

eTable 1. Treatment comparisons and data used for pooling disease remission

Author	Year	Duration of treatment (weeks)	Intervention	Remission	Non- remission
BZDs vs placebo					
Ballenger	1988	8	BZD	136	111
			Placebo	75	159
Klosko	1990	15	BZD	8	8
			Placebo	4	7
Lydiard	1992	6	BZD	14	9
			Placebo	5	28
Schweizer	1993	6	BZD	74	13
			Placebo	37	24
Pecknold	1994	6	BZD	55	14
			Placebo	34	36
Davidson	1994	4	BZD	56	42
			Placebo	40	61
Carter	1995	4	BZD	109	119
			Placebo	36	45
Noyes Jr	1996	8	BZD	52	13
			Placebo	19	15
Rosenbaum	1997	9	BZD	49	18
			Placebo	38	31
Moroz	1999	6	BZD	137	84
			Placebo	79	137
Valenca	2003	6	BZD	14	4
			Placebo	1	11
TCAs vs placebo					
Lydiard	1993	12	TCA	22	4
			Placebo	13	4
Wade	1997	8	TCA	50	48
			Placebo	32	64
SSRIs vs placebo					
Black	1993	8	Fluvoxamine	18	7
			Placebo	6	19
Hoehn-Saric	1993	8	Fluvoxamine	11	7
			Placebo	4	14
Sandmann	1998	6	Fluvoxamine	8	9
			Placebo	6	12
Asnis	2001	8	Fluvoxamine	60	27

Author	Year	Duration of treatment (weeks)	Intervention	Remission	Non- remission
			Placebo	42	50
Londborg	1998	12	Sertraline	72	55
			Placebo	18	26
Pohl	1998	10	Sertraline	49	30
			Placebo	40	47
Pollack	1998	10	Sertraline	50	38
			Placebo	41	47
Michelson	1998	10	Fluoxetine	18	62
			Placebo	11	61
Michelson	2001	12	Fluoxetine	38	52
			Placebo	25	65
Oehrberg	1995	12	Paroxetine	19	41
			Placebo	8	52
Sheehan	2005	10	Paroxetine	236	141
			Placebo	208	187
Bergink	2005	9	Paroxetine	3	6
			Placebo	5	5
Stahl	2003	10	Escitalopram	63	62
			Placebo	43	71
TCAs vs BZDs					
Uhlenhuth	1989	8	TCA	10	10
			BZD	9	9
			Placebo	6	14
Taylor	1990	8	TCA	15	6
			BZD	15	9
			Placebo	10	10
Andersch	1991	8	TCA	15	26
			BZD	14	27
			Placebo	9	32
	1992	8	TCA	274	117
			BZD	270	116
			Placebo	196	195
Schweizer	1993	8	TCA	9	11
			BZD	19	14
			Placebo	4	11
Holland (alprazolam)	1999	12	TCA	83	45
			BZD	80	49
SNRIs vs placebo					

Author	Year	Duration of treatment (weeks)	Intervention	Remission	Non- remission
Bradwejn	2005	10	Venlafaxine	88	72
			Placebo	88	80
Liebowitz	2009	10	Venlafaxine	80	75
			Placebo	67	88
TCAs vs SSRIs					
Bystritsky	1995	10	TCA	6	5
			Fluoxetine	7	3
Amore	1999	24	TCA	13	4
			Fluoxetine	14	4
Nair	1996	8	TCA	31	17
			Fluvoxamine	19	31
			Placebo	24	26
Bakker	1999	12	TCA	17	15
			Paroxetine	21	11
			Placebo	11	21
Lecrubier	1997	12	TCA	40	81
			Paroxetine	56	67
			Placebo	37	86
SNRIs vs SSRIs vs placebo					
Pollack	2007	12	Venlafaxine	86	72
			Paroxetine	98	63
			Placebo	55	101
Pollack	2007	12	Venlafaxine	101	55
			Paroxetine	88	63
			Placebo	75	82
TCAs vs buspirone vs placebo					
Pohl	1989	8	TCA	1	13
			Buspirone	4	12
			Placebo	2	12
Sheehan	1990	8	TCA	10	8
			Buspirone	9	9
			Placebo	7	11
Other treatment comparisons					
Munjack	1989	5	BZD	15	5
			Beta-blocker	7	12
			Placebo	7	9
Pollack	2003	8	Paroxetine+BZD	4	16
			Paroxetine	4	18

Author	Year	Duration of treatment (weeks)	Intervention	Remission	Non- remission
Sheehan	1993	8	BZD	20	14
			Buspirone	8	19
			Placebo	10	21
Tiller	1999	8	MAOI	97	85
			Fluoxetine	104	80
Versiani	2002	8	NRI	19	18
			Placebo	9	29
Nardi	2011	8	BZD	49	14
			Paroxetine	39	18
Bertani	2004	12.8	NRI	9	18
			Paroxetine	17	13

BZDs, benzodiazepine; MAOIs, monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants

eTable 2. Exploring source of heterogeneity for remission by a meta-regression

Paroxetine vs placebo	N	Tau²	I²
None	7	0.02568	55.77
- Duration of treatment	7	0.02093	38.78
- Percent female	7	0.02892	56.99
- Mean age	6	0.02573	59.29
- Duration of panic disorder	4	0.05144	70.10
Venlafaxine vs placebo	N	Tau²	I²
None	4	0.01382	52.02
- Duration of treatment	4	5.3e-07	0
- Percent female	4	8.9e-07	0.01
- Mean age	4	0.01145	45.21
- Duration of panic disorder	4	2.2e-07	0

eTable 3. Estimation of the relative treatment effects (95% confidence intervals) from sensitivity analysis of disease remission

Placebo	1.51 (0.43,5.35)	1.29 (0.81,2.07)	1.27 (1.12,1.45)	1.38 (1.26,1.51)	1.10 (0.72,1.68)	1.30 (0.99,1.71)	1.47 (1.31,1.65)	1.39 (1.24,1.55)
	SSRI+BZD	0.85 (0.22,3.27)	0.84 (0.24,2.99)	0.91 (0.26,3.20)	0.73 (0.19,2.75)	0.86 (0.24,3.10)	0.97 (0.27,3.44)	0.92 (0.26,3.25)
		NRI	0.98 (0.61,1.59)	1.06 (0.67,1.70)	0.85 (0.45,1.60)	1.00 (0.59,1.71)	1.14 (0.70,1.83)	1.07 (0.66,1.73)
			SNRI	1.08 (0.94,1.24)	0.86 (0.56,1.34)	1.02 (0.76,1.36)	1.15 (0.97,1.37)	1.09 (0.92,1.29)
				SSRI	0.80 (0.52,1.23)	0.94 (0.73,1.22)	1.07 (0.94,1.22)	1.01 (0.88,1.15)
					Buspirone	1.18 (0.72,1.94)	1.33 (0.87,2.04)	1.26 (0.83,1.92)
						MAOI	1.13 (0.85,1.51)	1.07 (0.80,1.43)
							BZD	0.94 (0.84,1.06)
								TCA

Results are risk ratios (95% confidence intervals) between each pair of treatments from network meta-analysis. Comparisons are read from right to left. For example, the risk ratio for remission with TCA compared to BZD is 0.94 (95% CI: 0.84 to 1.06).

BZD, benzodiazepine; MAOI, monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitors; TCA, tricyclic antidepressants

eTable 4. Treatment comparisons and data used for pooling dropout rate

Author	Year	Duration of treatment	Definition of drop out	Intervention	Dropout	Non-dropout
BZDs vs placebo						
Ballenger	1988	8	AE, inefficacy	BZD	21	226
				Placebo	102	132
Klosko	1990	15	AE, inefficacy, protocol violation	BZD	1	16
				Placebo	7	11
Ciraulo	1990	14	AE, inefficacy	BZD	4	21
				Placebo	5	6
Tesar	1991	6	AE, inefficacy	BZD	4	20
				Placebo	14	8
Lydiard	1992	6	AE, inefficacy, administrative	BZD	7	21
				Placebo	18	15
Schweizer	1993	6	AE, intercurrent illness, patient withdraw, lost to F/U	BZD	15	87
				Placebo	31	61
Beauclair	1994	4	AE, inefficacy	BZD	1	12
				Placebo	8	8
Pecknold	1994	6	AE, inefficacy	BZD	9	60
				Placebo	20	49
Davidson	1994	4	Responded & dropped out, AE, protocol violation, inefficacy, patient withdraw	BZD	12	87
				Placebo	15	88
Carter	1995	4	AE, inefficacy, intercurrent illness, protocol violation, loss to F/U, patient withdraw	BZD	29	203
				Placebo	10	73
Noyes Jr	1996	8	AE, inefficacy	BZD	13	65
				Placebo	34	45
Rosenbaum	1997	9	AE, inefficacy	BZD	30	37
				Placebo	18	51
Moroz	1999	6	AE, inefficacy, loss to F/U, patient withdraw	BZD	41	181
				Placebo	55	161
Valenca	2003	6	Inefficacy	BZD	1	13
				Placebo	0	9
Savoldi	1995	4	AE, inefficacy	BZD	1	14

Author	Year	Duration of treatment	Definition of drop out	Intervention	Dropout	Non-dropout
				Placebo	6	9
TCAs vs placebo						
Lydiard	1993	12	Not reported	TCA	2	26
				Placebo	11	17
Mavissakalian	1995	8	Inefficacy, protocol violation, medication/pharmacy error	TCA	3	17
				Placebo	2	15
Caillard	1999	8	Inefficacy/worsening of symptoms, AE	TCA	15	46
				Placebo	25	32
Barlow	2000	12	Inefficacy, perceived improvement, lost to F/U, noncompliant, AE, unrelated to treatment	TCA	32	51
				Placebo	10	14
Broocks	1998	10	Not reported	TCA	0	15
				Placebo	4	11
TCAs vs BZDs vs placebo						
Uhlenhuth	1989	8	Not reported	TCA	10	10
				BZD	7	13
				Placebo	12	8
Taylor	1990	8	Not reported	TCA	5	22
				BZD	2	24
				Placebo	6	20
Andersch	1991	8	AE, inefficacy, refused treatment	TCA	11	30
				BZD	2	39
				Placebo	22	19
	1992	8	AE, inefficacy, refused treatment	TCA	118	273
				BZD	67	319
				Placebo	171	220
Keller	1993	16	NR	TCA	10	36
				BZD	8	35
				Placebo	13	24
Schweizer	1993	8	AE, inefficacy, unknown reasons	TCA	14	20
				BZD	4	33
				Placebo	20	15
Sheikh	1999	8	NR	TCA	1	9
				BZD	0	8
				Placebo	6	1

Author	Year	Duration of treatment	Definition of drop out	Intervention	Dropout	Non-dropout
Holland (adinazolam)	1999	24	Patient withdraw (most common reason)	TCA	42	86
				BZD	17	112
Holland (alprazolam)	1999	12	AE, inefficacy, others	TCA	22	144
				BZD	42	107
SSRIs vs Placebo						
Black	1993	8	AE, inefficacy, protocol violation, attempt suicide, intercurrent illness, loss to F/U	Fluvoxamine	21	4
				Placebo	18	7
Hoehn-Saric	1993	8	AE, inefficacy, loss F/U	Fluvoxamine	6	19
				Placebo	7	18
Sharp	1996	12	Not reported	Fluvoxamine	77	29
				Placebo	99	28
Sandmann	1998	6	AE, noncompliance, protocol violation, inefficacy	Fluvoxamine	6	17
				Placebo	5	18
Asnis	2001	8	AE, inefficacy, intercurrent illness, loss to F/U, protocol violation, attempt suicide, non-drug associated events	Fluvoxamine	29	58
				Placebo	29	63
Oehrberg	1995	12	AE, inefficacy, noncompliance, uncertain diagnosis	Paroxetine	5	55
				Placebo	8	52
Ballenger	1998	10	AE, inefficacy, anxiety-like symptom, non-compliance	Paroxetine	22	45
				Placebo	23	46
Sheehan	2005	10	AE, inefficacy, protocol violation, loss to F?U, other	Paroxetine	133	311
				Placebo	117	328
Hendriks	2010	14	NR	Paroxetine	3	14
				Placebo	1	11
Londborg	1998	12	AE, inefficacy, lost of F/U, noncompliance, protocol violation,	Sertraline	49	83
				Placebo	14	31

Author	Year	Duration of treatment	Definition of drop out	Intervention	Dropout	Non-dropout
			intercurrent illness, lab abnormality, other			
Pohl	1998	10	AE, inefficacy	Sertraline	21	59
				Placebo	15	73
Pollack	1998	10	AE, inefficacy, protocol violation, loss to F/U, patient withdraw, other	Sertraline	17	71
				Placebo	15	73
Michelson	1998	10	AE, inefficacy, lost to F/U, patient withdraw, protocol violation, satisfactory response	Fluoxetine	35	49
				Placebo	46	32
Stahl	2003	10	Lost to F/U, AE, patient withdraw, protocol violation, other	Escitalopram	331	97
				Placebo	547	72
SNRIs vs placebo						
Pollack	1996	8	Patient withdrawal, inefficacy, loss to F/U, AE	Venlafaxine	2	11
				Placebo	8	4
Liebowitz	2009	10	AE, loss to F/U, inefficacy, protocol violation, other, patient withdraw	Venlafaxine	65	110
				Placebo	53	115
Bradwejn	2005	10	AE, inefficacy	Venlafaxine	30	130
				Placebo	33	135
MAOIs vs placebo						
Van Vliet	1993	12	Inefficacy	MAOI	0	15
				Placebo	1	14
Loerch	1999	8	Inefficacy, protocol violation, AE	MOAI	7	9
				Placebo	2	9
TCAs vs SSRIs vs placebo						
Bakish	1996	8	AE, inefficacy	TCA	5	13
				Fluvoxamine	11	7
				Placebo	10	8
Nair	1996	8	AE, inefficacy	TCA	16	32
				Fluvoxamine	31	19
				Placebo	29	21

Author	Year	Duration of treatment	Definition of drop out	Intervention	Dropout	Non-dropout
Lecrubier	1997	12	Inefficacy, AE, noncompliance, loss to F/U, patient improvement, others	TCA	33	88
				Paroxetine	36	87
				Placebo	44	79
Bakker	1999	12	AE, inefficacy, non-compliance, patient improvement	TCA	3	29
				Paroxetine	4	28
				Placebo	2	30
Amore	1999	24	AE	TCA	1	18
				Fluoxetine	2	17
Lepola	2003	26	AE, inefficacy, patient withdraw, lost to F/U, others	TCA	37	32
				Sertraline	57	81
Wade	1997	8	AE, inefficacy, patient withdraw, lost to F/U, non-compliance, concurrent illness, no longer met study criteria	TCA	25	73
				Citalopram	26	71
				Placebo	25	71
SNRIs vs SSRIs vs placebo						
Pollack	2007	12	AE, inefficacy, patient withdrawal, loss to F/U, protocol violation, other, patient request	Venlafaxine	25	135
				Paroxetine	27	124
				Placebo	38	119
Pollack	2007	12	AE, loss to F/U, inefficacy, protocol violation, other, patient request	Venlafaxine	24	134
				Paroxetine	25	136
				Placebo	35	121
SSRIs+BZDs vs SSRIs						
Goddard	2001	12	AE, non-compliance, protocol violation, loss to F/U, clinical worsening	Sertraline + BZD	6	18
				Sertraline	10	16
Pollack	2003	8	Not reported	Paroxetine + BZD	11	9
				Paroxetine	11	11
TCAs vs buspirone vs placebo						
Pohl	1989	8	Loss to F/U, inefficacy, AE, administrative	TCA	4	10
				Buspirone	5	13
				Placebo	3	11

Author	Year	Duration of treatment	Definition of drop out	Intervention	Dropout	Non-dropout
Robinson	1989	8	Not reported	TCA	4	24
				Buspirone	8	26
				Placebo	4	25
Sheehan	1990	8	Not reported	TCA	0	18
				Buspirone	2	16
				Placebo	0	18
BZDs vs buspirone vs placebo						
Schweizer	1988	4	Not reported	BZD	0	9
				Buspirone	5	2
Sheehan	1993	8	AE	BZD	1	33
				Buspirone	11	23
				Placebo	4	29
Other treatment comparisons						
Munjack	1989	5	Patient withdraw, inefficacy, AE	BZD	0	20
				Beta-blocker	4	15
				Placebo	5	11
Versiani	2002	8	AE, loss to F/U, protocol violation, patient withdraw, medical illness	NRI	11	31
				Placebo	21	17
Woods	1992	4	AE, inefficacy	TCA	9	16
				TCA + BZD	6	17
Nardi	2011	8	Inefficacy	BZD	1	62
				Paroxetine	2	55
Pini	2003	16	AE, inefficacy, early improvement, patient withdraw, loss to F/U, noncompliance, protocol violation, medical illness, others	MAOI	4	14
				Paroxetine	2	12
Ribeiro	2001	8	AE	NaSSA	2	12
				Fluoxetine	3	10
Kruger	1999	8	Inefficacy, AE, protocol violation, others	MAOI	15	38
				TCA	15	38
Bertani	2004	12.8	AE, protocol violation	NRI	7	27
				Paroxetine	4	30

AE, adverse event; BZD, benzodiazepine; F/U, follow-up; MAOIs, monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants

eTable 5. Exploring sources of heterogeneity for dropout rate by a meta-regression

BZDs vs placebo	N	Tau²	I²
Including co-variable			
None	24	0.2995	71.69
- Duration of treatment	24	0.3137	72.58
- Percent female	21	0.3268	74.42
- Mean age	20	0.1436	53.19
- Duration of panic disorder	10	0.7212	79.83
- Percent agoraphobia	16	0.3815	75.75
TCAs vs BZDs	N	Tau²	I²
None	9	0.3971	78.55
- Percent female	8	0.02192	15.23
- Duration of treatment	8	0.0	0
- Mean age	7	0.01889	12.87
- Percent agoraphobia	5	0.1316	36.25

BZD, benzodiazepine; TCA, tricyclic antidepressants

eTable 6. Estimation of the relative treatment effects (95% confidence intervals) of sensitivity analysis of dropout

Placebo	0.84 (0.43,1.64)	0.58 (0.10,3.29)	0.69 (0.34,1.38)	0.83 (0.59,1.16)	0.94 (0.79,1.11)	1.65 (0.90,3.02)	1.68 (0.44,6.51)	0.39 (0.29,0.53)	0.70 (0.57,0.87)
	TCA plus BZD	0.69 (0.11,4.36)	0.82 (0.31,2.13)	0.99 (0.47,2.06)	1.12 (0.59,2.13)	1.96 (0.80,4.82)	2.00 (0.44,9.05)	0.47 (0.23,0.97)	0.84 (0.42,1.67)
		NaSSA	1.18 (0.18,7.63)	1.43 (0.25,8.33)	1.62 (0.29,9.08)	2.84 (0.45,17.83)	2.90 (0.32,26.16)	0.68 (0.12,3.93)	1.21 (0.21,6.93)
			NRI	1.21 (0.56,2.63)	1.37 (0.67,2.78)	2.41 (0.95,6.07)	2.46 (0.54,11.28)	0.57 (0.27,1.23)	1.03 (0.49,2.13)
				SNRI	1.13 (0.79,1.62)	1.99 (1.00,3.97)	2.03 (0.50,8.17)	0.47 (0.30,0.74)	0.85 (0.57,1.26)
					SSRI	1.76 (0.94,3.29)	1.80 (0.46,7.01)	0.42 (0.30,0.59)	0.75 (0.58,0.96)
						Buspirone	1.02 (0.23,4.49)	0.24 (0.12,0.46)	0.43 (0.23,0.79)
							MAOI	0.23 (0.06,0.93)	0.42 (0.11,1.64)
								BZD	1.79 (1.28,2.49)
									TCA

Results are risk ratios (95% confidence intervals) between each pair of treatments from network meta-analysis. Comparisons are read from right to left. For example, the risk ratio for dropout with TCA compared to BZD is 1.79 (95% CI: 1.28 to 2.49).

