

	: virtual reality exposure plus 50 mg of d-cycloserine, virtual reality plus 0.25 mg of alprazolam, or virtual reality plus pill placebo."		months posttreatment conducted by blind independent evaluators. (…) The study staff were blind to medication condition."	(x2=3.36, df=2, p=0.19) or at the 3-month (x2=3.63, df=2, p=0.16), 6-month (x2=2.75,df=2, p=0.25), or 12-month (x2=1.11, df=2, p=0.57) follow-up. Dropouts did not significantly differ from completers on baseline demographic characteristics or symptom variables. Little's test suggested that the missing cases met the assumption for missing completely at random (χ^2=124.89,df=127, p=0.54)." "There were no meaningful between-group differences at baseline (Table 1)." "Weaknesses of the current study include	State-Trait Anxiety Inventory, and Beck Depression Inventory).	

				the high dropout rate. It should be noted that 31 participants dropped out before the first treatment session."		

[a] Higgins, J.P.T. & Altman, D.G. on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group (2008). *Assessing risk of bias in included studies.* In: Cochrane Handbook of Systematic Reviews of Interventions, Higgins, J. & Green, S. (Eds.). The Cochrane Collaboration and John Wiley & Sons Ltd.: West Sussex, England.

Abbreviations: SP social phobia; SAD social anxiety disorder; PD / A panic disorder with or without agoraphobia; OCD obsessive-compulsive disorder; PTSD posttraumatic stress disorder.

eTable 8. Multilevel model coefficients for the effect of D-cycloserine (DCS) vs placebo (PBO) in the augmentation of exposure-based cognitive-behavior therapy (CBT) in 2 subsamples

	All studies except for Gutner et al.				All studies except for Gutner et al. and Rodebaugh et al.		
	Regression coefficient	Standard error	p-value		Regression coefficient	Standard error	p-value
Intercept	50.40	1.04	<0.001***		50.20	1.10	<0.001***
Group (DCS/PBO)[a]	0.38	1.10	0.730		0.40	1.13	0.723
Antidepressants	2.41	1.33	0.070		2.43	1.37	0.075
Baseline Severity	0.59	0.04	<0.001***		0.57	.04	<0.001***
Time pre-to-mid-treatment	-26.06	3.77	<0.001***		-27.59	3.62	<0.001***
Time pre-to-post-treatment	-37.79	3.64	<0.001***		-38.27	3.52	<0.001***
Time pre-to-follow-up	-37.65	3.02	<0.001***		-38.72	2.97	<0.001***
Group × Antidepressants	0.77	2.47	0.754		0.75	2.53	0.766
Group × Time pre-to-mid-treatment	-1.54	1.68	0.362		-1.54	1.71	0.367
Group × Time pre-to-post-treatment	-2.96	1.49	0.046*		-2.85	1.52	0.061
Group × Time pre-to-follow-up	-2.85	1.57	0.070		-2.84	1.58	0.073
Antidepressants × Time pre-to-mid-treatment	-0.89	2.20	0.688		-0.98	2.23	0.661
Antidepressants × Time pre-to-post-treatment	-2.00	1.82	0.273		-2.42	1.88	0.198

Antidepressants × Time pre-to-follow-up	-4.42	1.91	0.021		-4.54	1.93	0.019
Group × Time pre-to-mid-treatment × Antidepressants	-2.34	4.02	0.560		-2.32	4.06	0.568
Group × Time pre-to-post-treatment × Antidepressants	-4.61	3.33	0.167		-4.49	3.41	0.188
Group × Time pre-to-follow-up × Antidepressants	1.04	3.54	0.768		1.06	3.58	0.768

Significance codes: ≤0.001 '***'; ≤0.01 '**'; ≤0.05 '*'

[a] Group was coded PBO=0, DCS=1.

eTable 9. Standardized effect sizes for the pre-to-post-treatment change in each of the eligible studies calculated on raw and transformed data and taking into account the effects of antidepressants (corresponding to analyses in primary aim 1)

Standardized effect sizes for the pre-to-post-treatment change in each of the eligible studies calculated on raw and transformed data and taking into account the effects of antidepressants. Negative effect sizes indicate that DCS is superior to placebo.