BZDs, benzodiazepines; MAOIs, monoamine oxidase inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants

eTable 7. Treatment comparisons and data used for pooling treatment effects on anxiety score

Author	Year	Measurement	Intervention	N	Mean	SD
TCAs vs placebo						
Lydiard	1993	HAM-A	TCA	28	9.3	7.7
			Placebo	28	11.8	8
Broocks	1998	HAM-A	TCA	15	8.5	3.7
			Placebo	15	22.9	9.8
Caillard	1999	HAM-A	TCA	51	10.2	8.6
			Placebo	51	15.9	9.8
BZDs vs placebo						
Klosko	1990	HAM-A	BZD	16	13.68	7.02
			Placebo	11	13.36	5.63
Schweizer	1993	HAM-A	BZD	102	-11.6	7.9
			Placebo	92	-6.1	8.5
Pecknold	1994	HAM-A	BZD	69	-10.4	9.14
			Placebo	70	-6.7	8.2
Beauchair	1994	Modified HAM-A	BZD	13	22.2	11.8
			Placebo	16	45.1	9.6
Davidson	1994	HAM-A	BZD	99	10.9	5.97
			Placebo	103	13.3	6.09
Savoldi	1995	HAM-A	BZD	14	9.79	5.19
			Placebo	9	18.56	4.25
Noyes Jr	1996	HAM-A	BZD	78	9.9	8.4
			Placebo	79	15.4	10
SSRIs vs placebo						
Westernberg	1989	HAM-A	Fluvoxamine	20	9.8	2.83
			Placebo	20	20.63	2.37
Asnis	2001	CAS	Fluvoxamine	87	6.7	6.1
			Placebo	92	9.1	6.1
Hoehn-Saric	1993	CAS	Fluvoxamine	18	3.71	1.71
			Placebo	18	7.93	2.79
Ballenger	1998	HAM-A	Paroxetine	67	11.3	8.3
			Placebo	69	13.1	8.3
Sheehan	2005	HAM-A	Paroxetine	361	11.49	7.41
			Placebo	384	13.72	7.45
Michelson	1998	HAM-A	Fluoxetine	79	-7.3	7.6
			Placebo	74	-5.3	7.8
Michelson	2001	HAM-A	Fluoxetine	90	-14.9	9.1
			Placebo	90	-10	9.9
Pollack	1998	HAM-A	Sertraline	88	-9.5	8.21

			Placebo	88	-8.32	8.53
Stahl	2003	HAM-A	Escitalopram	125	-6.1	7.83
			Placebo	114	-4.6	8.54
SNRI vs placebo						
Pollack	1996	HAM-A	Venlafaxine	13	12.33	8.6
			Placebo	12	15.55	8.02
Liebowitz	2009	HAM-A	Venlafaxine	104	-9.51	6.93
			Placebo	105	-7.65	6.97
MAOIs vs placebo						
Van Vilet	1993	HAM-A	MAOI	15	15.05	3.06
			Placebo	14	23.29	2.02
Loerch	1999	HAM-A	MAOI	16	19.88	9.75
			Placebo	11	20.82	12.56
TCAs vs SSRIs						
Bystritsky	1995	HAM-A	TCA	11	15	11
			Fluoxetine	10	8	6
Lepola	2003	CAS	TCA	69	7.1	6
			Sertraline	138	7.1	5.2
MAOIs vs SSRIs						
Van Vilet	1996	HAM-A	MAOI	15	6.1	2.71
			Fluvoxamine	15	5.5	2.71
Pini	2003	HAM-A	MAOI	18	11.56	1.84
			Paroxetine	14	5.86	1.96
TCAs vs BZDs vs placebo						
Schweizer	1993	HAM-A	TCA	30	9.4	8.8
			BZD	37	6.3	6.7
			Placebo	32	9.9	8.4
Sheikh	1999	HAM-A	TCA	9	5.3	3.65
			BZD	8	3.87	5.62
			Placebo	4	15	10.55
Other comparisons						
Woods	1992	HAM-A	TCA	25	15.59	4.01
			TCA + BZD	23	13.11	3.6
Pollack	2003	HAM-A	Paroxetine	22	16	7.2
			Paroxetine + BZD	20	16.8	6.8
Nardi	2011	HAM-A	BZD	63	10.5	3.9
			Paroxetine	57	10.4	3.7
Ravaris	1991	HAM-A	BZD	14	9.89	3.93
			Beta-blocker	15	7.64	4.82
Hirschmann	2000	HAM-A	Fluoxetine + beta-blocker	13	3.4	2.5

			Fluoxetine	12	9.9	3.4
Seedat	2003	HAM-A	NRI	8	15.3	8.8
			Citalopram	9	13.3	14.9
Bakker	1999	HAM-A	Paroxetine	32	12.4	7.5
			TCA	32	12.9	6
			Placebo	32	16.9	8.2
Munjack	1989	HAM-A	BZD	20	12.7	7.79
			Beta-blocker	19	14.68	6.22
			Placebo	16	19.56	11.92
Sheehan	1993	HAM-A	BZD	33	12.5	8.1
			Buspirone	23	16.1	8.1
			Placebo	29	17.9	7.1
Sheehan	1990	HAM-A	TCA	18	15.3	9.1
			Buspirone	16	15.9	8.3
			Placebo	18	18.7	7.7

BZDs, benzodiazepine; MAOIs, monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs; tricyclic antidepressants; BB, beta-blockers; HAM-A, Hamilton Scale for Anxiety; CAS, Clinical Anxiety Scale

eTable 8. Exploring sources of heterogeneity for anxiety score by a meta-regression

TCA vs placebo	N	Tau2	I2
Including co-variable			
None	7	14.71	73.75
- Mean age	5	27.89	83.68
- Duration of treatment	7	19.54	77.79
- Percent of female	6	14.08	73.38
- Duration of panic disorder	3	27.87	85.39
- Percent of agoraphobia	3	60.62	91.63
BZDs vs placebo		Tau2	I2
None	10	2.241	45.6
- Duration of treatment	10	3.109	52.70
- Percent of female	9	2.493	50.42
- Mean age	9	1.641	42.11
- Duration of panic disorder	3	0	0
- Percent of agoraphobia	5	0	0

BZD, benzodiazepine; TCA, tricyclic antidepressants

eTable 9. Treatment comparisons and data used for pooling of depression score

Author	Year	Measurement	Intervention	N	mean	SD
BZDs vs placebo						
Schweizer	1993	HAM-D	BZD	102	-5.5	6.3
			Placebo	92	-3.5	5.7
Beauclair	1994	HAM-D	BZD	12	5.8	2.2
			Placebo	14	12.6	4.7
Pecknold	1994	HAM-D	BZD	69	-8	9.14
			Placebo	70	-4.3	6.02
Savoldi	1995	HAM-D	BZD	14	5.1	1.59
			Placebo	9	13.22	2.99
Pollack	1996	HAM-D	BZD	13	8.92	7.4
			Placebo	12	10.64	4.34
SSRIs vs placebo						
Michelson	1998	HAM-D	Fluoxetine	71	-3.5	5.4
			Placebo	58	-1.9	5.1
Michelson	2001	HAM-D	Fluoxetine	90	-6.5	4.7
			Placebo	90	-4.2	5.8
MAOI vs placebo						
Van Vilet	1993	MADRS	MAOI	15	6.6	3.4
			Placebo	14	9.7	2.5
Loerch	1999	HAM-D	MAOI	16	12	7.4
			Placebo	11	11.09	7.38
TCA vs SSRI						
Lepola	2003	MADRS	TCA	69	11.2	10.4
			Sertraline	138	11.1	10.8
Byrtritsky	1995	HAM-D	TCA	11	10	7
			Fluoxetine	10	7	6
Bakker	1999	MADRS	TCA	32	8.5	5.3
			Paroxetine	32	6.7	7.3
			Placebo	32	10.2	6.7
Other comparisons						
Broocks	1998	MADRS	TCA	15	6.1	2.9
			Placebo	15	17.3	7.4
Pini	2003	HAM-D	MAOI	18	10.94	5.90
			Paroxetine	14	7.07	8.23
Hirschmann	2000	HAM-D	Fluoxetine + Beta-blocker	12	3.7	1.9
			Fluoxetine	11	8.5	3
Pollack	2003	HAM-D	Paroxetine	22	9.2	5.4
			paroxetine + BZD	20	11.8	4.4

Author	Year	Measurement	Intervention	N	mean	SD
Seedat	2003	MADRS	NRI	8	11.5	5.7
			Citalopram	9	7.4	6.2
Munjack	1989	HAM-D	BZD	20	12.3	8.24
			Beta-blocker	19	13.95	5.71
			Placebo	16	17.31	10.74
Sheehan	1993	HAM-D	BZD	33	10.1	7
			Buspirone	23	11.5	7.2
			Placebo	29	13.3	6.6
Sheehan	1990	HAM-D	TCA	18	7.9	5.5
			Buspirone	16	9.8	6.5
			Placebo	18	11.2	5.3
Sheikh	1999	HAM-D	TCA	9	3.2	2.39
			BZD	8	3.88	6.11
			Placebo	4	9	7.44

BZD, benzodiazepine; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; HAM-D, Hamilton rating scale for depression; MADRS, Montgomery-Åsberg depression rating scale

eTable 10. Results from meta-regression of depression score

BZDs vs placebo	N	Tau²	I²
Including co-variable			
None	8	4.651	68.29
- Percent of female	6	6.079	79.57
- Mean age	6	5.974	78.60
- Duration of treatment	7	1.044	31.10
- Percent of agoraphobia	3	0	0

BZDs; benzodiazepine

eTable 11. Treatment comparisons and data used for pooling of adverse events

Author	Year	Most common reported Adverse events	Intervention	Adverse events	No adverse events
BZDs vs placebo					
Tesar	1991	Sedation	BZD	15	9
		Sedation	Placebo	8	16
Lydiard	1992	Sedation	BZD	7	23
		Sedation	Placebo	7	26
Schweizer	1993	Nervousness	BZD	90	12
		Nervousness	Placebo	36	56
Beauclair	1994	Sedation	BZD	9	4
		Headache	Placebo	5	11
Pecknold	1994	Sedation	BZD	59	10
		Sedation	Placebo	34	35
Davidson	1994	Sedation	BZD	71	28
		Sedation	Placebo	41	62
Carter	1995	Nausea	BZD	146	86
		Incoordination	placebo	26	57
Savoldi	1995	Sedation	BZD	5	10
		Dizziness	Placebo	2	13
Noyes Jr	1996	Sedation	BZD	59	18
		Sedation	Placebo	32	45
Rosenbaum	1997	Sedation	BZD	28	40
		Sedation	Placebo	21	48
Moroz	1999	Sedation	BZD	105	125
		Headache	Placebo	52	173
Valenca	2000	Sedation	BZD	7	6
		Dizziness	Placebo	6	3
SSRIs vs placebo					
Hoehn-Saric	1993	Sedation	Fluvoxamine	5	13
		Dry mouth	Placebo	3	15
Sandmann	1998	Nausea	Fluvoxamine	9	14
		Nausea	Placebo	6	17
Asnis	2001	Nausea	Fluvoxamine	84	9
		Nausea	Placebo	70	25
Oehrberg	1995	Nausea	Paroxetine	46	9
		Nausea	Placebo	33	19
Ballenger	1998	Headache	Paroxetine	19	48
		Headache	Placebo	30	39
Sheehan	2005	Abnormal ejaculation	Paroxetine	120	324

Author	Year	Most common reported Adverse events	Intervention	Adverse events	No adverse events
		Nausea	Placebo	76	369
Londborg	1998	Nausea	Sertraline	42	85
		Headache	Placebo	18	26
Pohl	1998	Nausea	Sertraline	26	54
		Nausea	Placebo	15	73
Pollack	1998	Insomnia	Sertraline	83	5
		Headache	Placebo	77	11
Stahl	2003	Headache	Escitalopram	20	108
		Headache	Placebo	18	101
Michelson	2001	Not reported	Fluoxetine	25	65
		Not reported	Placebo	19	71
SNRI vs placebo					
Pollack	1996	Headache	Venlafaxine	6	7
		Headache	Placebo	2	10
Bradwejn	2005	Insomnia	Venlafaxine	152	25
		Dry mouth	Placebo	138	40
Liebowitz	2009	Nausea	Venlafaxine	12	143
		Nausea	Placebo	7	148
TCAs vs BZDs					
Holland (adinazolam)	1999	Dry mouth	TCA	41	87
		Sedation	BZD	40	89
Holland (alprazolam)	1999	Dry mouth	TCA	77	72
		Sedation	BZD	24	142
Andersch	1991	Dry mouth	TCA	29	11
		Sedation	BZD	35	6
		Headache	Placebo	18	20
	1992	Dry mouth	TCA	203	188
		Sedation	BZD	224	162
		Dry mouth	Placebo	86	305
Schweizer	1993	Dry mouth	TCA	28	6
		Sedation	BZD	33	4
		Sedation	Placebo	18	17
TCAs vs SSRIs					
Lepola	2003	Dry mouth	TCA	37	30
		Nausea	Sertraline	40	94
Nair	1996	Dry mouth	TCA	48	0
		Nausea	Fluvoxamine	45	5
		Headache	Placebo	45	5
Bakish	1996	Dry mouth	TCA	5	13
		Dry mouth	Fluvoxamine	5	13

Author	Year	Most common reported Adverse events	Intervention	Adverse events	No adverse events
		-	Placebo	2	16
Wade	1997	Dry mouth	TCA	32	66
		Headache	Citalopram	32	65
		Headache	Placebo	27	69
Lecrubier	1997	Dry mouth	TCA	108	13
		Sweating	Paroxetine	90	33
		Headache	Placebo	83	40
SNRIs vs SSRIs					
Pollack	2007	Not reported	Venlafaxine	138	22
		Not reported	Paroxetine	129	32
		Not reported	Placebo	129	33
Pollack	2007	Sweating	Venlafaxine	117	41
		Sedation	Paroxetine	121	40
		Sweating	Placebo	105	51
SSRIs+BZDs vs SSRIs					
Goddard	2001	Sexual dysfunction	Sertraline + BZD	8	14
		Sexual dysfunction	Sertraline	8	16
Pollack	2003	Sedation	Paroxetine + BZD	17	3
		GI	Paroxetine	15	7
SSRIs vs NRIs					
Bertani	2004	Sexual dysfunction	Paroxetine	15	15
		Dry mouth	Reboxetine	12	15
Seedat	2003	Dry mouth	Citalopram	7	5
		Dry mouth	Reboxetine	6	7
SSRIs vs MAOI					
Tiller	1999	Nausea	Fluoxetine	128	56
		Headache	MAOI	115	67
Van Vliet	1996	Nausea	Fluvoxamine	10	5
		Nausea	MAOI	10	5
Other comparisons					
Van Vliet	1993	Sleep disturbance	MAOI	13	1
		Nausea	Placebo	4	12
Versiani	2002	Dry mouth	NRI	30	7
		Blurred vision	Placebo	27	10
Woods	1992	Not reported	TCA + BZD	5	18
		Not reported	TCA	5	20
Kruger	1999	Dry mouth	TCA	63	5
		Nausea	MAOI	50	17

Author	Year	Most common reported Adverse events	Intervention	Adverse events	No adverse events
Nardi	2011	Sedation	BZD	46	17
		Sedation	Paroxetine	54	3
Pohl	1989	Dry mouth	TCA	14	6
		Dizziness	Buspirone	6	12
		Dry mouth	Placebo	8	14
Sheehan	1993	Sedation	BZD	22	12
		Sedation	Buspirone	5	22
		Cognitive impairment	Placebo	6	25
Ribeiro	2001	Sedation	Mirtazapine	9	5
		Nausea	Fluoxetine	5	8

BZD, benzodiazepine; MAOIs; monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants

eTable 12. Results from meta-regression of adverse events

TCAs vs placebo	N	Tau²	I²
Including co-variables			
None	8	0.06528	82.47
- Percent female	8	0.07521	82.54
- Mean age	7	0.06741	85.49
- Percent of agoraphobia	7	0.06587	79.28

TCAs; tricyclic antidepressants

eTable 13. Estimation of the relative treatment effects (95% confidence intervals) of sensitivity analysis of adverse events

Placebo	1.41 (0.91,2.19)	1.96 (0.82,4.67)	1.06 (0.76,1.48)	1.19 (0.95,1.50)	1.17 (1.03,1.33)	0.69 (0.38,1.25)	1.14 (0.86,1.53)	1.86 (1.54,2.24)	1.53 (1.28,1.83)
	SSRI+BZD	1.38 (0.53,3.60)	0.75 (0.44,1.29)	0.84 (0.52,1.37)	0.83 (0.54,1.26)	0.49 (0.23,1.02)	0.81 (0.49,1.34)	1.31 (0.82,2.11)	1.08 (0.68,1.72)
		NaSSA	0.54 (0.22,1.37)	0.61 (0.25,1.49)	0.60 (0.25,1.41)	0.35 (0.12,1.01)	0.59 (0.24,1.45)	0.95 (0.39,2.30)	0.78 (0.32,1.89)
			NRI	1.12 (0.75,1.67)	1.10 (0.79,1.54)	0.65 (0.33,1.28)	1.08 (0.70,1.65)	1.75 (1.20,2.55)	1.44 (1.00,2.09)
				SNRI	0.98 (0.77,1.25)	0.58 (0.31,1.09)	0.96 (0.67,1.37)	1.56 (1.16,2.08)	1.29 (0.97,1.70)
					SSRI	0.59 (0.32,1.07)	0.98 (0.74,1.29)	1.59 (1.27,1.97)	1.31 (1.08,1.59)
						Buspirone	1.66 (0.87,3.15)	2.69 (1.49,4.85)	2.22 (1.24,3.99)
							MAOI	1.62 (1.18,2.23)	1.34 (1.01,1.77)
								BZD	0.83 (0.68,1.00)
									TCA

Results are risk ratios (95% confidence intervals) between each pair of treatments from network meta-analysis. Comparisons are read from right to left. For example, the risk ratio for dropout with TCA compared to BZD is 0.83 (95% CI: 0.68 to 1.00).

BZDs, benzodiazepines; MAOIs, monoamine oxidase inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants

eTable 14. Evaluation of the certainty of evidence from network meta-analysis of remission for drug classes

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
<i>Mixed estimates</i>								
Beta-blocker:BZD	1	Major concerns	Low risk	Some concerns	No concerns	Some concerns	No concerns	Very low
Bupirone:BZD	1	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low
BZD:Placebo	18	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
BZD:SSRI	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
BZD:TCA	6	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Low
Beta-blocker:Placebo	1	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Bupirone:Placebo	3	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Bupirone:TCA	2	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
MAOI:SSRI	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low

NRI:Placebo	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Low
NRI:SSRI	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
Placebo:SNRI	4	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Placebo:SSRI	18	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Placebo:TCA	12	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
SNRI:SSRI	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
SSRI:SSRI+BZD	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SSRI:TCA	5	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
<i>Indirect estimates</i>								
BZD:MAOI	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
BZD:NRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
BZD:SNRI	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
BZD:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

Beta-blocker:Buspirone	0	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Beta-blocker:MAOI	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Beta-blocker:NRI	0	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Beta-blocker:SNRI	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Beta-blocker:SSRI	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Beta-blocker:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:TCA	0	Major concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low
Buspirone:MAOI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:NRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:SSRI	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Buspirone:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:NRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

MAOI:Placebo	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
MAOI:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SNRI:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SNRI:TCA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
SSRI+BZD:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

BZDs, benzodiazepines; MAOIs, monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCAs, tricyclic anti-depressants

eTable 15. Evaluation of the certainty of evidence from network meta-analysis of drop-out for drug classes

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
<i>Mixed estimates</i>								
Beta-blocker:BZD	1	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Buspirone:BZD	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
BZD:Placebo	24	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
BZD:SSRI	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
BZD:TCA	9	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
Beta-blocker:Placebo	1	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Buspirone:Placebo	4	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Buspirone:TCA	3	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
MAOI:Placebo	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:SSRI	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

MAOI:TCA	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:Placebo	1	Some concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
NRI:SSRI	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:SSRI	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:SNRI	5	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:SSRI	21	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:TCA	20	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
SNRI:SSRI	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SSRI:SSRI+BZD	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SSRI:TCA	7	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
TCA:TCA+BZD	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
<i>Indirect estimates</i>								
BZD:MAOI	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
BZD:NRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

BZD:NaSSA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
BZD:SNRI	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
BZD:SSRI+BZD	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
BZD:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:Buspirone	0	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Beta-blocker:MAOI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:NRI	0	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
Beta-blocker:NaSSA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:SSRI	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:TCA	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Beta-blocker:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

Buspirone:MAOI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:NRI	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Buspirone:NaSSA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:SNRI	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Buspirone:SSRI	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
Buspirone:SSRI+BZD	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Buspirone:TCA+BZD	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
MAOI:NRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:NaSSA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:NRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

NRI:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NRI:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:SNRI	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SNRI:SSRI+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SNRI:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

SNRI:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SSRI:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SSRI+BZD:TCA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
SSRI+BZD:TCA+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

BZDs, benzodiazepines; MAOIs, monoamine oxidase inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCAs, tricyclic anti-depressant

eTable 16. Evaluation of the certainty of evidence from network meta-analysis of adverse drug events for drug classes

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
<i>Mixed estimates</i>								
Buspirone:BZD	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
BZD:Placebo	16	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Very low
BZD:TCA	5	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
Buspirone:Placebo	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:TCA	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
MAOI:SSRI	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:TCA	1	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
NRI:Placebo	1	Some concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low
NRI:SSRI	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:SSRI	1	Some concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low
Placebo:SNRI	4	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:SSRI	13	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	Low
Placebo:TCA	6	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate
SNRI:SSRI	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
SSRI:SSRI+BZD	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
SSRI:TCA	3	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
TCA:TCA+BZD	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
<i>Indirect estimates</i>								
BZD:MAOI	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
BZD:NRI	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
BZD:NaSSA	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
BZD:SNRI	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
BZD:SSRI	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
BZD:SSRI+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
BZD:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:MAOI	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Buspirone:NRI	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Buspirone:NaSSA	0	Some concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	Low
Buspirone:SNRI	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Buspirone:SSRI	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Buspirone:SSRI+BZD	0	Some concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	Low

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Buspirone:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:NRI	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:NaSSA	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:Placebo	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
MAOI:SNRI	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:SSRI+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
MAOI:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:NRI	0	Some concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low
NRI:SNRI	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
NRI:SSRI+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
NRI:TCA	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Moderate
NRI:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:Placebo	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
NaSSA:SNRI	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
NaSSA:SSRI+BZD	0	Some concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Very low
NaSSA:TCA	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
NaSSA:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:SSRI+BZD	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low
Placebo:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
SNRI:SSRI+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
SNRI:TCA	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low
SNRI:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
SSRI:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
SSRI+BZD:TCA	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low
SSRI+BZD:TCA+BZD	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low

BZDs, benzodiazepines; MAOIs, monoamine oxidase inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCAs, tricyclic anti-depressants

eTable 17. Evaluation of the certainty of evidence from network meta-analysis of remission for individual SSRIs

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
<i>Mixed estimates</i>								
Citalopram:Escitalopram	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram:Fluoxetine	1	Major concerns	Low risk	Some concerns	Some concerns	Some concerns	No concerns	Very low
Citalopram:Paroxetine	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram:Placebo	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Placebo	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine:Placebo	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine:Placebo	5	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Paroxetine:Paroxetine+BZD	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine:Placebo	7	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Placebo:Sertraline	3	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
<i>Indirect estimates</i>								
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine+BZD:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine+BZD:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

BZD, benzodiazepine

eTable 18. Evaluation of the certainty of evidence from network meta-analysis of adverse drug events for individual SSRIs

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
<i>Mixed estimates</i>								
Citalopram:Escitalopram	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram:Paroxetine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Placebo	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram:Placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Placebo	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Placebo	5	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:Paroxetine+BZD	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Paroxetine:Placebo	6	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
Paroxetine:Sertraline	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
Placebo:Sertraline	3	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline:Sertraline+BZD	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
<i>Indirect estimates</i>								
Citalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Citalopram:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluoxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Fluvoxamine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Paroxetine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Sertraline	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:Paroxetine	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low
Fluvoxamine:Paroxetine+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Fluvoxamine:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine+BZD:Placebo	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low
Paroxetine+BZD:Sertraline	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
Paroxetine+BZD:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Placebo:Sertraline+BZD	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

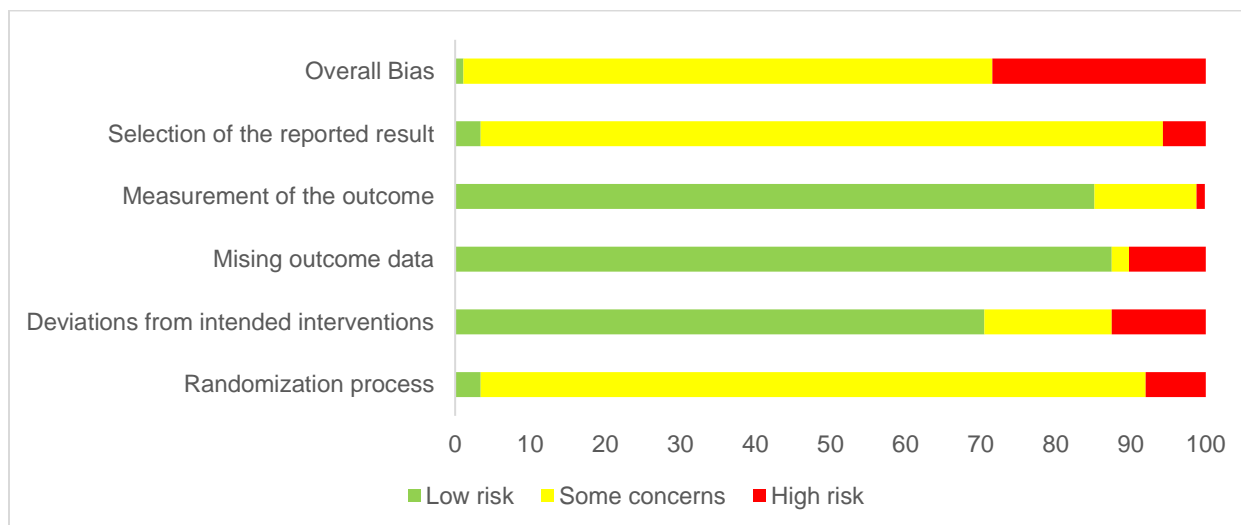
BZD, benzodiazepine

eTable 19. Comparisons of one-stage and two-stage network meta-analyses for outcomes with zero events