STUDY (in order of publication within each disorder)	Sample size *n*	Raw data		Transformed data	
		ES *d*	ES 95% Confidence Interval	ES *d*	ES 95% Confidence Interval
SP (n = 124)					
Ressler et al., 2004[18]	27	-0.63*	-0.95 to -0.31	-0.30*	-0.59 to -0.02
Nave et al., 2012[35]	20	0.72*	0.15 to 1.60	0.62*	0.28 to 0.97
Gutner et al., 2012[36]	48	-0.40*	-0.54 to -0.25	-0.50*	-0.66 to -0.34
Tart et al., 2013[37]	29	0.48	-0.27 to 1.20	0.75	0.26 to 1.20
SAD (n = 291)					
Hofmann et al., 2006[19]	32	-0.71*	-0.99 to -0.44	-0.88*	-1.10 to -0.64
Guastella et al., 2008[38]	56	-0.41*	-0.57 to -0.26	-0.40*	-0.57 to -0.22
Hofmann et al., 2013[21]	169	-0.13	-0.30 to 0.04	0.01	-0.12 to 0.14
Rodebaugh et al., 2013[39]	34	-0.39*	-0.62 to -0.17	-0.24*	-0.47 to -0.01
PD / A (n = 77)					
Otto et al., 2010[40]	33	-0.68*	-1.10 to -0.30	-0.12	-0.41 to 0.17
Siegmund et al., 2011[41]	44	-0.30*	-0.58 to -0.01	-0.19	-0.45 to 0.08
OCD (n = 292)					
Storch et al., 2007[42]	29	0.39	-0.24 to 1.00	-0.33	-0.71 to 0.05
Kushner et al., 2007[20]	32	-0.29	-0.77 to 0.19	-0.08	-0.39 to 0.24
Wilhelm et al., 2008[43]	29	-0.98*	-1.50 to -0.45	-0.35*	-0.68 to -0.02
Storch et al., 2010[44]	30	-0.56*	-1.10 to -0.06	0.42*	0.07 to 0.76
Farrell et al., 2013[45]	17	-0.20	-0.85 to 0.46	-0.39	-0.81 to 0.03