Treatment comparisons	One-stage approach	Two-stage approach
	RR (95% CI)	RR (95% CI)
<i>Dropout</i>		
TCA vs placebo	0.71 (0.64, 0.79)	0.71 (0.58, 0.88)
BZD vs placebo	0.46 (0.41, 0.52)	0.46 (0.37, 0.58)
Beta-blocker vs placebo	0.90 (0.11, 1.69)	0.81 (0.23, 2.81)
MAOI vs placebo	0.85 (0.50, 1.20)	0.99 (0.49, 2.02)
Buspirone vs placebo	1.37 (0.97, 1.74)	1.79 (0.97, 3.31)
SSRI vs placebo	0.71 (0.83, 0.99)	0.92 (0.77,1.10)
SNRI	0.89 (0.75, 1.03)	0.81 (0.56,1.18)
NRI	0.66 (0.32, 1.01)	0.70 (0.33,1.47)
NaSSA	0.54 (0.01, 1.28)	0.57 (0.10, 3.34)
TCA+BZD	0.59 (0.06, 1.12)	0.52 (0.17,1.59)
SSRI+BZD	0.91 (0.43, 1.39)	0.82 (0.40,1.67)
<i>Adverse drug events</i>		
TCA vs placebo	1.75 (1.55, 1.94)	1.79 (1.47,2.19)
BZD vs placebo	1.67 (1.51, 1.83)	1.76 (1.50,2.06)
MAOI vs placebo	1.07 (0.86, 1.29)	1.25 (0.84, 1.85)
Buspirone vs placebo	0.84 (0.48, 1.21)	0.73 (0.39, 1.38)
SSRI vs placebo	1.19 (1.09, 1.30)	1.19 (1.01, 1.41)
SNRI	1.31 (1.13, 1.51)	1.24 (0.90, 1.69)
NRI	1.16 (0.81, 1.51)	1.06 (0.71, 1.60)
NaSSA	1.73 (0.98, 2.48)	1.99 (0.77, 5.14)
TCA+BZD	1.64 (0.98, 2.31)	1.94 (0.57, 6.63)
SSRI+BZD	1.46 (0.97, 1.95)	1.43 (0.84, 2.45)



*Bold letters represent comparisons with zero cells

eFigure 1. Risk of bias summary for all included studies



eFigure 2. Risk of bias analysis for individual studies

Studies	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Lydiard 1993	Desipramine	Placebo	?	+	+	+	?	!
Mavissakalian 1995	Imipramine	Placebo	?	-	-	+	?	-
Caillard 1999	Clomipramine	Placebo	?	+	+	+	?	!
Bandelow 2000	Clomipramine	Placebo	?	+	+	+	?	!
Barlow 2000	Imipramine	Placebo	?	+	+	+	?	!
Ballenger 1988	Alprazolam	Placebo	+	+	+	+	+	+
Ciraulo 1990	Alprazolam	Placebo	-	+	+	?	?	-
Klosko 1990	Alprazolam	Placebo	-	+	+	+	?	-
Tesar 1991	Alprazolam	Placebo	?	+	+	+	?	!
Lydiard 1992	Alprazolam	Placebo	-	+	+	+	?	-
Schweizer 1993	Alprazolam	Placebo	?	+	+	+	?	!
Pecknold 1994	Alprazolam	Placebo	?	+	+	+	?	!
Beauchair 1994	Clonazepam	Placebo	?	+	+	+	?	!
Davidson 1994	Adinazolam	Placebo	?	+	+	?	?	!
Carter 1995	Adinazolam	Placebo	?	+	+	+	?	!
Savoldi 1995	Etizolam	Placebo	?	-	+	+	?	-
Noyes Jr 1996	Alprazolam	Placebo	?	+	+	+	?	!
Rosenbaum 1997	Clonazepam	Placebo	?	+	+	+	?	!
Moroz 1999	Clonazepam	Placebo	?	+	+	+	?	!
Valenca 2000	Clonazepam	Placebo	?	?	+	?	?	!
Valenca 2003	Clonazepam	Placebo	?	?	+	+	?	!
Oehrberg 1995	Paroxetine	Placebo	?	+	+	+	?	!
Ballenger 1998	Paroxetine	Placebo	?	+	+	+	?	!
Bergink 2005	paroxetine	Placebo	?	+	+	+	?	!
Sheehan 2005	Paroxetine	Placebo	?	+	+	+	?	!
Hendriks 2010	Paroxetine	Waitlist	+	+	+	?	?	!
Westenberg 1989	Fluvoxamine	Placebo	?	?	+	?	?	!
Black 1993	Fluvoxamine	Placebo	-	+	+	+	?	-
Hoehn-Saric 1993	Fluvoxamine	Placebo	?	?	?	?	?	-
Sandmann 1998	Fluvaxamine	Placebo	?	+	+	+	?	!
Asnis 2001	Fluvoxamine	Placebo	?	+	+	+	?	!

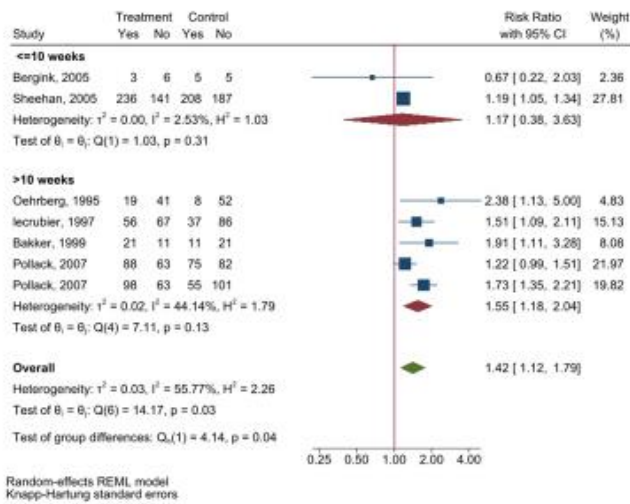
 Low risk
 Some concerns
 High risk

Sharp 1996	Fluvoxamine	Placebo	?	-	-	+	-	-
Michelson 1998	Fluoxetine	Placebo	?	+	+	+	?	!
Michelson 2001	Fluoxetine	Placebo	?	?	+	+	?	!
Pohl 1998	Sertraline	Placebo	?	+	+	+	?	!
Londberg 1998	Sertraline	Placebo	?	+	+	+	?	!
Pollack 1998	Sertraline	Placebo	?	+	+	+	?	!
Pollack 1996	Venlafaxine	Placebo	?	+	+	+	?	!
Bradwejn 2005	Venlafaxine	Placebo	?	+	+	+	?	!
Liebowitz 2009	Venlafaxine	Placebo	?	+	+	+	+	!
Van Vliet 1993	Brofaromine	Placebo	?	?	+	+	?	!
Loerch 1999	Moclobemide	Placebo	?	+	+	+	?	!
Holland 1999	Alprazolam	Clomipramine	?	?	-	+	?	-
Holland 1999	Adinazolam	Clomipramine	?	+	+	?	?	!
Uhlenhuth 1989	Alprazolam	Imipramine	?	+	+	+	?	!
Taylor 1990	Alprazolam, Imipramine	Placebo	?	?	-	+	?	-
Andersch 1991	Imipramine	Alprazolam	-	+	+	+	?	-
1992	Alprazolam, Imipramine	Placebo	?	+	+	+	+	!
Keller 1993	Alprazolam, Imipramine	Placebo	?	+	+	+	?	!
Schweizer 1993	Alprazolam	Imipramine	?	?	+	?	?	!
Sheikh 1999	Alprazolam, Imipramine	Placebo	?	-	+	+	?	-
Amore 1999	Fluoxetine	Citalopram	?	+	+	+	-	-
2010	Sertraline	Paroxetine	?	?	?	+	?	!
Bandelow 2004	Sertraline	Paroxetine	?	+	+	+	?	!
Perna 2001	Citalopram	Paroxetine	?	-	+	+	?	-
Marchesi 2006	Paroxetine	Citalopram	?	-	+	+	?	-
Stahl 2003	Escitalopram	Placebo	?	?	+	+	?	!
Bystritsky 1995	Desipramine	Fluoxetine	?	+	+	+	?	!
Amore 1999	Imipramine	Fluoxetine	?	+	+	+	-	-
Lepola 2003	Sertraline	Imipramine	?	+	+	+	?	!
Bakker 1999	Paroxetine, Clomipramine	Placebo	-	+	+	+	?	-
Lecrubier 1997	Paroxetine, Clomipramine	Placebo	?	+	+	?	?	!
Nair 1996	Fluvoxamine, Imipramine	Placebo	?	+	+	+	?	!
Bakish 1996	Fluvoxamine	Imipramine	?	-	-	+	?	-
Wade 1997	Citalopram, Clomipramine	Placebo	?	+	+	+	?	!
Fisekovic 2005	Sertraline	Alprazolam	?	?	-	?	?	-
Nardi 2011	Clonazepam	Paroxetine	?	+	+	+	?	!
Ravaris 1991	Alprazolam	Propranolol	?	-	-	-	-	-
Munjack 1989	Alprazolam	Placebo	?	-	-	+	?	-
Pini 2003	Paroxetine	Moclobemide	+	?	+	+	?	!
Tiller 1999	Moclobemide	Fluoxetine	?	+	+	?	?	!

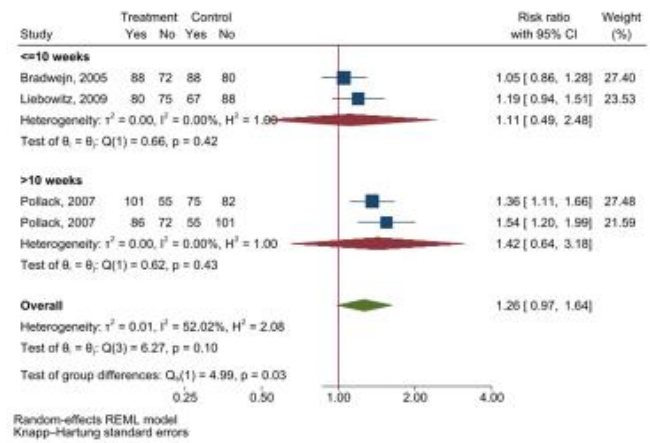
van Vliet 1996	Brofaromine	Fluvoxamine	?	+	+	+	?	!
Pollack 2007	Venlafaxine, Paroxetine	Placebo	?	+	+	+	?	!
Pollack 2007	Venlafaxine, Paroxetine	Placebo	?	+	+	+	?	!
Bertani 2004	Paroxetine	Reboxetine	?	-	+	+	?	-
Seedat 2003	Reboxetine	Citalopram	?	?	+	+	?	!
Goddard 2001	Sertraline + Clonazepam	Sertraline	?	+	+	+	?	!
Pollack 2003	Paroxetine + Clonazepam	Paroxetine	?	+	+	+	?	!
Robinson 1989	Buspirone, Imipramine	Placebo	?	+	+	?	?	!
Pohl 1989	Buspirone	Placebo	?	+	+	+	?	!
Schweizer 1988	Buspirone	Clorazepate	?	-	-	+	?	-
Sheehan 1990	Buspirone, Imipramine	Placebo	-	+	+	+	?	-
Sheehan 1993	Alprazolam	Placebo	?	?	+	+	-	-
Woods 1992	Alprazolam, Imipramine	Placebo	?	+	+	+	?	!
Kruger 1999	Moclobemide	Clomipramine	?	+	+	+	?	!
Hirschmann 2000	Fluoxetine + pindolol	Fluoxetine	?	+	+	+	?	!
Ribeiro 2001	Mirtazapine	Fluoxetine	?	+	+	+	?	!
Versiani 2002	Reboxetine	Placebo	?	+	+	+	?	!

eFigure 4. Subgroup analyses of paroxetine vs placebo and venlafaxine vs placebo

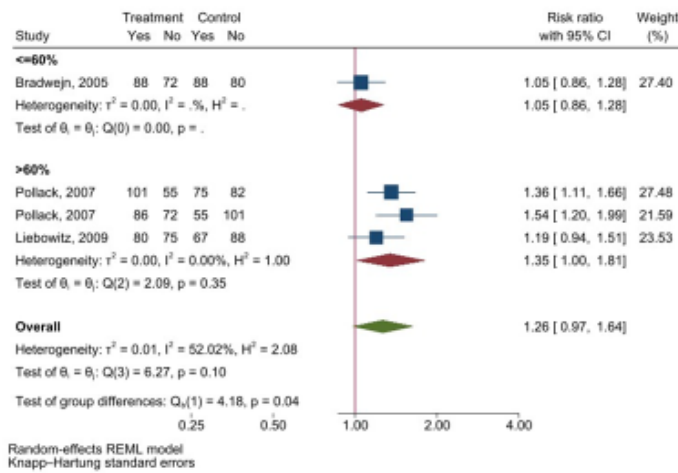
a) Paroxetine vs placebo; Duration of treatment



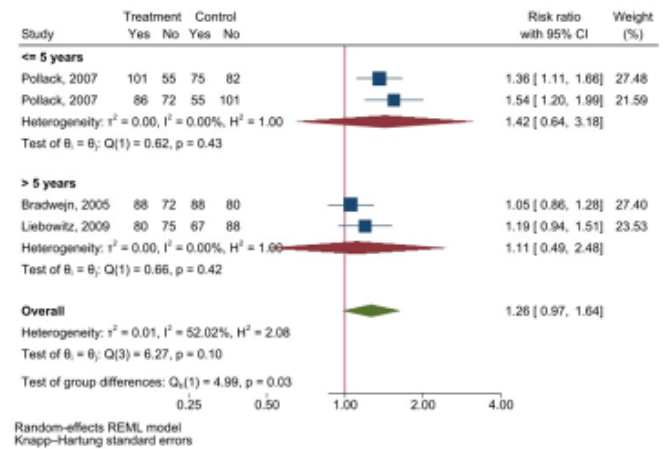
b) Venlafaxine vs placebo; Duration of treatment



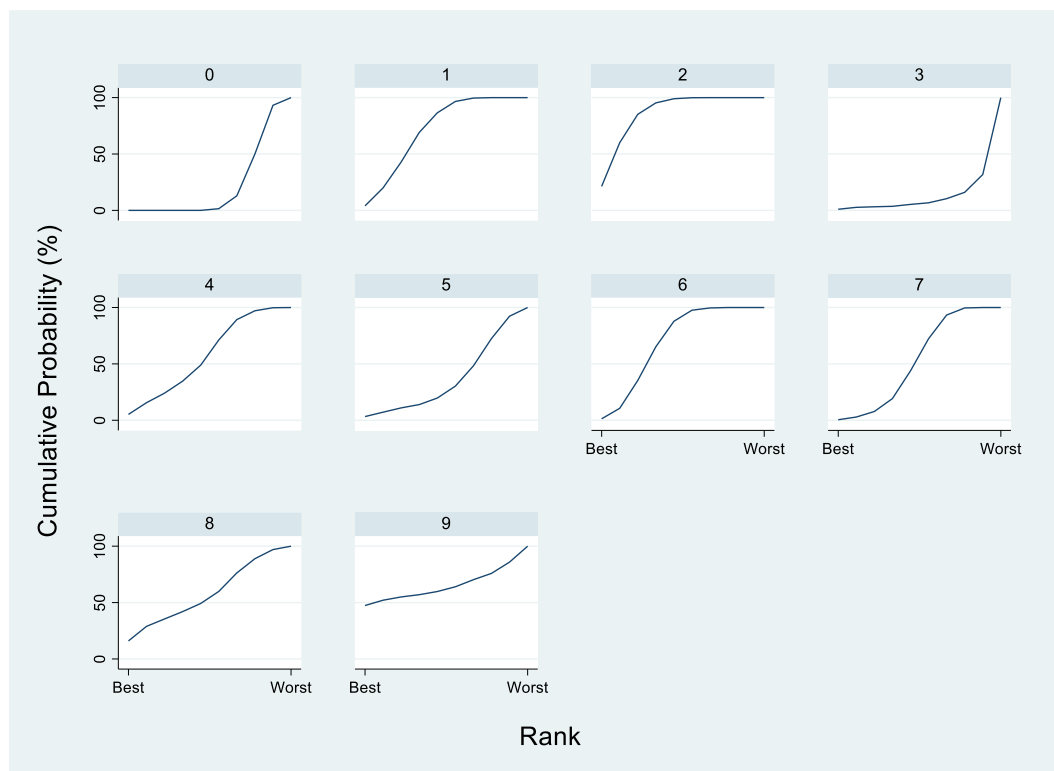
c) Venlafaxine vs placebo; Percentage of female



d) Venlafaxine vs placebo; Duration of panic disorder



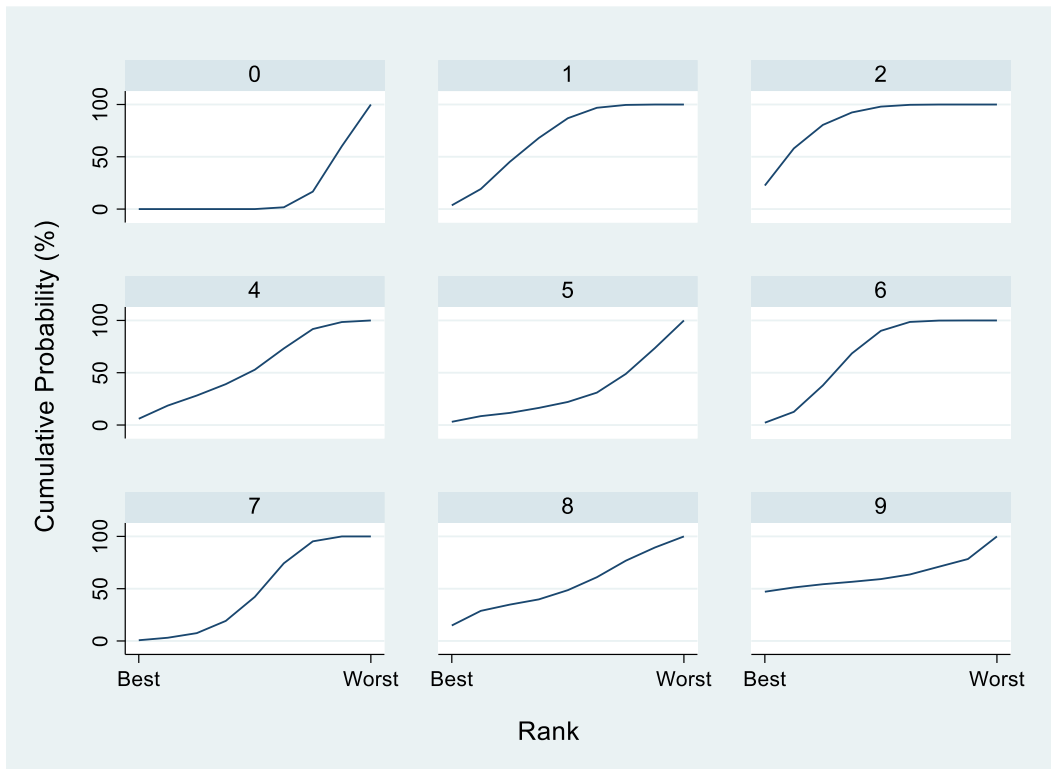
eFigure 5. Surface under the cumulative ranking curve of disease remission



0) Placebo; 1) Tricyclic antidepressants; 2) Benzodiazepines; 3) Beta-blocker; 4) Monoamine oxidase inhibitors; 5) Buspirone; 6) Selective serotonin reuptake inhibitor; 7) Serotonin norepinephrine reuptake inhibitor; 8) Norepinephrine reuptake inhibitor; 9) Selective serotonin reuptake inhibitor plus benzodiazepine

Treatment	SUCRA	PrBest	MeanRank
Placebo	17.5	0.0	8.4
TCA	68.7	4.0	3.8
BZD	84.5	21.3	2.4
Betablocker	9.0	1.0	9.2
MOAI	54.0	5.2	5.1
Buspirone	33.2	3.3	7.0
SSRI	66.4	1.3	4.0
SNRI	48.8	0.5	5.6
NRI	54.9	16.0	5.1
SSRIplusBZD	63.0	47.4	4.3

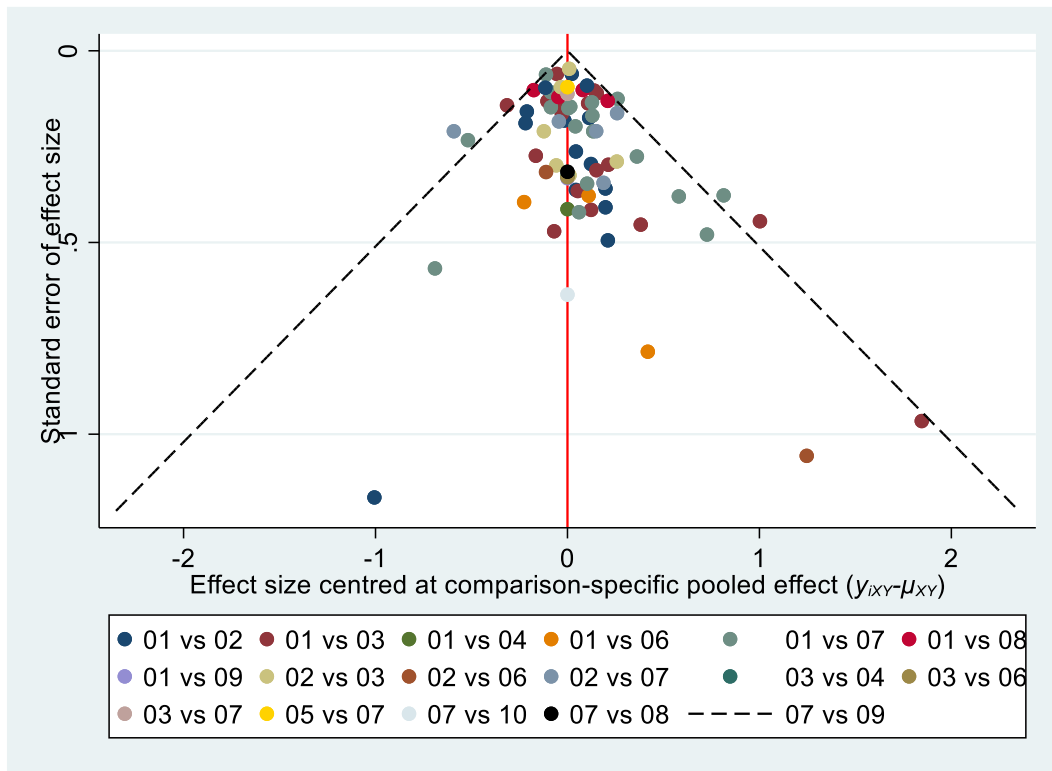
eFigure 6. Surface under the cumulative ranking curve of sensitivity analysis of disease remission according to duration of treatment



0) Placebo; 1) Tricyclic antidepressants; 2) Benzodiazepines; 4) Monoamine oxidase inhibitors; 5) Buspirone; 6) Selective serotonin reuptake inhibitor; 7) Serotonin norepinephrine reuptake inhibitor; 8) Norepinephrine reuptake inhibitor; 9) Selective serotonin reuptake inhibitor plus benzodiazepine

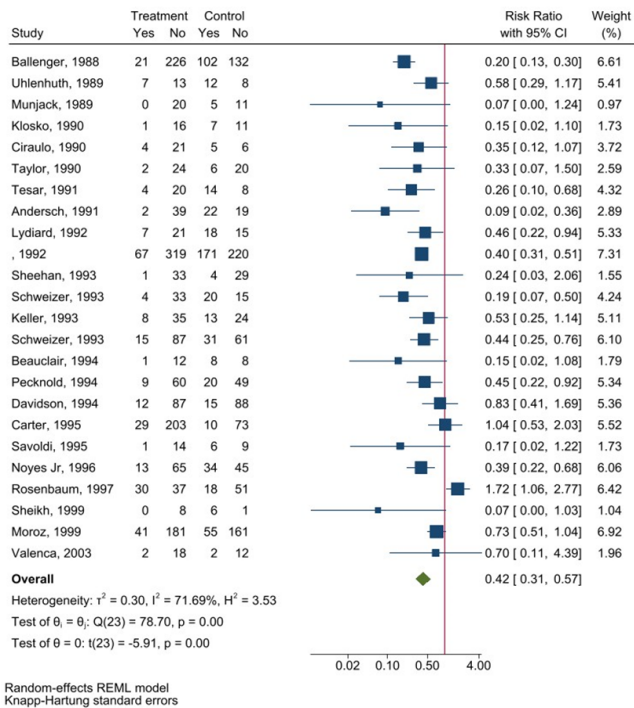
Treatment	SUCRA	PrBest	MeanRank
Placebo	9.8	0.0	8.2
TCA	64.9	3.6	3.8
BZD	81.4	22.5	2.5
MOAI	51.0	6.0	4.9
Buspirone	26.9	3.1	6.8
SSRI	63.7	2.2	3.9
SNRI	42.8	0.7	5.6
NRI	49.3	14.8	5.1
SSRIplusBZD	60.2	47.1	4.2

eFigure 7. Comparison-adjusted funnel plot of disease remission

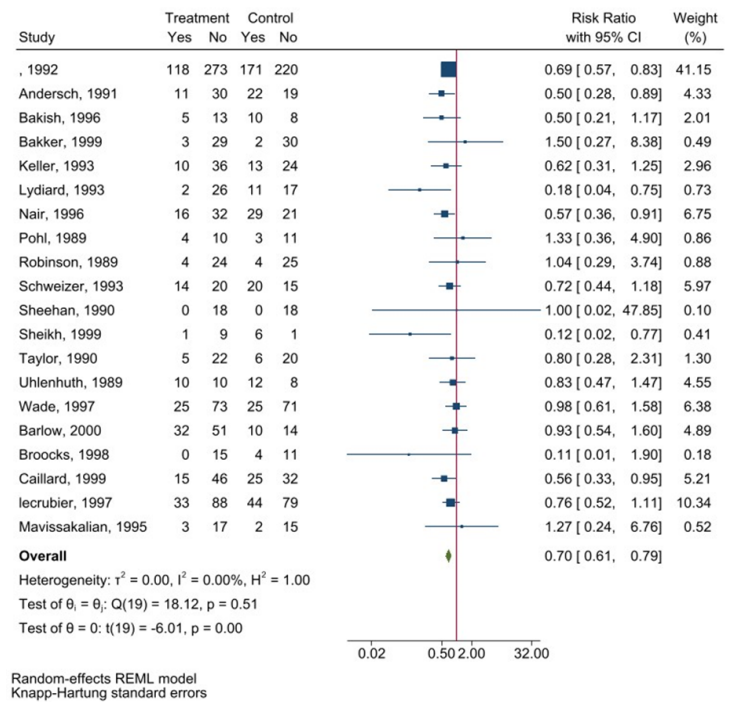


eFigure 8. Estimation of pooled risk ratio of dropout rate between treatment comparisons: Direct meta-analysis

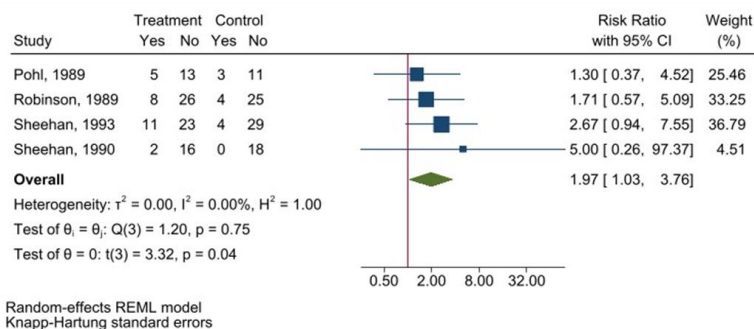
a) TCA vs placebo



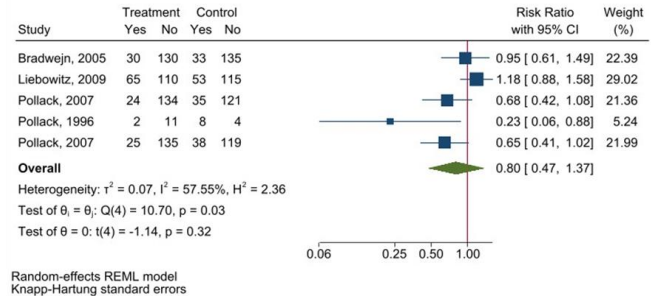
b) BZD vs placebo



c) Buspirone vs placebo

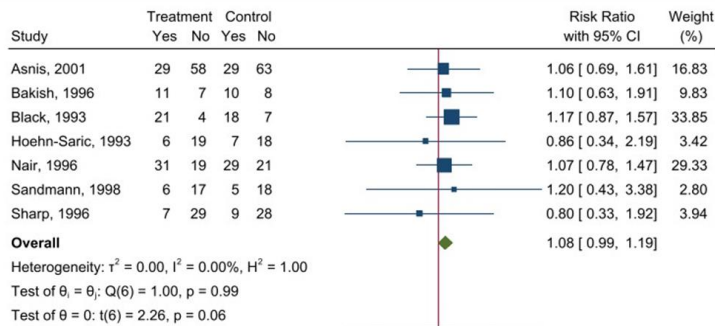


d) Venlafaxine vs placebo



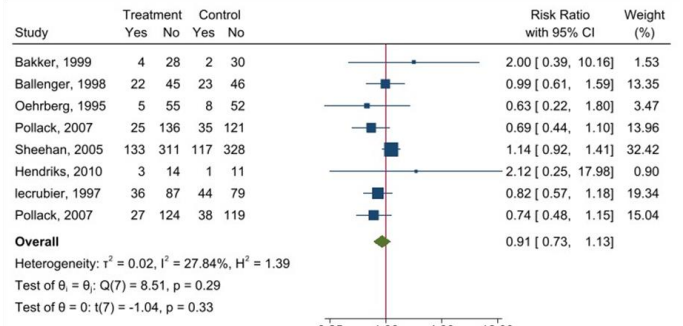
eFigure 8 (continued)

e) Fluvoxamine vs placebo



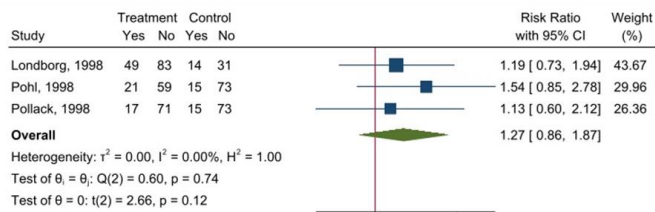
Random-effects REML model
Knapp-Hartung standard errors

f) Paroxetine vs placebo



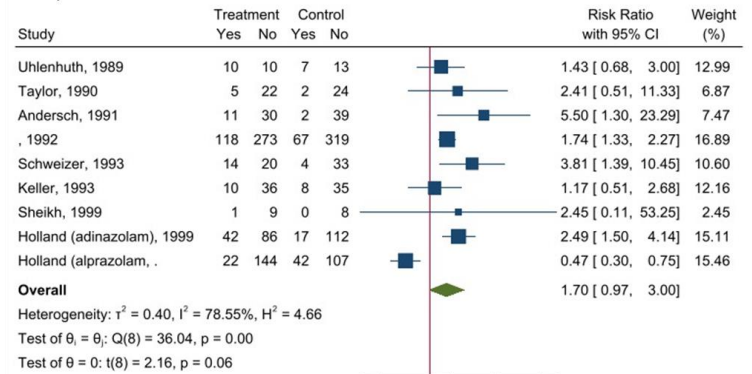
Random-effects REML model
Knapp-Hartung standard errors

g) Sertraline vs placebo



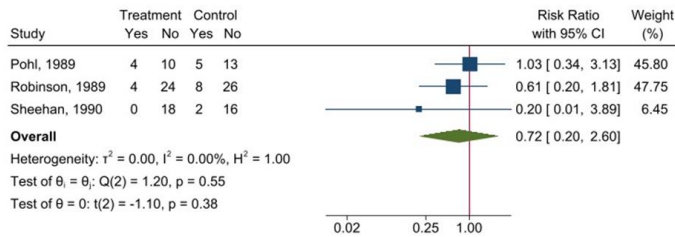
Random-effects REML model
Knapp-Hartung standard errors

h) TCA vs BZD



Random-effects REML model
Knapp-Hartung standard errors

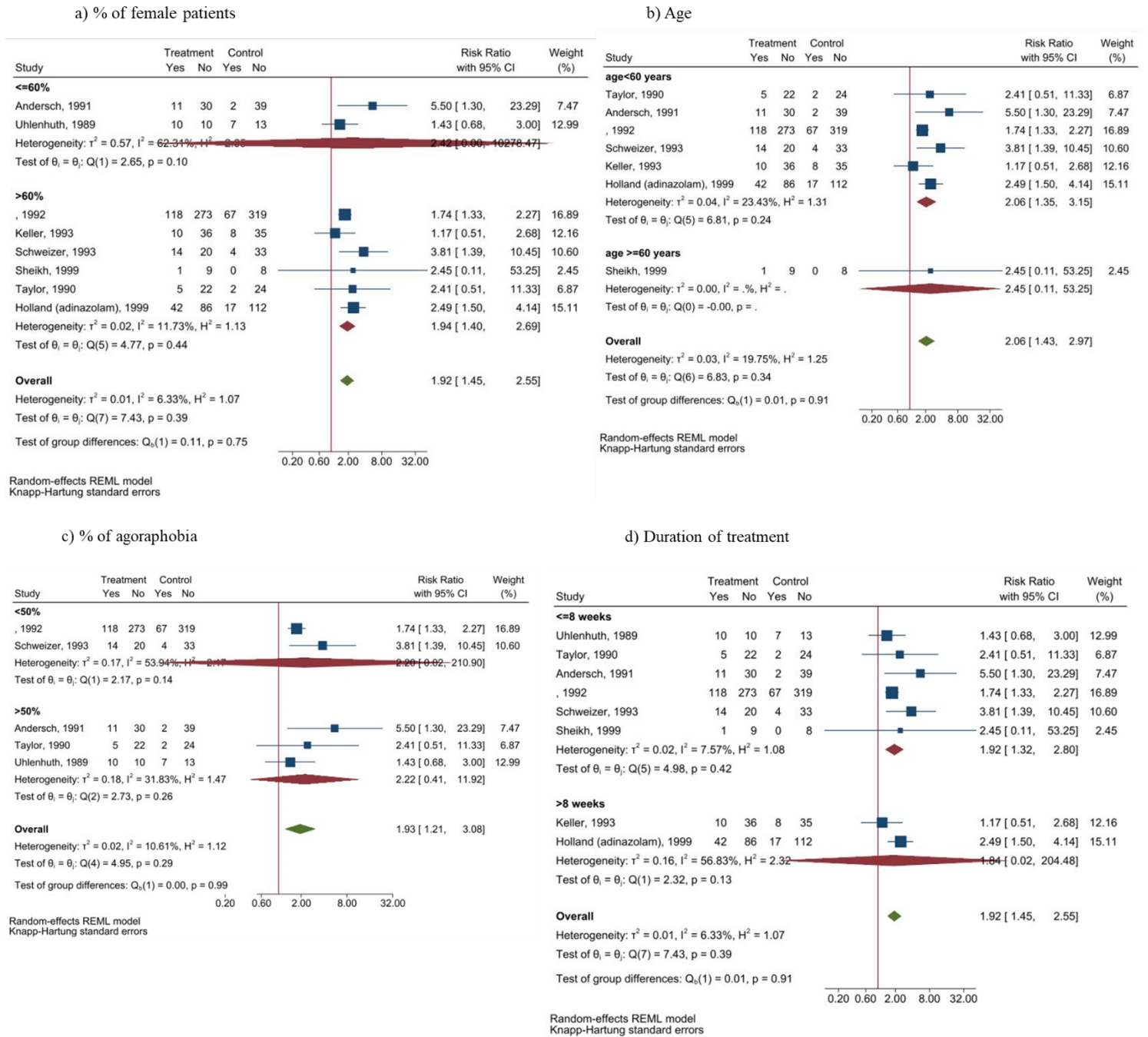
i) TCA vs buspirone



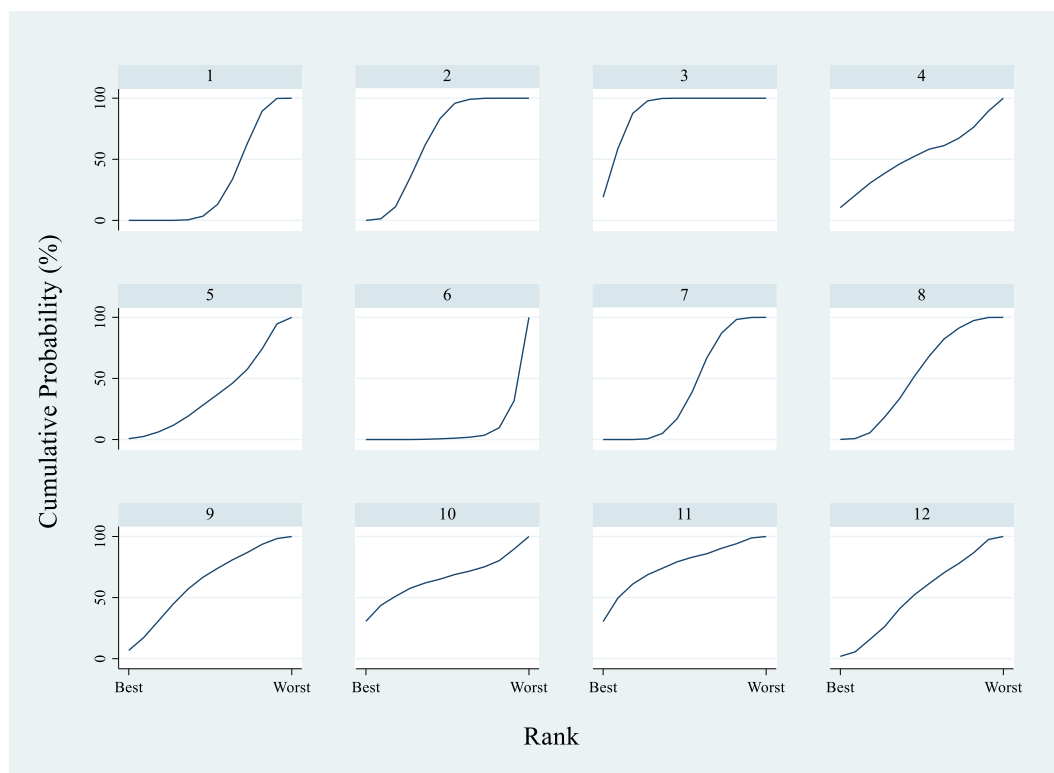
Random-effects REML model
Knapp-Hartung standard errors

BZD; benzodiazepine, TCA; tricyclic antidepressants

eFigure 9. Subgroup analysis of tricyclic antidepressants and benzodiazepines on dropout rate by percent female, mean age, percent agoraphobia, and duration of treatment



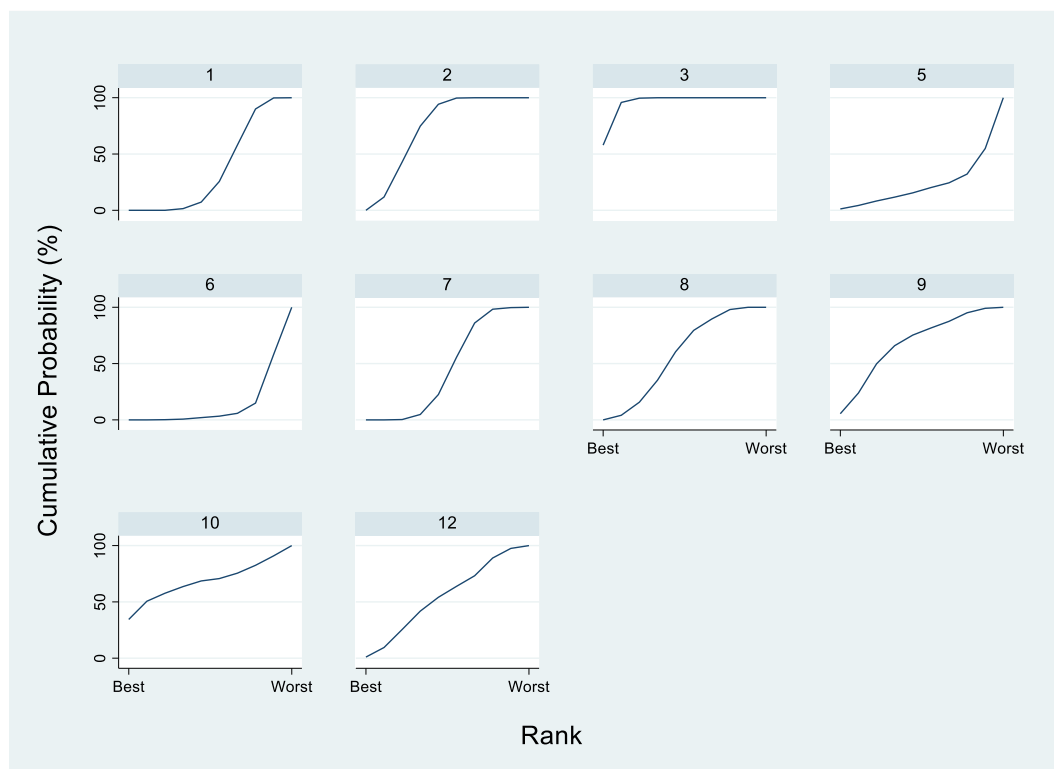
eFigure 10. Surface under the cumulative ranking curve of dropout rate



1) Placebo; 2) Tricyclic ant-depressants; 3) Benzodiazepines; 4) Beta-blocker; 5) Monoamine oxidase inhibitors; 6) Buspirone; 7) Selective serotonin reuptake inhibitors; 8) Serotonin norepinephrine reuptake inhibitor; 9) Norepinephrine reuptake inhibitor; 10) Noradrenergic and specific serotonergic antidepressants; 11) Tricyclic antidepressant plus benzodiazepine; 12) Selective serotonin reuptake inhibitor plus benzodiazepine

Treatment	SUCRA	PrBest	MeanRank
Placebo	27.5	0.0	9.0
TCA	62.5	0.0	5.1
BZD	87.5	19.0	2.4
Betablocker	50.1	10.5	6.5
MOAI	34.3	0.7	8.2
Buspirone	4.4	0.0	11.5
SSRI	37.6	0.0	7.9
SNRI	49.9	0.1	6.5
NRI	59.7	6.8	5.4
NaSSA	63.3	30.6	5.0
TCAplusBZD	74.1	30.4	3.8
SSRIplusBZD	48.8	1.9	6.6

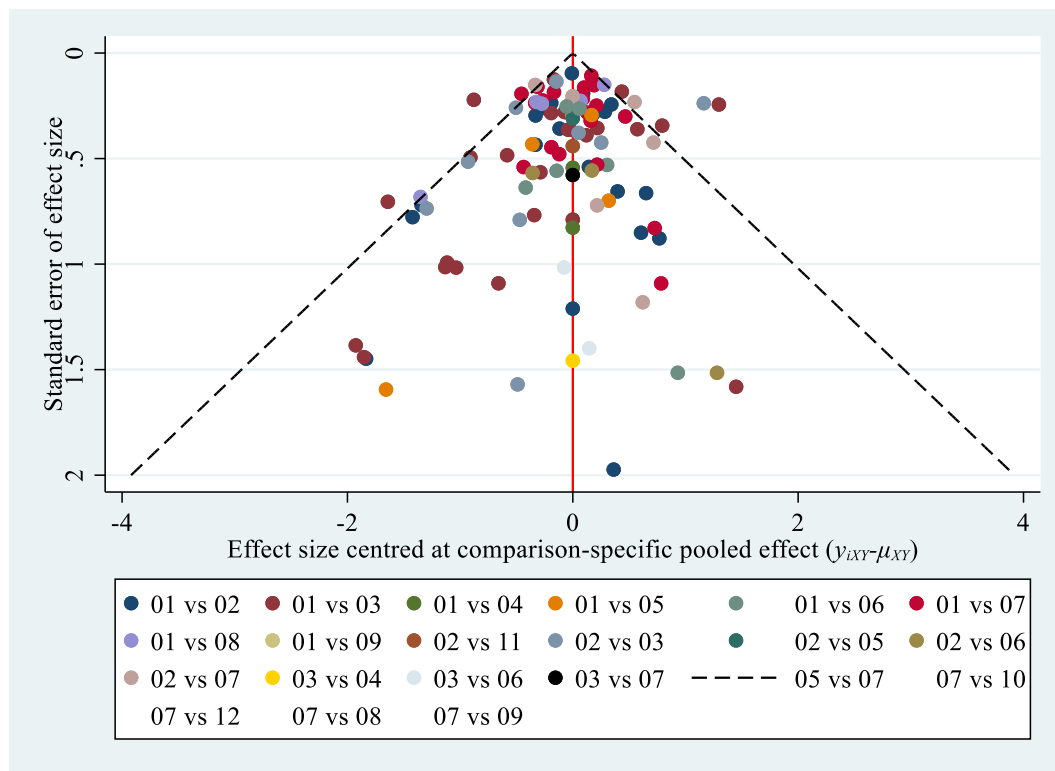
eFigure 11. Surface under the cumulative ranking curve of sensitivity analysis of dropout rate



1) Placebo; 2) Tricyclic ant-depressants; 3) Benzodiazepines; 5) Monoamine oxidase inhibitors; 6) Buspirone; 7) Selective serotonin reuptake inhibitors; 8) Serotonin norepinephrine reuptake inhibitor; 9) Norepinephrine reuptake inhibitor; 10) Noradrenergic and specific serotonergic antidepressants; 11) Tricyclic antidepressant plus benzodiazepine; 12) Selective serotonin reuptake inhibitor plus benzodiazepine