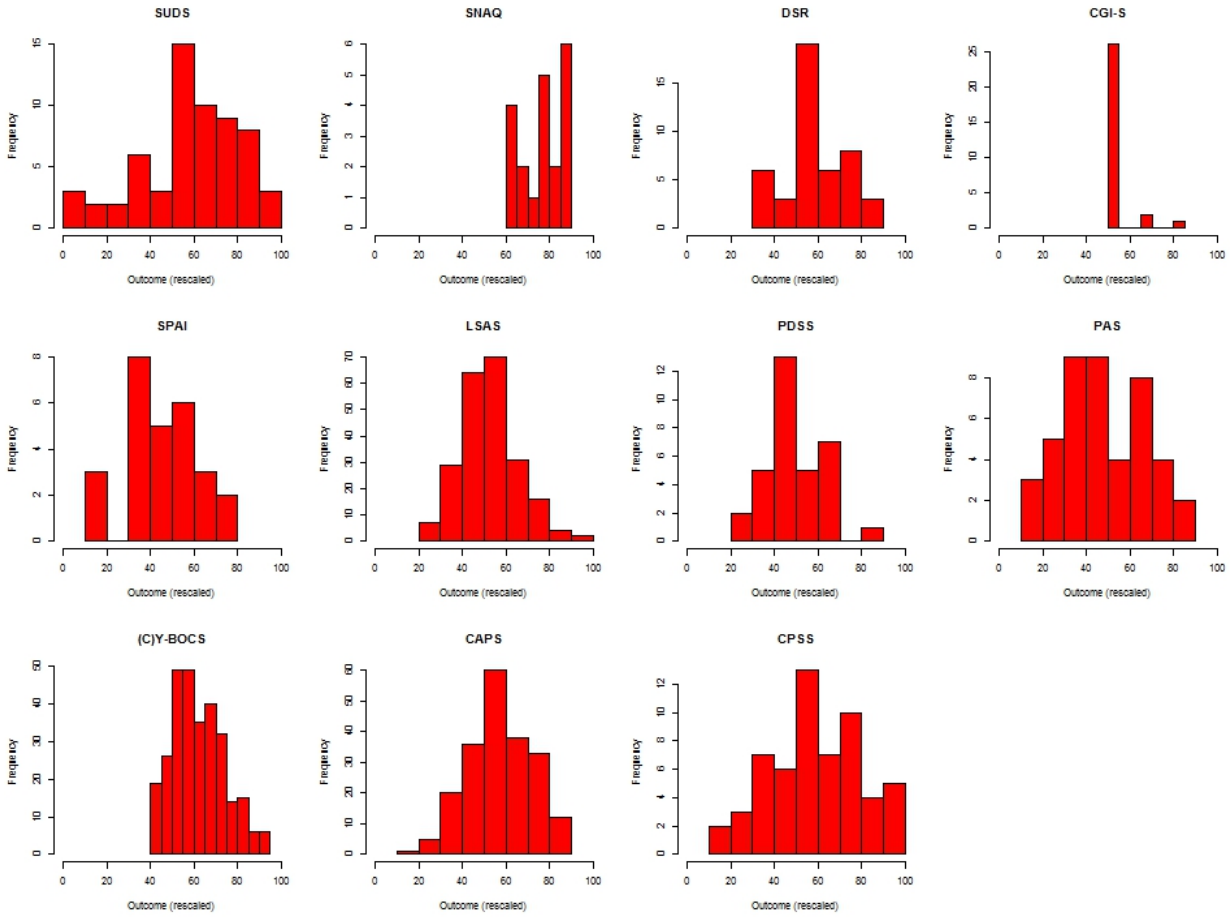
Mataix-Cols et al., 2014[46]	27	-0.37	-1.10 to 0.39	-0.48*	-0.88 to -0.09
Andersson et al., 2015[22]	128	0.40*	0.13 to 0.68	-0.03	-0.17 to 0.11
PTSD (n = 289)					
de Kleine et al., 2012[47]	75	0.58	-0.02 to 1.17	-0.11	-0.34 to 0.12
Litz et al., 2012[48]	26	-0.68[a]	-1.51 to 0.15	–	–
Scheeringa et al., 2014[49]	57	-0.68*	-1.31 to -0.06	-0.11	-0.36 to 0.13
Difede et al., 2014[50]	25	0.43	-0.53 to 1.39	-0.27	-0.61 to 0.07
Rothbaum et al., 2014[51]	106	-0.12	-0.64 to 0.39	-0.19*	-0.37 to -0.01

Abbreviations: ES effect size; SP specific phobia; SAD social anxiety disorder; PD / A panic disorder with or without agoraphobia; OCD obsessive-compulsive disorder; PTSD posttraumatic stress disorder.

[a] Cohen's d calculated using the data provided in the original report – IPD not available.

***** The pre-to-post-treatment change in outcome was significant ($p<.05$).

eFigure. Distribution of the outcome measures at baseline, rescaled from 0 to 100



Abbreviations: SUDS Subjective Units of Distress Scale; SNAQ Snake Questionnaire; DSR Disgust Scale Revised; CGI-S Clinical Global Impression – Severity; SPAI Social Phobia and Anxiety Inventory; LSAS Leibowitz Social Anxiety Scale; PDSS Panic Disorder Severity Scale; PAS Panic and Agoraphobia Scale; (C)Y-BOCS (Children's) Yale-Brow Obsessive Compulsive Scale; CAPS Clinician Administered PTSD Scale; CPSS Child PTSD Symptoms Scale.