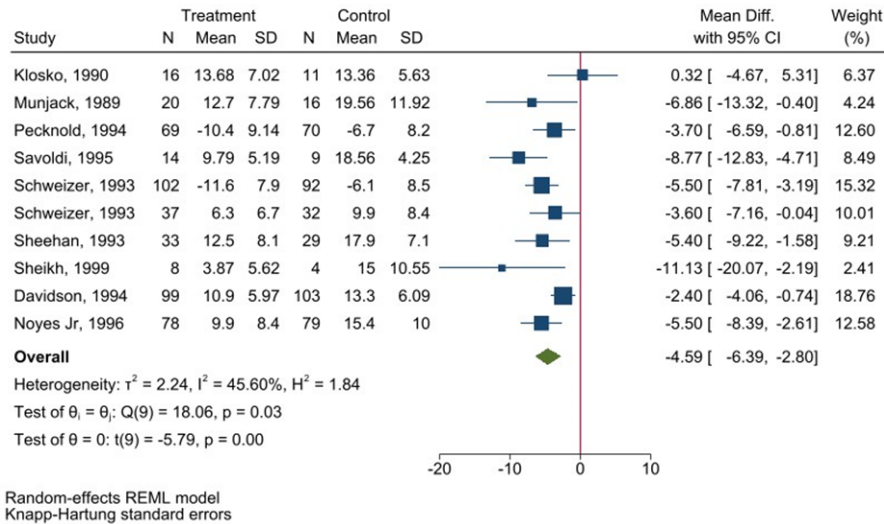
Treatment	SUCRA	PrBest	MeanRank
Placebo	31.4	0.0	7.2
TCA	69.3	0.0	3.8
BZD	94.8	57.9	1.5
MOAI	19.2	1.2	8.3
Buspirone	9.4	0.0	9.1
SSRI	40.8	0.0	6.3
SNRI	53.6	0.0	5.2
NRI	64.9	5.5	4.2
NaSSA	66.1	34.4	4.1
TCAplusBZD	50.6	1.0	5.4

eFigure 12. Comparison-adjusted funnel plot of dropout rate

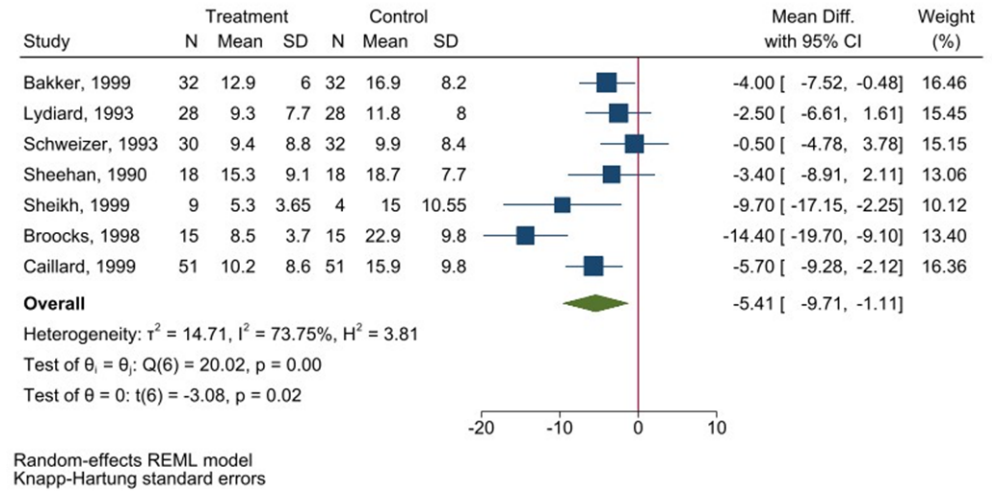


eFigure 13. Estimation of pooled mean difference of anxiety score between intervention and placebo: Direct meta-analysis

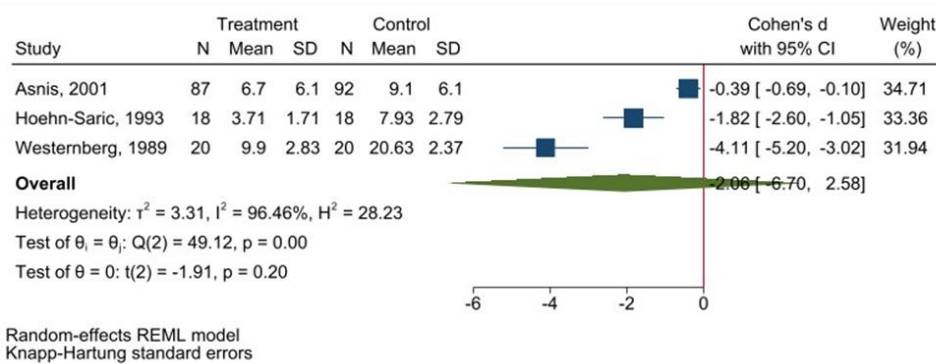
a) BZD vs placebo



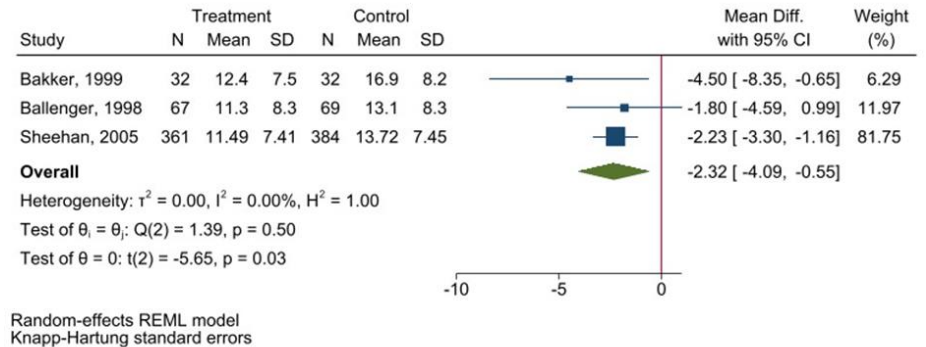
b) TCA vs placebo



c) Fluvoxamine vs placebo



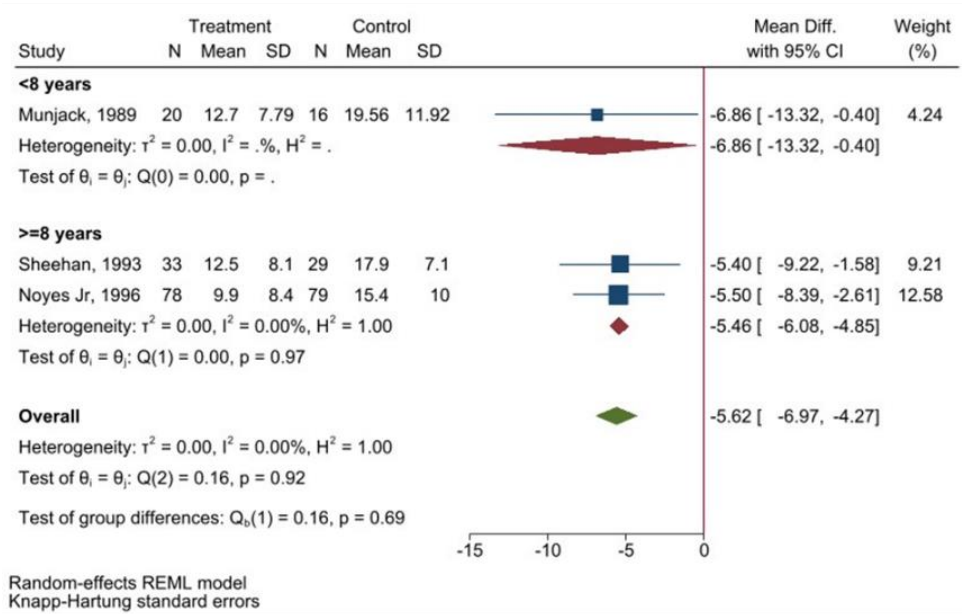
d) Paroxetine vs placebo



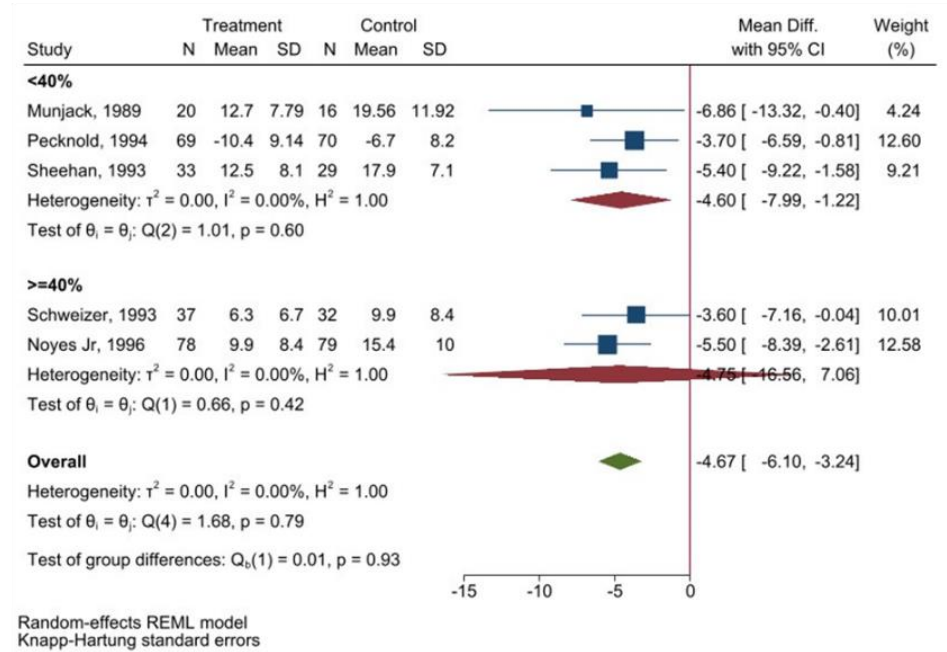
BZD; benzodiazepine, TCA; tricyclic antidepressant

eFigure 14. Subgroup analysis of mean difference of anxiety score between benzodiazepines and placebo

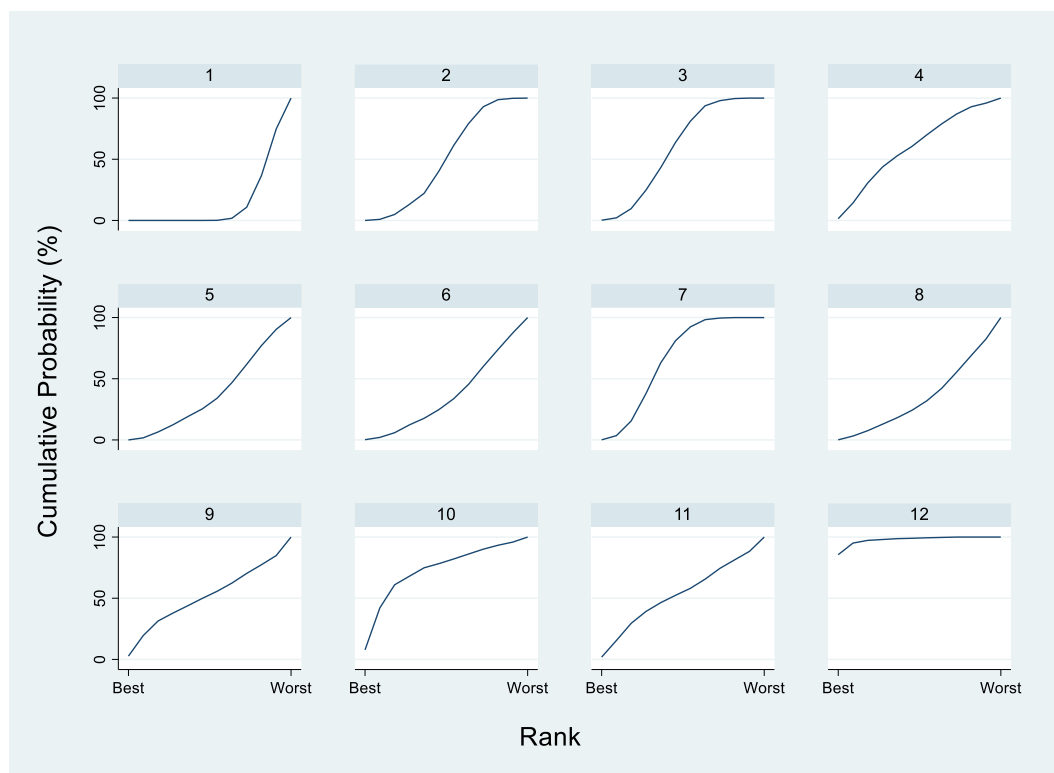
a) Duration of panic disorder



b) % of agoraphobia



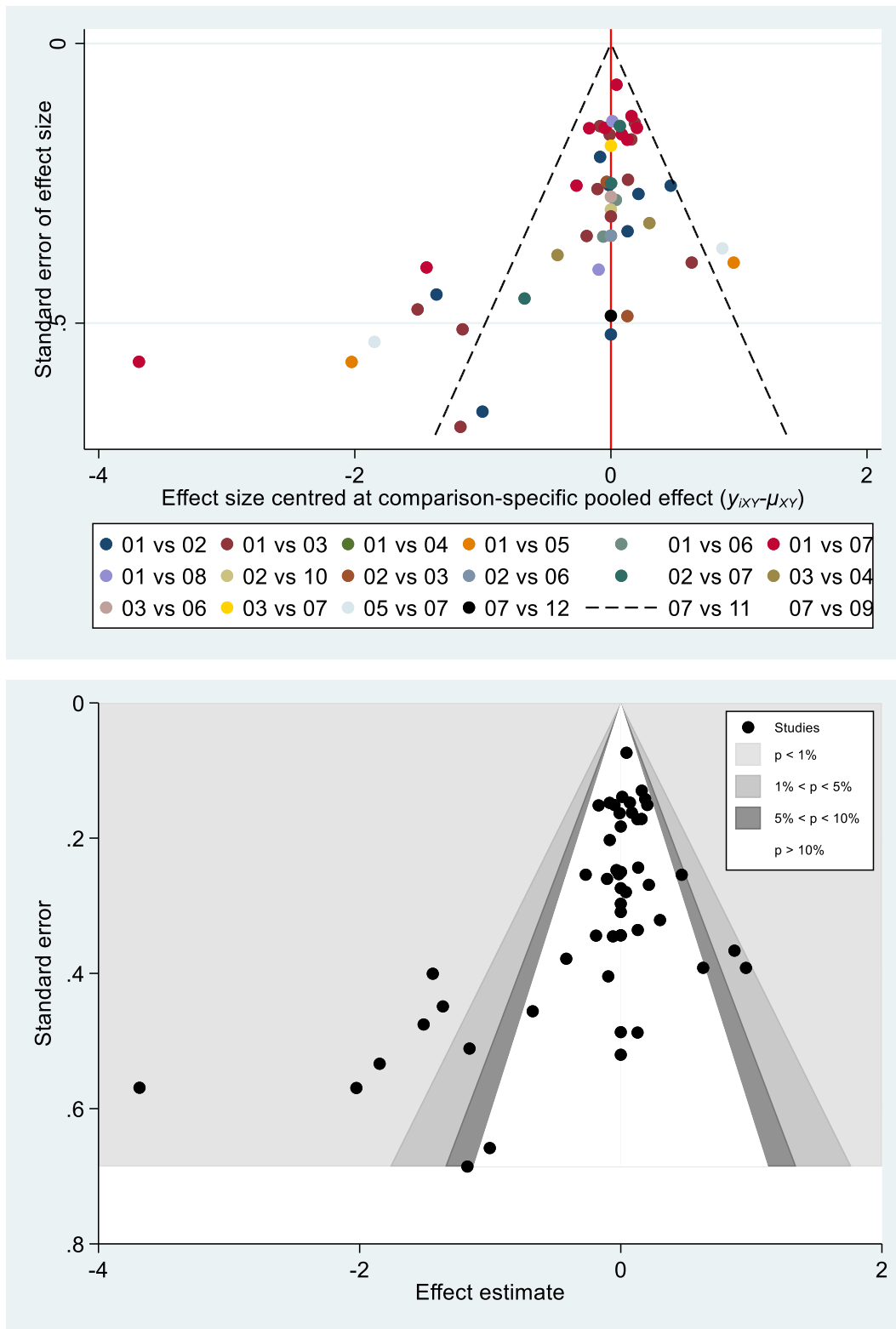
eFigure 15. Surface under the cumulative ranking curve of anxiety score



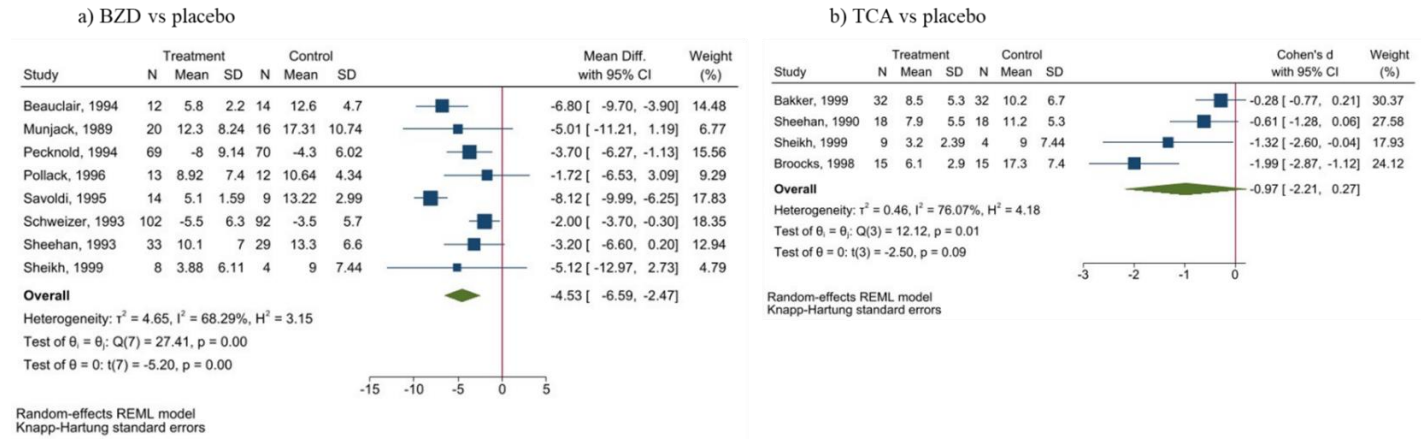
1) Placebo; 2) Tricyclic ant-depressants; 3) Benzodiazepines;4) Beta-blockers; 5) Monoamine oxidase inhibitors; 6) Buspirone; 7) Selective serotonin reuptake inhibitors; 8) Serotonin norepinephrine reuptake inhibitors; 9) Norepinephrine reuptake inhibitor; 10) Tricyclic antidepressants plus benzodiazepines;11) Selective serotonin reuptake inhibitor plus benzodiazepines; 12) Selective serotonin reuptake inhibitors plus beta-blockers

Treatment	SUCRA	PrBest	MeanRank
Placebo	11.3	0.0	10.8
TCA	46.7	0.0	6.9
BZD	56.0	0.2	5.8
Betablocker	57.1	1.4	5.7
MAOI	34.1	0.0	8.2
Buspirone	33.0	0.2	8.4
SSRI	62.9	0.1	5.1
SNRI	31.6	0.1	8.5
NRI	48.7	2.7	6.6
TCAplusBZD	70.9	7.8	4.2
SSRIplusBZD	50.2	1.9	6.5
SSRIplusBetablocker	97.5	85.6	1.3

eFigure 16. Comparison-adjusted and contour enhanced funnel plots of anxiety score

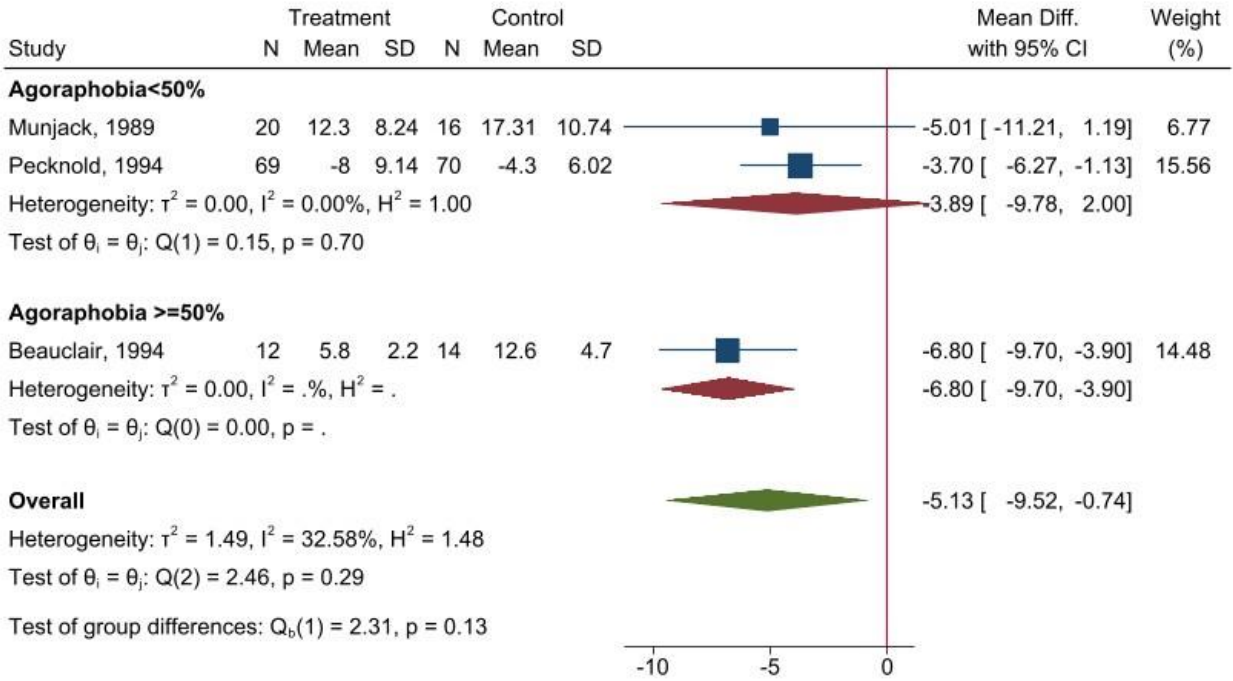


eFigure 17. Estimation of pooled mean difference of depression score between intervention and placebo: Direct meta-analysis



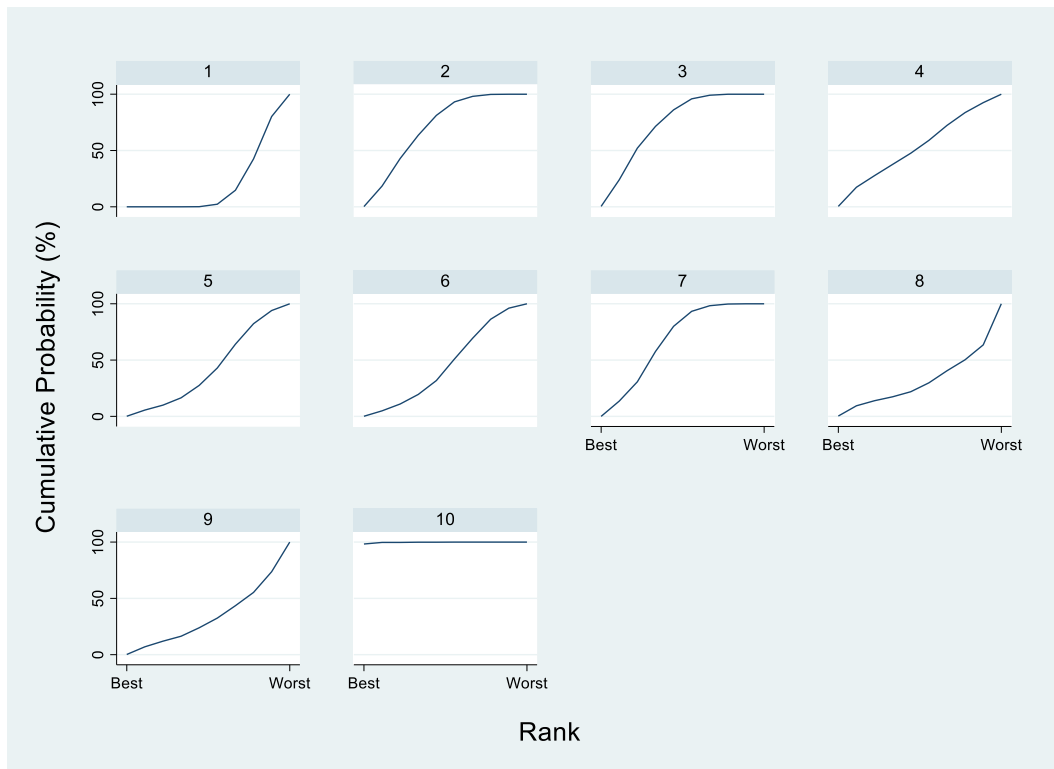
BZD; benzodiazepine, TCA; tricyclic antidepressants

eFigure 18. Subgroup analysis of mean difference of depression score between benzodiazepines and placebo



Random-effects REML model
Knapp-Hartung standard errors

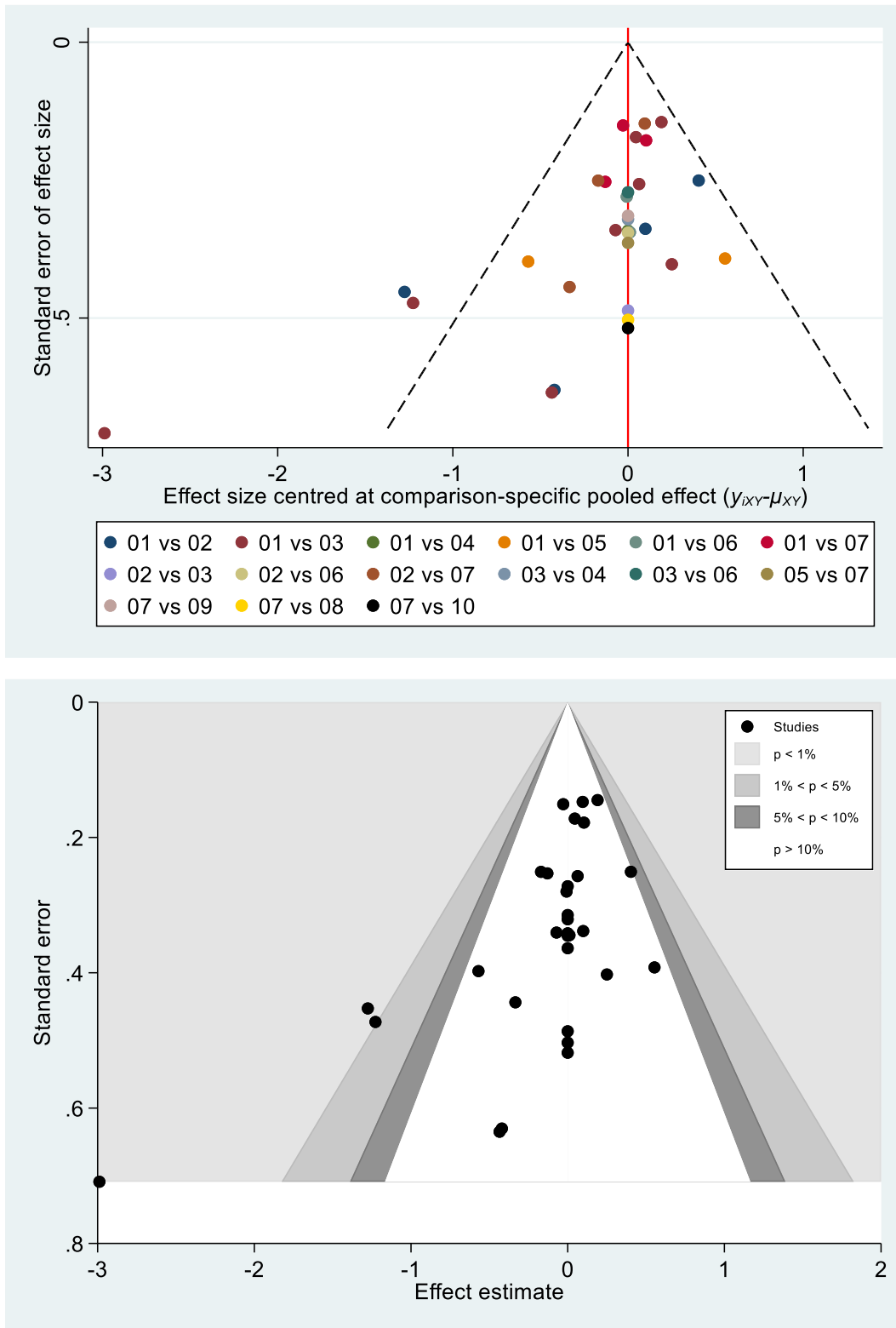
eFigure 19. Surface under the cumulative ranking curve of depression score



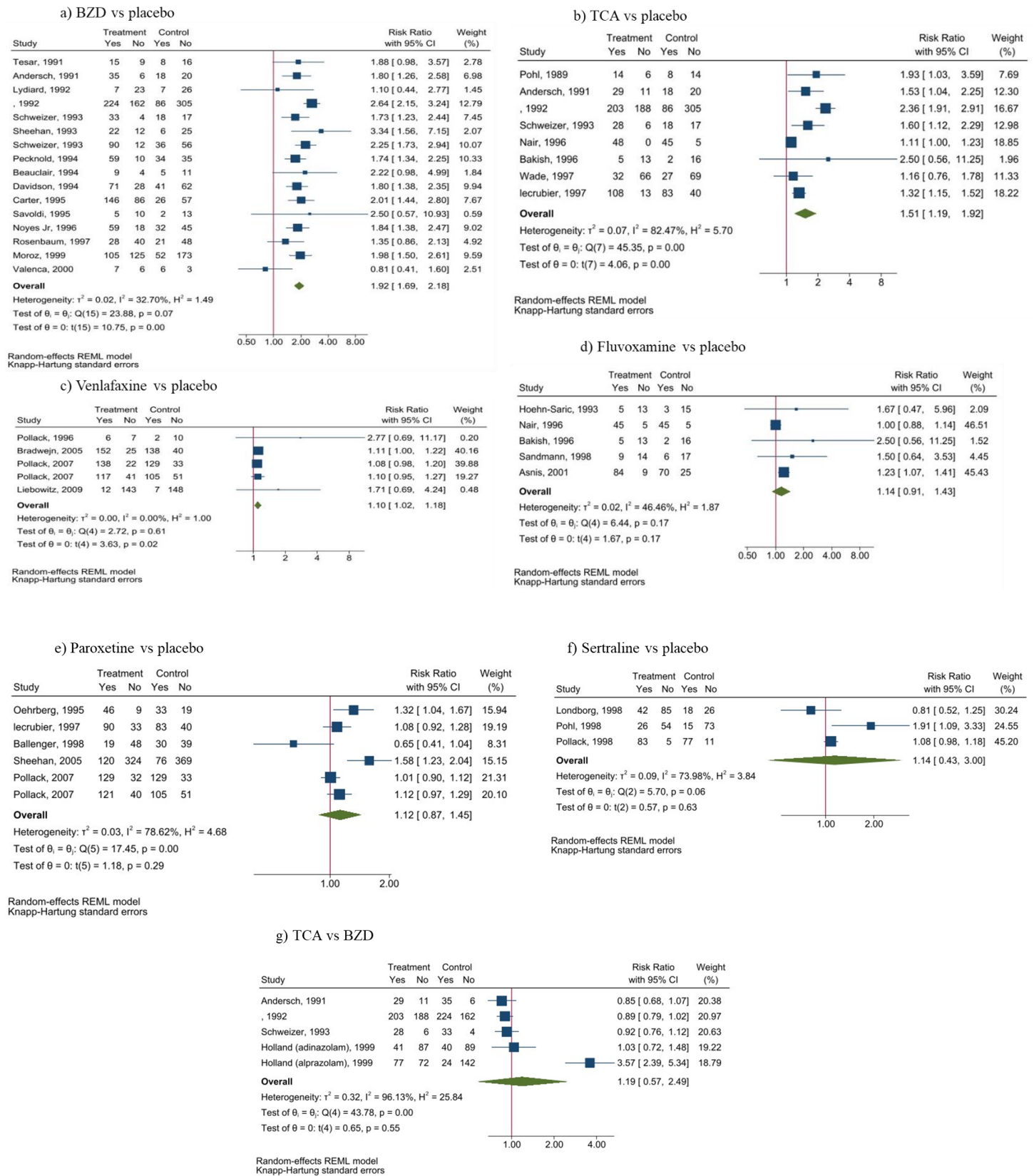
1) Placebo; 2) Tricyclic ant-depressants; 3) Benzodiazepines; 4) Beta-blockers; 5) Monoamine oxidase inhibitors; 6) Buspirone; 7) Selective serotonin reuptake inhibitor; 8) Norepinephrine reuptake inhibitor; 9) Selective serotonin reuptake inhibitor plus benzodiazepine; 10) Selective serotonin reuptake inhibitor plus beta-blockers

Treatment	SUCRA	PrBest	MeanRank
Placebo	15.5	0.0	8.6
TCA	66.4	0.2	4.0
BZD	69.9	0.4	3.7
Betablocker	48.7	0.4	5.6
MAOI	38.1	0.1	6.6
Buspirone	41.1	0.1	6.3
SSRI	63.7	0.0	4.3
NRI	27.4	0.3	7.5
SSRIplusBZD	29.4	0.2	7.4
SSRIplusBetablocker	99.7	98.3	1.0

eFigure 20. Comparison-adjusted funnel plot of depression score

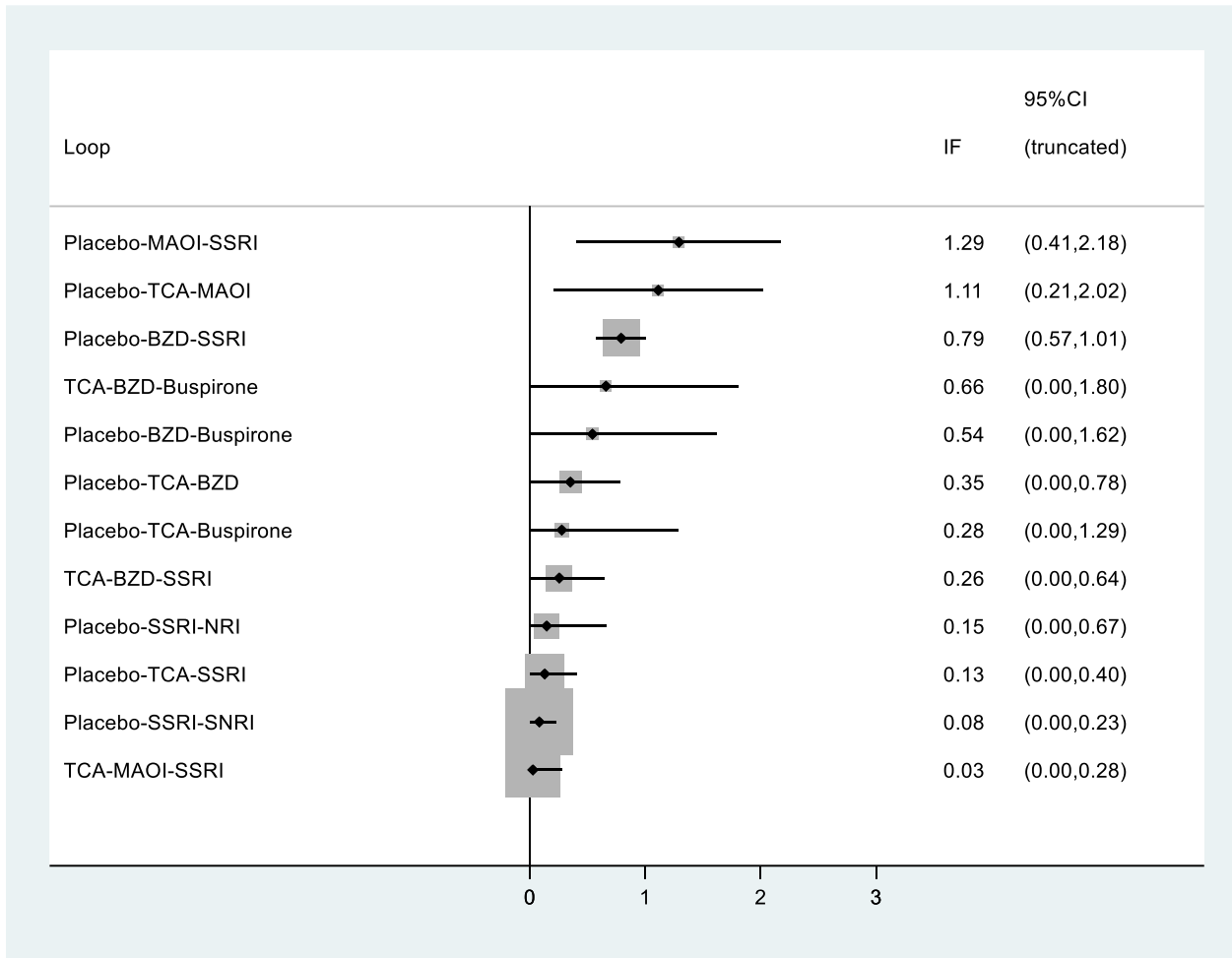


eFigure 21. Estimation of pooled risk ratio of adverse events between treatment comparisons: Direct meta-analysis



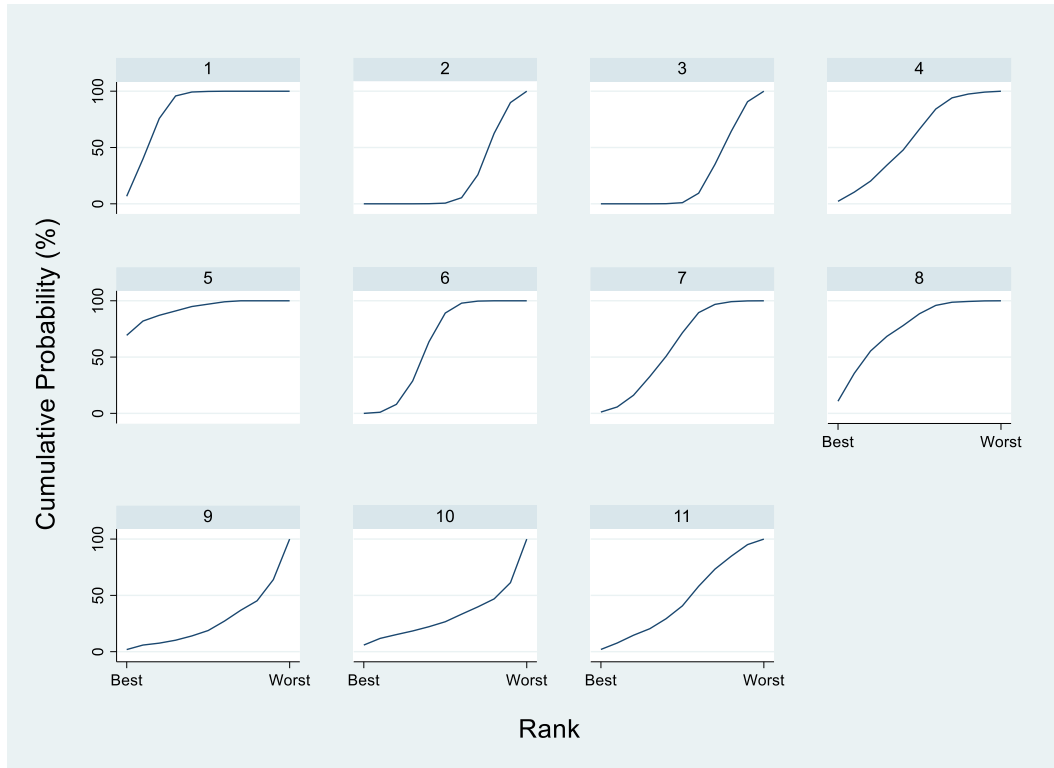
BZD; benzodiazepine, TCA; tricyclic antidepressants

eFigure 22. Inconsistency factors of adverse events



IF, inconsistency factor is a ratio of $\ln[\text{RR}(\text{direct})/\text{RR}(\text{indirect})]$. BZDs, benzodiazepine; MAOIs, monoamine oxidase inhibitors; NRI, norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCAs, tricyclic antidepressants

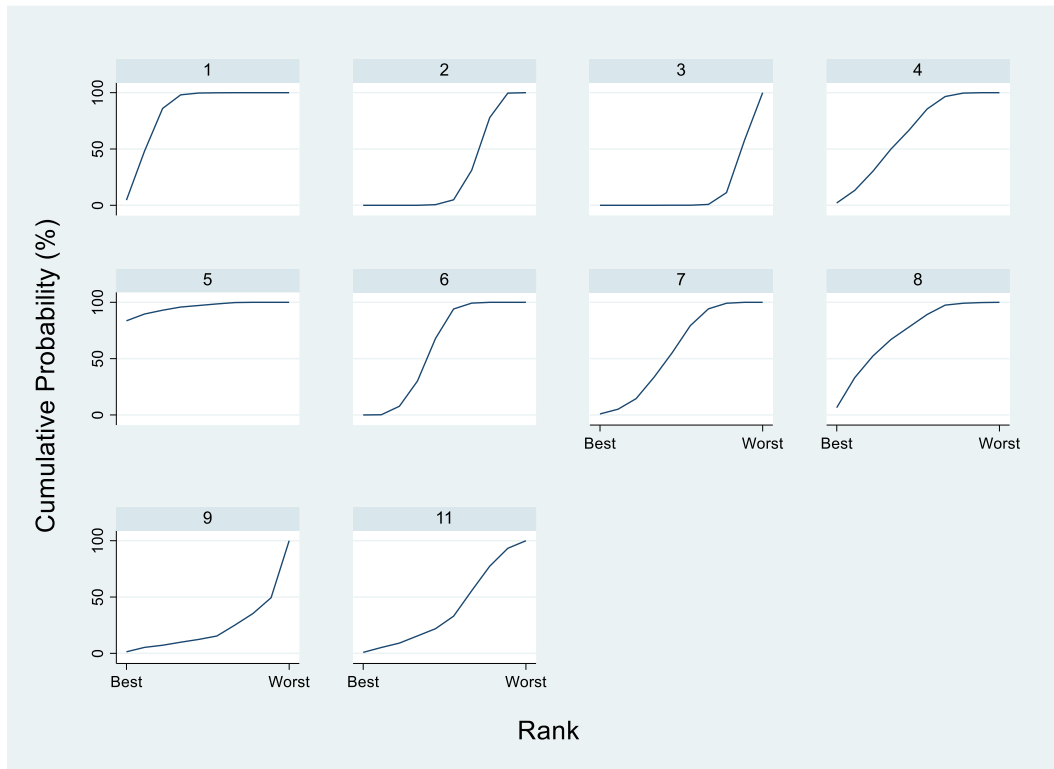
eFigure 23. Surface under the cumulative ranking curve of adverse events



1) Placebo; 2) Tricyclic antidepressants; 3) Benzodiazepines; 4) Monoamine oxidase inhibitors; 5) Buspirone; 6) Selective serotonin reuptake inhibitor; 7) Selective serotonin reuptake inhibitor plus benzodiazepine; 8) Norepinephrine reuptake inhibitor; 9) noradrenergic and specific serotonergic antidepressants ;10) Tricyclic antidepressants plus benzodiazepine; 11) Selective serotonin reuptake inhibitor plus beta-blockers

Treatment	SUCRA	PrBest	MeanRank
Placebo	81.7	6.7	2.8
TCA	18.4	0.0	9.2
BZD	20.1	0.0	9.0
MAOI	55.6	2.2	5.4
Buspirone	92.0	69.3	1.8
SSRI	58.8	0.0	5.1
SNRI	56.3	1.2	5.4
NRI	73.1	10.8	3.7
NaSSA	23.2	1.9	8.7
TCAplusBZD	28.1	5.9	8.2
SSRIplusBZD	42.6	2.0	6.7

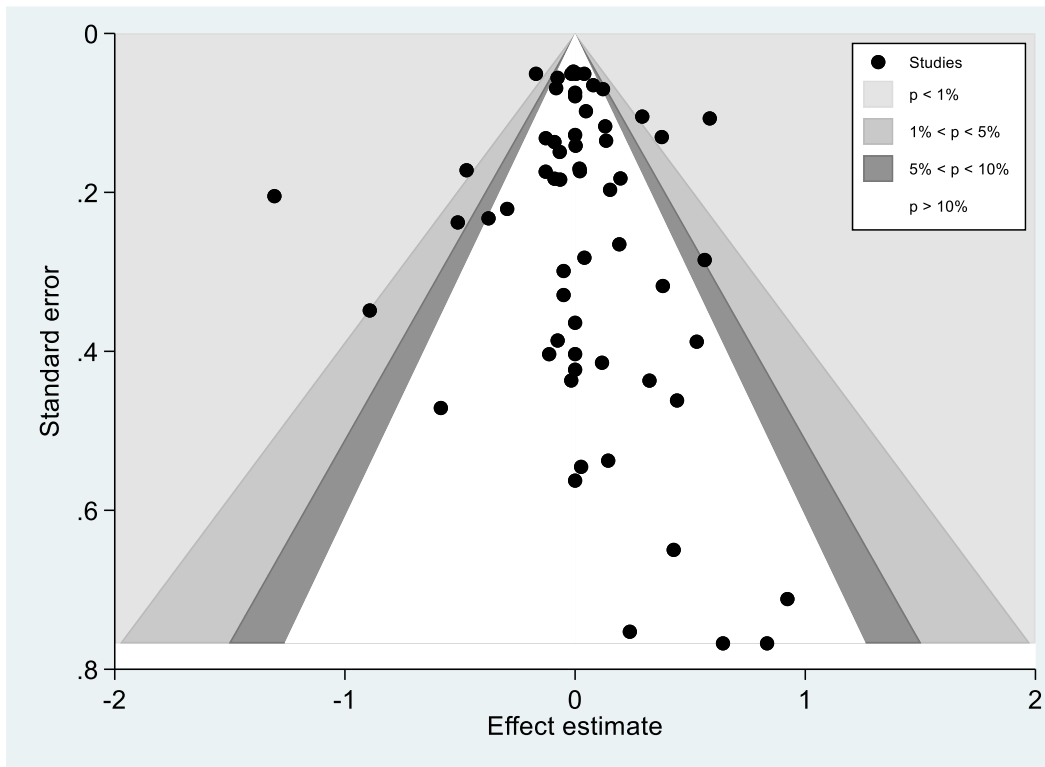
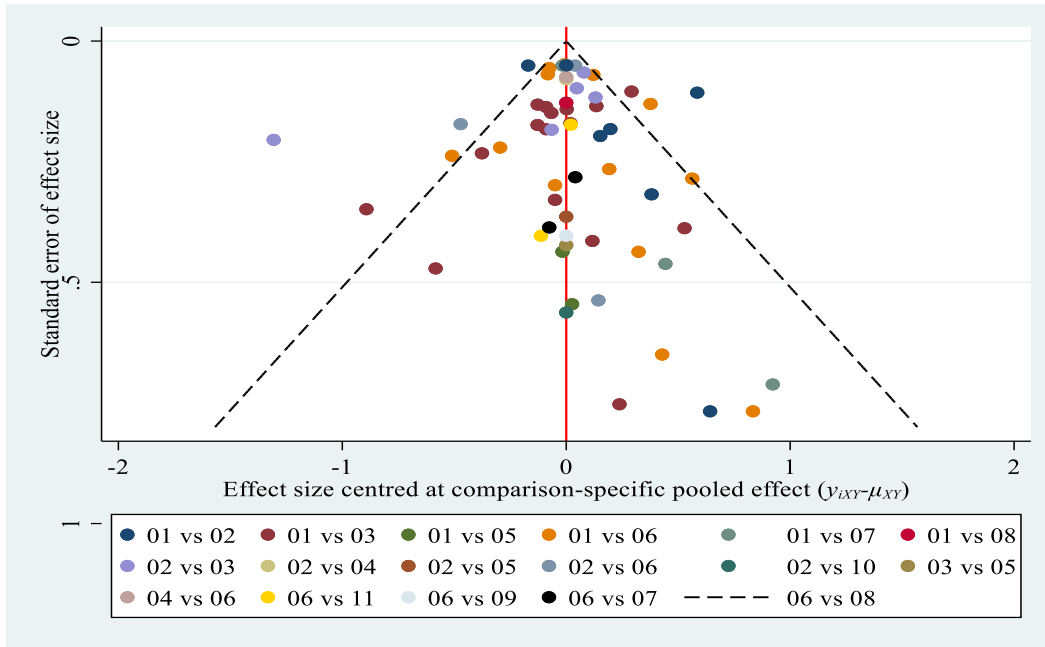
eFigure 24. Surface under the cumulative ranking curve of sensitivity analysis of adverse events



1) Placebo; 2) Tricyclic antidepressants; 3) Benzodiazepines; 4) Monoamine oxidase inhibitors; 5) Buspirone; 6) Selective serotonin reuptake inhibitor; 7) Selective serotonin reuptake inhibitor plus benzodiazepine; 8) Norepinephrine reuptake inhibitor; 9) noradrenergic and specific serotonergic antidepressants ;10) Tricyclic antidepressants plus benzodiazepine; 11) Selective serotonin reuptake inhibitor plus beta-blockers

Treatment	SUCRA	PrBest	MeanRank
Placebo	81.8	4.6	2.6
TCA	23.8	0.0	7.9
BZD	7.8	0.0	9.3
MOAI	60.4	2.1	4.6
Buspirone	95.3	83.6	1.4
SSRI	55.5	0.0	5.0
SNRI	53.6	0.9	5.2
NRI	69.2	6.5	3.8
NaSSA	17.9	1.4	8.4
SSRIplusBZD	34.7	0.9	6.9

Figure 25. Comparison-adjusted and contour enhanced funnel plots of adverse events



eAppendix1: Search terms and strategy

Search terms and strategy for EMBASE:

('panic'/exp OR 'panic' OR 'panic attack' OR 'panic disorder') AND ('antidepressant agent'/exp OR 'anti depressant agent' OR 'antidepressant' OR 'antidepressant agent' OR 'antidepressant drug' OR 'antidepressants' OR 'antidepressants, miscellaneous' OR 'antidepressant drug' OR 'antidepressive agent' OR 'antidepressive agents' OR 'antidepressive agents, second generation' OR 'antidepressive agents, second-generation' OR 'antidepressive drug' OR 'neurothymoleptic agent' OR 'psychoenergizer' OR 'thymoleptic' OR 'thymoleptic agent' OR 'thymoleptic drug' OR 'thymolytic agent' OR 'tricyclic antidepressant agent'/exp OR 'antidepressant, tricyclic' OR 'antidepressants, tricyclic' OR 'antidepressive agents, tricyclic' OR 'tricyclic antidepressant' OR 'tricyclic antidepressant agent' OR 'tricyclic antidepressants' OR 'tricyclic antidepressive agent' OR 'clomipramine'/exp OR '2 chloro 5 (3 dimethylaminopropyl) 10, 11 dihydrodibenz [6, f] azepine' OR '3 chloro 5 (3 dimethylaminopropyl) 10, 11 dihydro (5h) dibenz [b, f] azepine' OR '3 chloro 5 [(3 dimethylamin) propyl] 10, 11 dihydro 5h dibenz [b, f] azepine' OR '3 chloro 5 [3 (dimethylamino) propyl] 10, 11 dihydro 5h dibenz (b, f) azepine' OR '3 chloroimipramine' OR '5 (gamma dimethylaminopropyl) 3 chloroiminodibenzyl' OR 'anafranil' OR 'anafranil 25' OR 'anafranil retard' OR 'anafranil sr' OR 'anafranilin' OR 'anafranyl' OR 'chlomipramine' OR 'chlorimipramine' OR 'chlorimipramine hydrochloride' OR 'chloroimipramine' OR 'clofranil' OR 'clomicalm' OR 'clomipramin' OR 'clomipramine' OR 'clomipramine chlorhydrate' OR 'clomipramine hydrochloride' OR 'clopress' OR 'domipramine' OR 'equinorm' OR 'g 34586' OR 'g34586' OR 'gromin' OR 'hydiphen' OR 'monochlor imipramine' OR 'monochlorimipramine' OR 'monochloroimipramine' OR 'placil' OR 'zoiral' OR 'desipramine'/exp OR 'dosulepin'/exp OR 'doxepin'/exp OR 'imipramine'/exp OR 'lofepramine'/exp OR 'maprotiline'/exp OR 'nortriptyline'/exp OR 'amitriptyline'/exp OR 'protriptyline'/exp OR 'trimipramine'/exp OR 'serotonin uptake inhibitor'/exp OR 'fluoxetine'/exp OR 'fluvoxamine'/exp OR 'sertraline'/exp OR 'citalopram'/exp OR 'paroxetine'/exp OR 'escitalopram'/exp OR 'vortioxetine'/exp OR 'monoamine oxidase inhibitor'/exp OR 'phenelzine'/exp OR 'isocarboxazid'/exp OR 'tranylcypromine'/exp OR 'moclobemide'/exp OR 'brofaromine'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'venlafaxine'/exp OR 'desvenlafaxine'/exp OR 'duloxetine'/exp OR 'milnacipran'/exp OR 'noradrenergic and dopaminergic reuptake inhibitors' OR 'amfebutamone'/exp OR '1 (3 chlorophenyl) 2 [(1, 1 dimethylethyl) amino] 1 propanone' OR '2 tert butylamino 3` chloropropiophenone' OR 'amfebutamone' OR 'amfebutamone hydrochloride' OR 'aplenzin' OR 'budeprion' OR 'budeprion xl' OR 'buprion hydrochloride' OR 'bupropin' OR 'bupropion' OR 'bupropion hydrobromide' OR 'bupropion hydrochloride' OR 'bupropion' OR 'buxon' OR 'bw 323' OR 'bw 323u66' OR 'bw323' OR 'bw323u66' OR 'forfivo' OR 'forfivo xl' OR 'odranal' OR 'quomen' OR 'wellbatrin' OR 'wellbutrin' OR 'wellbutrin retard' OR 'wellbutrin sr' OR 'wellbutrin xl' OR 'wellbutrin xr' OR 'zyban' OR 'zyban lp' OR 'zyban sr' OR 'zyban sr refill' OR 'zyban sustained release' OR 'noradrenergic and specific serotonergic antidepressant'/exp OR 'mirtazapine'/exp OR 'noradrenergic reuptake inhibitors' OR 'reboxetine'/exp OR 'agomelatine'/exp OR 'trazodone'/exp OR nefazodone OR mianserine OR maprotiline OR 'benzodiazepine derivative'/exp OR alprazolam OR 'bretazenil'/exp OR 'bromazepam'/exp OR 'chlordiazepoxide'/exp OR 'cinolazepam'/exp OR 'clonazepam'/exp OR 'cloxazolam'/exp OR clorazepam OR deloramzepam OR 'diazepam'/exp OR 'estazolam'/exp OR 'etizolam'/exp OR 'fludiazepam'/exp OR 'flunitrazepam'/exp OR 'flurazepam'/exp OR 'flutoprazepam'/exp OR 'halazepam'/exp OR 'ketazolam'/exp OR 'loprazolam'/exp OR lormetazepam OR 'medazepam'/exp OR nimatazepam OR 'nitrazepam'/exp OR nodazepam OR 'oxazepam'/exp OR 'phenazepam'/exp OR 'pinazepam'/exp OR 'nordazepam'/exp OR 'health care quality'/exp OR 'temazepam'/exp OR 'tetrazepam'/exp OR 'triazolam'/exp OR 'azapirone'/exp OR alnespirone OR 'binospirone'/exp OR 'buspirone'/exp OR enilospirone OR 'phenytoin'/exp OR 'gepirone'/exp OR 'ipsapirone'/exp OR 'revospirone'/exp OR 'tandospirone'/exp OR 'zalospirone'/exp OR 'neuroleptic agent'/exp OR 'quetiapine'/exp OR 'beta adrenergic receptor blocking agent'/exp OR 'clonidine'/exp) AND ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp)

Search terms and strategy for Medline:

Search (((((((((((((((((((((((((((("Antidepressive Agents"[Mesh]) OR clomipramine) OR desipramine) OR dosulepin) OR dothiepin) OR doxepin) OR imipramine) OR lofepramine) OR maprotiline) OR nortriptyline) OR amitriptyline) OR moclobemide) OR phenelzine) OR tranylcypromine) OR amoxapine) OR protriptyline) OR trimipramine) OR isocarboxazid) OR brofaromine)) OR (((((((("Selective serotonin reuptake inhibitors") OR "Selective serotonin reuptake inhibitor") OR citalopram) OR escitalopram) OR fluoxetine) OR fluvoxamine) OR paroxetine) OR sertraline) OR vortioxetine)) OR (((((((("Serotonin-noradrenaline reuptake inhibitors") OR "Serotonin-noradrenaline reuptake inhibitor") OR desvenlafaxine) OR duloxetine) OR milnacipran) OR venlafaxine) OR levomilnacipran) OR ("Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh])) OR "Serotonin Uptake Inhibitors"[Mesh])) OR (((("Noradrenergic and specific serotonergic antidepressants"))) OR ("Noradrenergic and specific serotonergic antidepressant"))) OR mirtazapine)) OR (((("Noradrenergic and dopaminergic reuptake inhibitors"))) OR ("Noradrenergic and dopaminergic reuptake inhibitor"))) OR bupropion)) OR (((("Noradrenergic reuptake inhibitors") OR "Noradrenergic reuptake inhibitor") OR reboxetine)) OR (((agomelatine) OR trazodone) OR nefazodone) OR mianserin) OR buspirone))) OR (((((((((((((((((((((((("Benzodiazepines"[Mesh]) OR Alprazolam) OR bretazenil) OR bromazepam) OR chlordiazepoxide) OR cinolazepam) OR clonazepam) OR cloxazolam) OR clorazepate) OR diazepam) OR estazolam) OR etizolam) OR fludiazepam) OR flunitrazepam) OR delorazepam) OR flurazepam) OR flutoprazepam) OR halazepam) OR ketazolam) OR loprazolam) OR lorazepam) OR lormetazepam) OR medazepam) OR nimatazepam) OR nitrazepam) OR nodazepam) OR oxazepam) OR phenazepam) OR pinazepam) OR prazepam) OR premapazepam) OR quazepam) OR temazepam) OR tetrazepam) OR triazolam)) OR ("Antipsychotic Agents"[Mesh]) OR quetiapine)) OR ("Adrenergic beta-Antagonists"[Mesh]) OR clonidine)) OR (((((((((((Azapirones) OR Azapirone) OR Alnespirone) OR binospirone) OR buspirone) OR enilospirone) OR eptapirone) OR gepirone) OR ipsapirone) OR revospirone) OR tandospirone) OR zalospirone))) AND ("Panic Disorder"[Mesh]) OR panic) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study

eAppendix2: Assessment of evidence certainty

The certainty of evidence for network meta-analysis (NMA) of primary outcomes (i.e., remission and drop-out) and outcome considered in cluster ranking plot (i.e., adverse events) were assessed using the Confidence in Network Meta-Analysis (CINeMA) tool. CINeMA tool consists 6 domains: 1) within-study bias, 2) reporting bias, 3) indirectness, 4) imprecision, 5) heterogeneity, and 6) incoherence. Confidence of each domain was graded as no concerns, some concerns, or major concerns. Criteria used for grading of each domain are described as follows.

1. Within-study bias

Risk of bias for each direct comparison was scored as 1 for low risk, 2 for some concern, and 3 for high risk of bias. The judgement of within-study bias for each treatment comparison in the network was estimated using a weighted average of the risk of bias from all direct estimates in the network. Weighted average of the risk of bias was calculated using the percentage of direct comparisons that were contributed for each mixed and indirect estimate from the NMA. Percent contributions of the direct comparisons were suggested by the contribution matrix of contribution plot (see eAppendix Figure 1, 2, 3, 4, and 5).

2. Indirectness

Transitivity of the studies included in NMA was assessed by comparing characteristics of patients (i.e., mean age, percentages of female and presence of agoraphobia, and mean duration of panic disorder) and interventions (i.e., duration of treatment) among studies included in the NMA (see eAppendix Table 1 and 2). Different distributions of these characteristics across treatment comparisons indicated intransitivity.

3. Imprecision

Clinically meaningful threshold of risk ratio was defined as 0.80 or 1.25. This domain was rated as major concern, if RR point estimate was ≥ 1 and the lower limit of its confidence interval (CI) was < 0.80 or RR point estimate was ≤ 1 and the upper limit of its CI > 1.25 . A rating of 'some concerns' was assigned, if the 95% CI of RR was over 1 but the lower and upper limits of 95% CI did not extend beyond 0.80 and 1.25.

4. Heterogeneity

Predictive interval plot was applied to assess the heterogeneity of NMA (see eAppendix Figures 11, 12, 13, 14, 15). Heterogeneity was judged as 'no concerns' if confidence and predictive intervals of treatment comparisons had the same conclusion. If confidence and predictive intervals had different conclusions but the upper or lower limits of predictive intervals did not extend beyond 0.80 or 1.25 (i.e., clinical meaningful threshold), the heterogeneity was rated as 'some concerns', otherwise this domain was rated as 'major concerns'.

5. Incoherence

For treatment comparisons that had both direct and indirect estimates, node splitting test that compared direct and indirect estimates of each treatment comparisons was applied to assess incoherence. If direct and indirect estimates had the same conclusion, incoherence was rated as 'no concerns'. If direct and indirect estimates had different conclusions but the upper or lower limits of indirect estimates did not extend beyond 0.80 or 1.25 (i.e., clinical meaningful threshold), the heterogeneity was rated as 'some concerns', otherwise this domain was rated as 'major concerns'. For treatment comparisons that had only indirect estimates, we used the P-value from global test to rate the confidence of this domain. P-values of global test for remission and drop-out were higher than 0.05, this

domain was rated 'no concerns' for these outcomes. For adverse events, firstly, P-value of global test was less than 0.05. We performed sensitivity analysis by excluding the studies that had different characteristics (i.e., high percentages of female and presence of agoraphobia). After excluding these studies, P-value from global test was higher than 0.05. Therefore, we assumed that the model was consistent, and incoherence was judged as 'no concerns'.

6. Publication bias

Comparison-adjusted funnel plot was applied to assess publication bias. This domain was rated as undetected, if there was no deviation suggested from comparison-adjusted funnel plot.

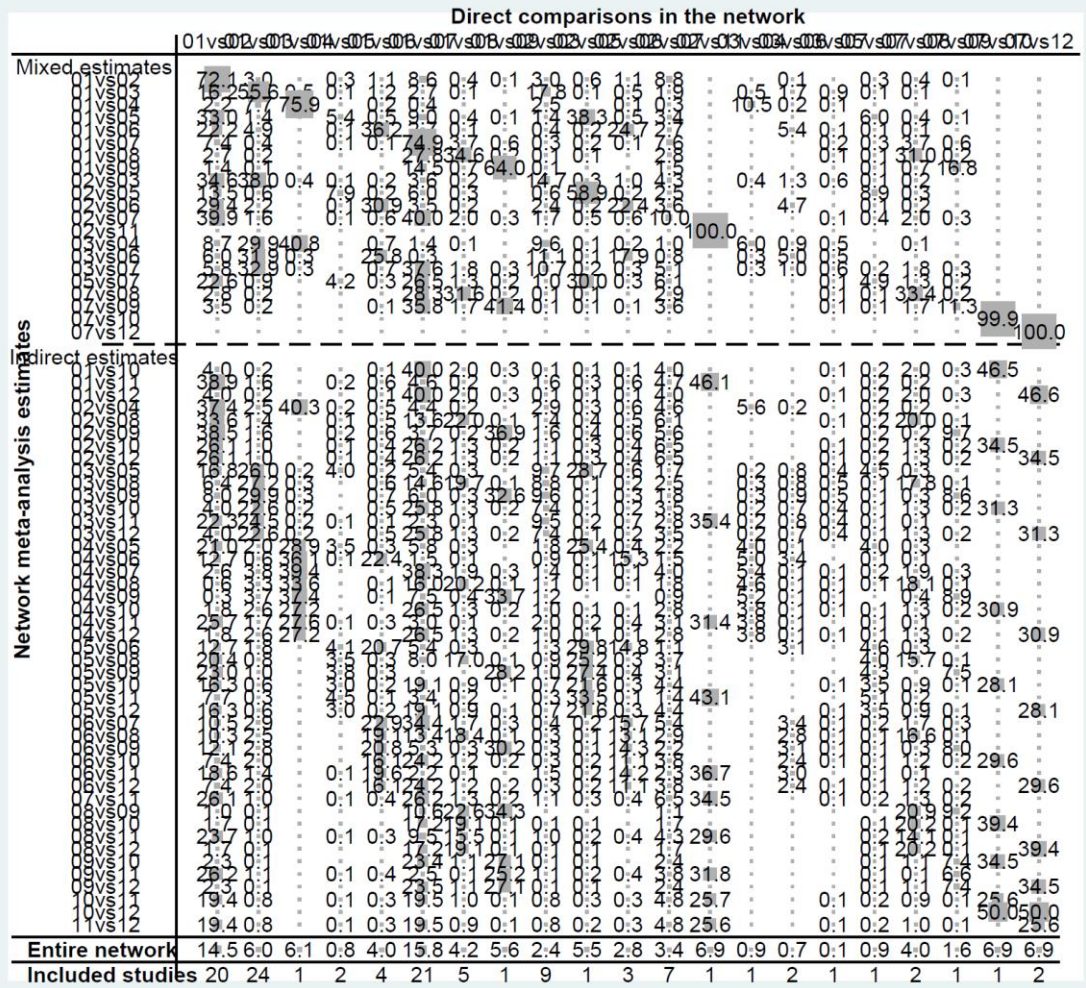
Overall confidence

Overall confidence was classified as high, moderate, low, and very low confidence. We started with high confidence and drop the level of confidence by 1 step for each domain with some concerns, and by 2 levels for each domain with major concerns. However, indirectness was related with incoherence and heterogeneity, imprecision, reporting, and within-study bias were also related with each other. Therefore, confidence of these domains was considered together rather than in separation.

eAppendix Figure 1. Contribution plot of network meta-analysis of remission outcome for drug classes

		Direct comparisons in the network																	
		01vs02	01vs03	01vs04	01vs06	01vs07	01vs08	01vs09	02vs03	02vs06	02vs07	03vs04	03vs06	03vs07	05vs07	07vs08	07vs09	07vs10	
Network meta-analysis estimates	Mixed estimates																		
	01vs02	39.4	27.6	0.2	0.4	4.5	0.7	0.1	25.4	0.2	2.9	0.2	0.2	2.5		0.7	0.1		
	01vs03	21.1	41.3	0.3	0.5	5.4	0.9	0.1	22.3		1.2	0.3	0.5	5.2		0.9	0.1		
	01vs04	9.9	19.4	20.6	0.2	2.5	0.4		10.5		0.6	32.6	0.2	2.4		0.4			
	01vs06	10.8	15.2	0.1	35.4	2.2	0.4		4.2	7.3	0.7	0.1	21.4	1.9		0.4			
	01vs07	6.9	8.8	0.1	0.1	49.0	8.1	0.7	1.5		5.3	0.1	0.1	10.5		8.1	0.7		
	01vs08	2.4	3.1			17.1	48.0	0.2	0.5		1.9			3.6		22.8	0.2		
	01vs09	2.9	3.7			20.5	3.4	28.1	0.6		2.2			4.4		3.4	30.6		
	02vs03	20.9	19.7	0.1	0.1	0.8	0.1		52.6	0.2	1.9	0.1	0.3	2.9		0.1			
	02vs06	20.3	4.7		26.9	1.6	0.3		21.7	5.7	1.6		16.6	0.3		0.3			
	02vs07	22.0	9.7	0.1	0.2	27.0	4.5	0.4	17.9	0.1	5.2	0.1	0.1	8.1		4.5	0.4		
	03vs04	7.5	14.7	24.7	0.2	1.9	0.3		8.0		0.4	39.7	0.2	1.9		0.3			
	03vs06	7.3	19.1	0.1	29.3	2.4	0.4		13.7	6.1	0.3	0.1	18.3	2.4		0.4			
	03vs07	10.0	22.5	0.2	0.3	27.9	4.6	0.4	14.2		4.2	0.2	0.3	10.3		4.6	0.4		
	05vs07														100.0				
	07vs08	3.4	4.4		0.1	24.6	32.9	0.4	0.8		2.7			5.3		25.1	0.4		
	07vs09	2.7	3.5			19.3	3.2	28.7	0.6		2.1			4.1		3.2	32.4		
	07vs10																	100.0	
		Indirect estimates																	
		01vs05	3.9	5.1		0.1	28.2	4.7	0.4	0.9		3.1		0.1	6.0	42.4	4.7	0.4	
		01vs10	4.0	5.1		0.1	28.2	4.7	0.4	0.9		3.1		0.1	6.0		4.7	0.4	
		02vs04	19.0	1.5	18.6	0.1	0.9	0.2		27.6	0.1	1.5	29.7	0.1	0.5		0.2		
		02vs05	15.1	6.7		0.1	18.6	3.1	0.3	12.3	0.1	3.6		5.6	31.1	3.1	0.3		
		02vs08	21.3	11.3		0.1	6.8	25.9	0.1	14.9	0.1	2.7	0.1	0.1	3.4		13.0	0.1	
		02vs09	19.2	9.8		0.1	10.2	1.7	17.3	13.9	0.1	2.9	0.1	0.1	4.0		1.7	18.8	
		02vs10	15.2	6.7		0.1	18.6	3.1	0.3	12.3	0.1	3.6		5.6		3.1	0.3	31.1	
		03vs05	6.8	15.3		0.1	0.2	18.9	3.1	0.3	9.7		2.9	0.1	0.2	7.0	3.1	0.3	
		03vs08	10.8	22.1	0.2	0.3	6.6	26.7	0.1	12.6		1.7	0.2	0.2	5.1		13.5	0.1	
		03vs09	9.5	19.8	0.1	0.2	10.2	1.7	17.8	11.6		2.1	0.1	0.2	5.6		1.7	19.5	
		03vs10	6.8	15.3		0.1	18.6	3.1	0.3	9.7		2.9	0.1	0.2	7.0		3.1	0.3	
		04vs05	2.6	6.8	10.7	0.1	17.0	2.8	0.2	4.9		2.3	16.9	0.1	5.2	27.5	2.8	0.2	
		04vs06	0.8	9.5	16.7	23.7	0.6	0.1	0.3	5.7	4.9		26.5	14.6	0.7	0.1			
		04vs07	3.6	9.3	14.7	0.1	23.5	3.9	0.3	6.7		3.2	23.3	0.1	7.1		3.9	0.3	
		04vs08	5.1	10.7	12.9	0.1	6.4	22.3	0.1	6.3		1.2	20.4	0.1	3.2		11.0	0.1	
	04vs09	4.3	9.4	12.1	0.1	9.4	1.6	14.9	5.8		1.5	19.1	0.1	3.8		1.6	16.3		
	04vs10	2.6	6.8	10.7	0.1	17.0	2.8	0.2	4.9		2.3	16.9	0.1	5.2		2.8	0.2		
	05vs06	2.2	3.5		16.4	18.8	3.1	0.3	1.3	3.4		2.5		10.0		3.1	0.3		
	05vs08	2.2	2.8			15.6	20.8	0.2	0.5		1.7					36.7	15.9		
	05vs09	1.7	2.1			12.0	2.0	17.8	0.4		1.3					38.0	2.0		
	05vs10														50.0		20.1		
	06vs07	3.2	5.0		23.4	26.8	4.4	0.4	1.9	4.8		3.5		14.2	7.3	4.4	0.4		
	06vs08	4.9	7.1	0.1	20.3	7.6	24.7	0.1	2.1	4.2	1.4		0.1	12.3	3.0	12.1	0.1		
	06vs09	4.1	6.0		18.9	10.8	1.8	16.4	1.9	3.9	1.7			11.4	3.6	1.8	17.8		
	06vs10	2.2	3.5		16.4	18.8	3.1	0.3	1.3	3.4		2.5		10.0	5.1	3.1	0.3		
	08vs09	0.7	0.9			5.0	28.4	21.8	0.2		0.5				1.1	17.4	24.0		
	08vs10	2.2	2.8			15.6	20.8	0.2	0.5		1.7				3.3	15.9	0.2		
	09vs10	1.7	2.1			12.0	2.0	17.8	0.4		1.3				2.6	2.0	20.1		
	Entire network	7.6	8.8	3.4	4.8	13.8	7.3	4.2	7.6	1.0	2.1	5.3	3.0	4.3	8.6	5.1	4.7	8.5	
	Included studies	12	18	1	3	18	4	1	6	2	5	1	1	1	1	2	1	1	

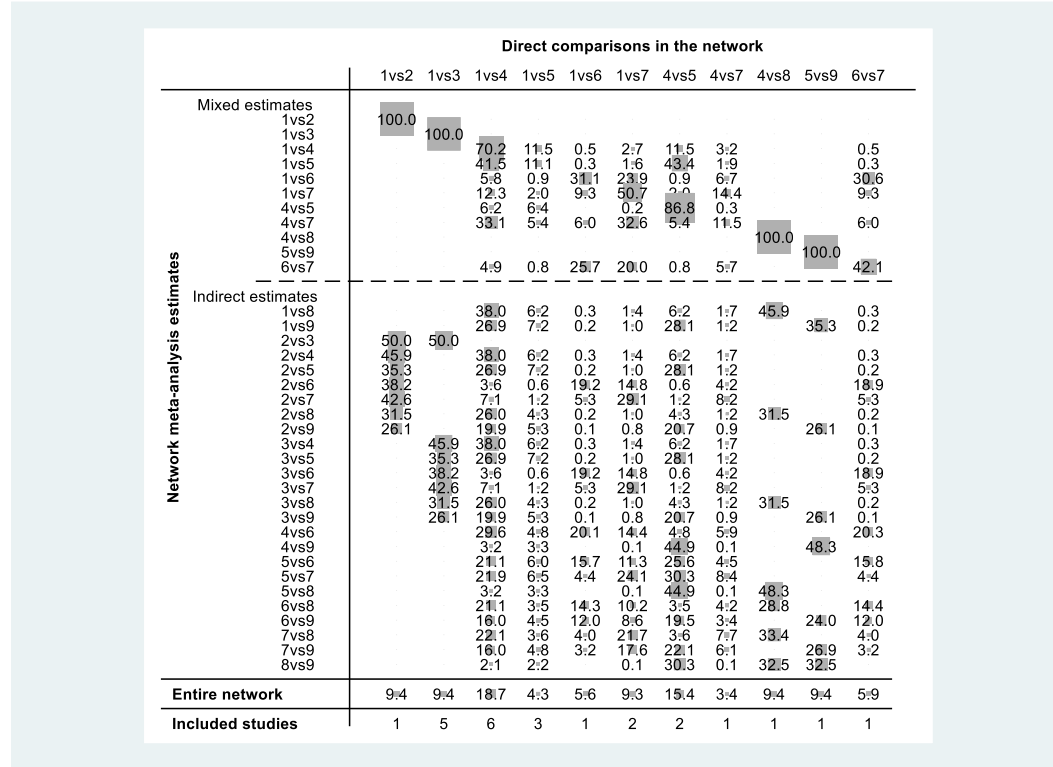
eAppendix Figure 2. Contribution plot of network meta-analysis of drop-out for drug classes



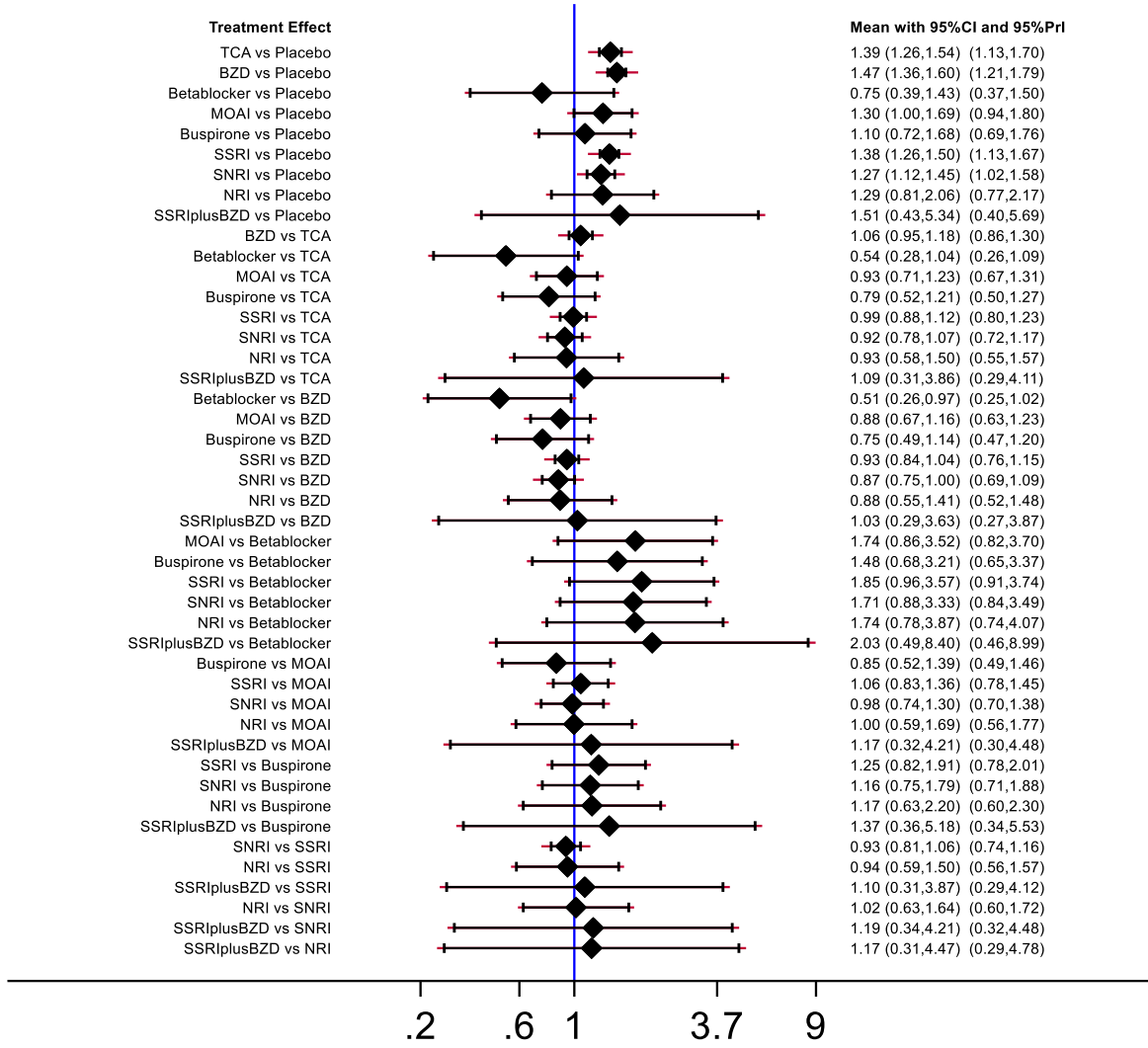
eAppendix Figure 4. Contribution plot of network meta-analysis of remission for individual SSRIs

		Direct comparisons in the network										
		1vs2	1vs3	1vs4	1vs5	1vs6	1vs7	2vs7	4vs7	4vs8	6vs7	
Network meta-analysis estimates	Mixed estimates											
	1vs2	41.3		1:9		8:7	13.5	24.1	1:9		8:7	
	1vs3		100.0									
	1vs4	0.7		90.4		1:2	1:9	0.7	3:8		1:2	
	1vs5				100.0							
	1vs6	6:2		2:2		43.3	15.7	6:2	2:2		24.1	
	1vs7	11.7		4:3		19.1	29.8	11.7	4:3		19.1	
	2vs7	27.3		2:2		9:8	15.3	33.3	2:2		9:8	
	4vs7	7:4		38.1		12.0	18.7	7:4	4:5		12.0	
	4vs8									100.0		
	6vs7	6:1		2:2		23.6	15.4	6:1	2:2		44.5	
		Indirect estimates										
		1vs8	0.4		46.5		0.6	1.0	0.4	2:0	48.5	0.6
		2vs3	25.0	39.5	1:2		5:2	8:2	14.6	1:2		5:2
		2vs4	25.7		38.3		4:9	7:7	15.5	2:9		4:9
		2vs5	25.0		1:2	39.5	5:2	8:2	14.6	1:2		5:2
		2vs6	26.5		0.2		25.0	1:3	22.6	0.2		24.1
		2vs8	18.2		27.1		3:5	5:4	11.0	2:0	29.2	3:5
		3vs4	0.4	48.5	46.5		0.6	1.0	0.4	2:0		0.6
		3vs5		50.0		50.0						
		3vs6	3:7	40.3	1:3		25.8	9:4	3:7	1:3		14.4
		3vs7	7:1	39.3	2:6		11.6	18.1	7:1	2:6		11.6
		3vs8	0.3	32.7	31.3		0.4	0.7	0.3	1:3	32.7	0.4
		4vs5	0.4		46.5	48.5	0.6	1:0	0.4	2:0		0.6
		4vs6	3:5		38.9		26.4	8:9	3:5	3:1		15.6
	5vs6	3:7		1:3	40.3	25.8	9:4	3:7	1:3		14.4	
	5vs7	7:1		2:6	39.4	11.6	18.1	7:1	2:6		11.6	
	5vs8	0.3		31.3	32.7	0.4	0.7	0.3	1:3	32.7	0.4	
	6vs8	2:5		27.4		18.6	6:3	2:5	2:2	29.6	11:0	
	7vs8	5:2		26.7		8:4	13.1	5:2	3:2	29.9	8:4	
	Entire network	9:3	11.6	19.4	11.6	10.5	8:3	7:2	2:0	11.6	8:7	
	Included studies	2	5	7	3	1	1	1	2	1	1	

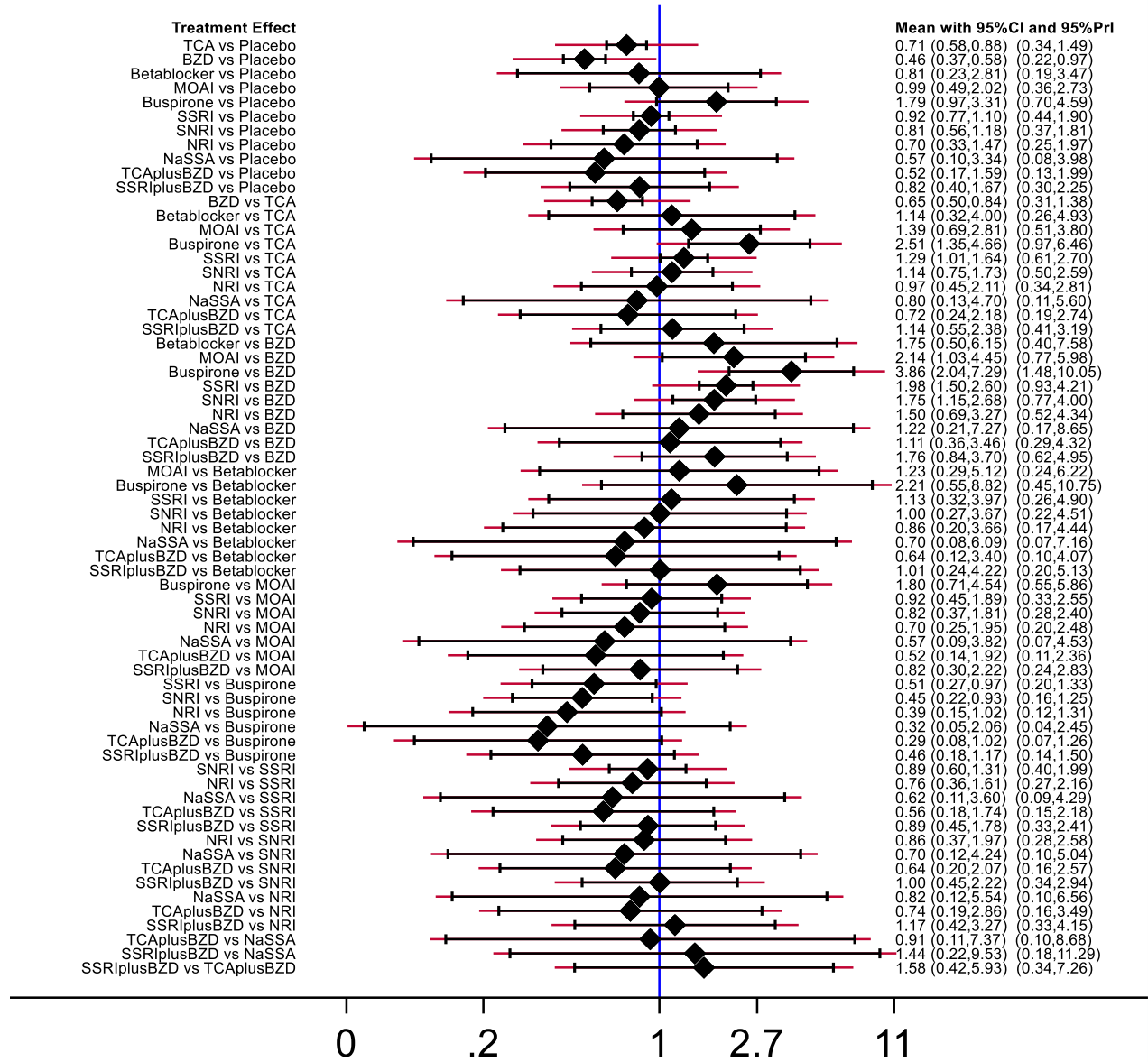
eAppendix Figure 5. Contribution plot of network meta-analysis of adverse drug events for individual SSRIs



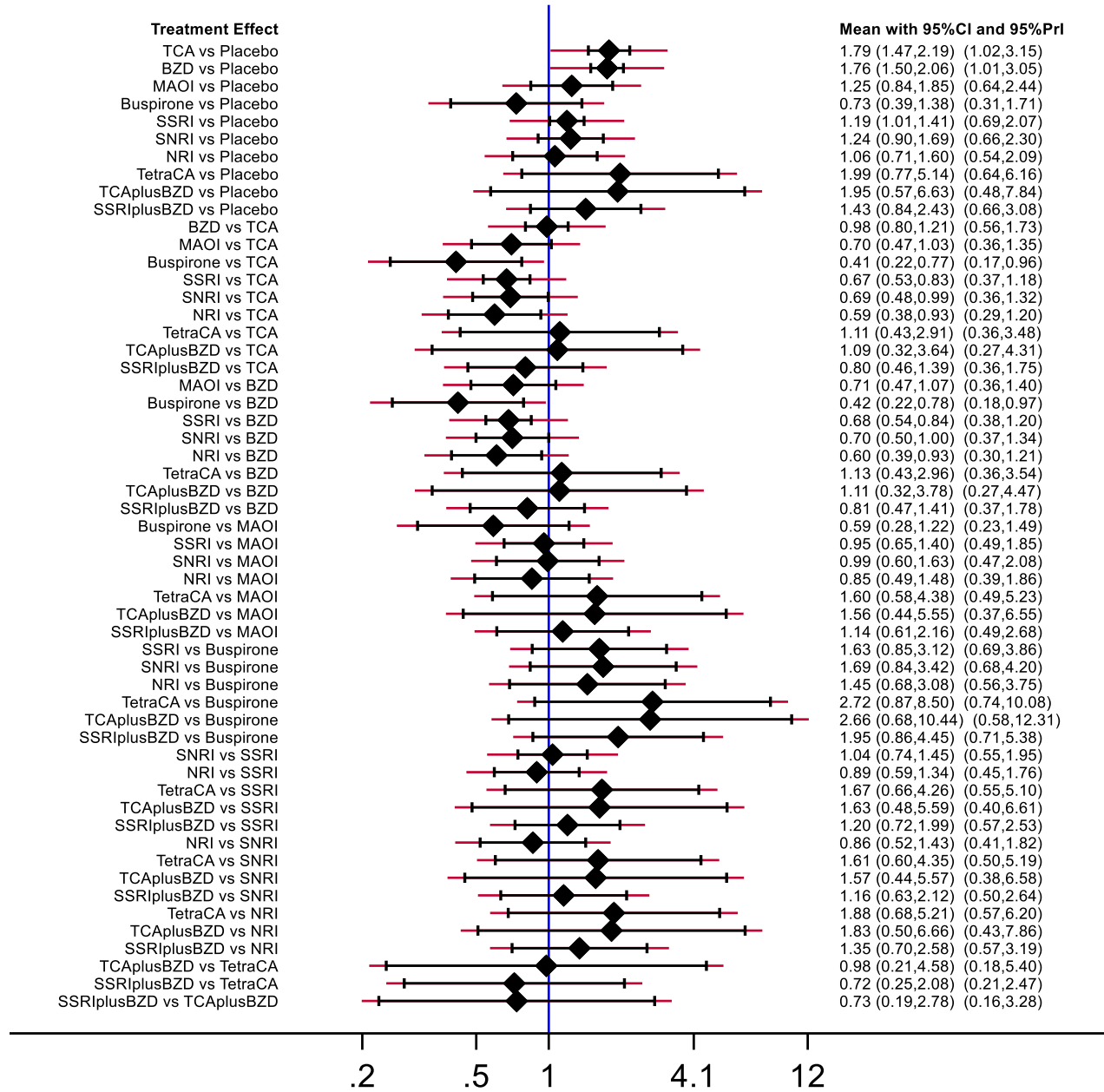
eAppendix Figure 6. Predictive interval plot of network meta-analysis of remission for drug classes



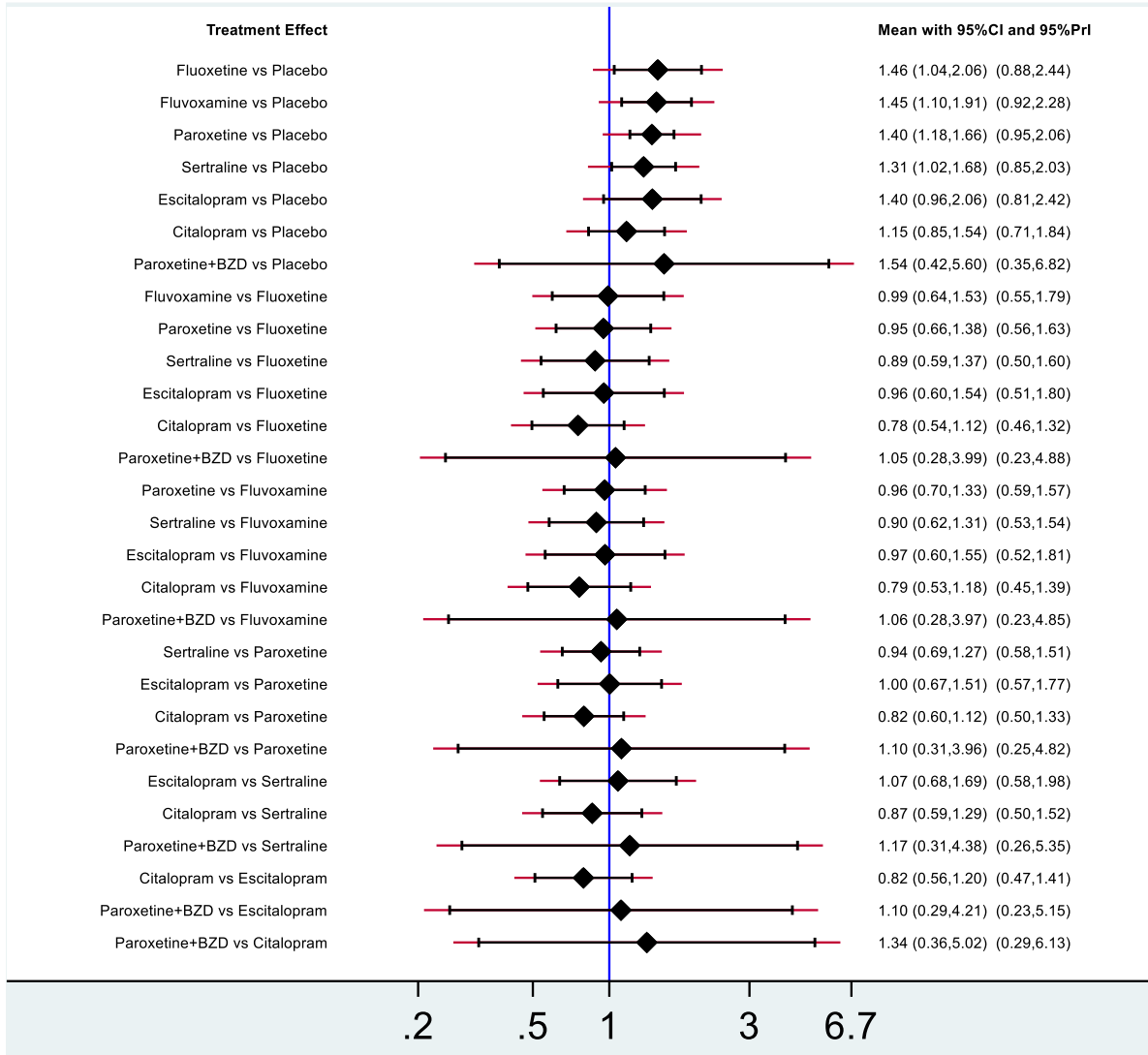
eAppendix Figure 7. Predictive interval plot of network meta-analysis of drop-out for drug classes



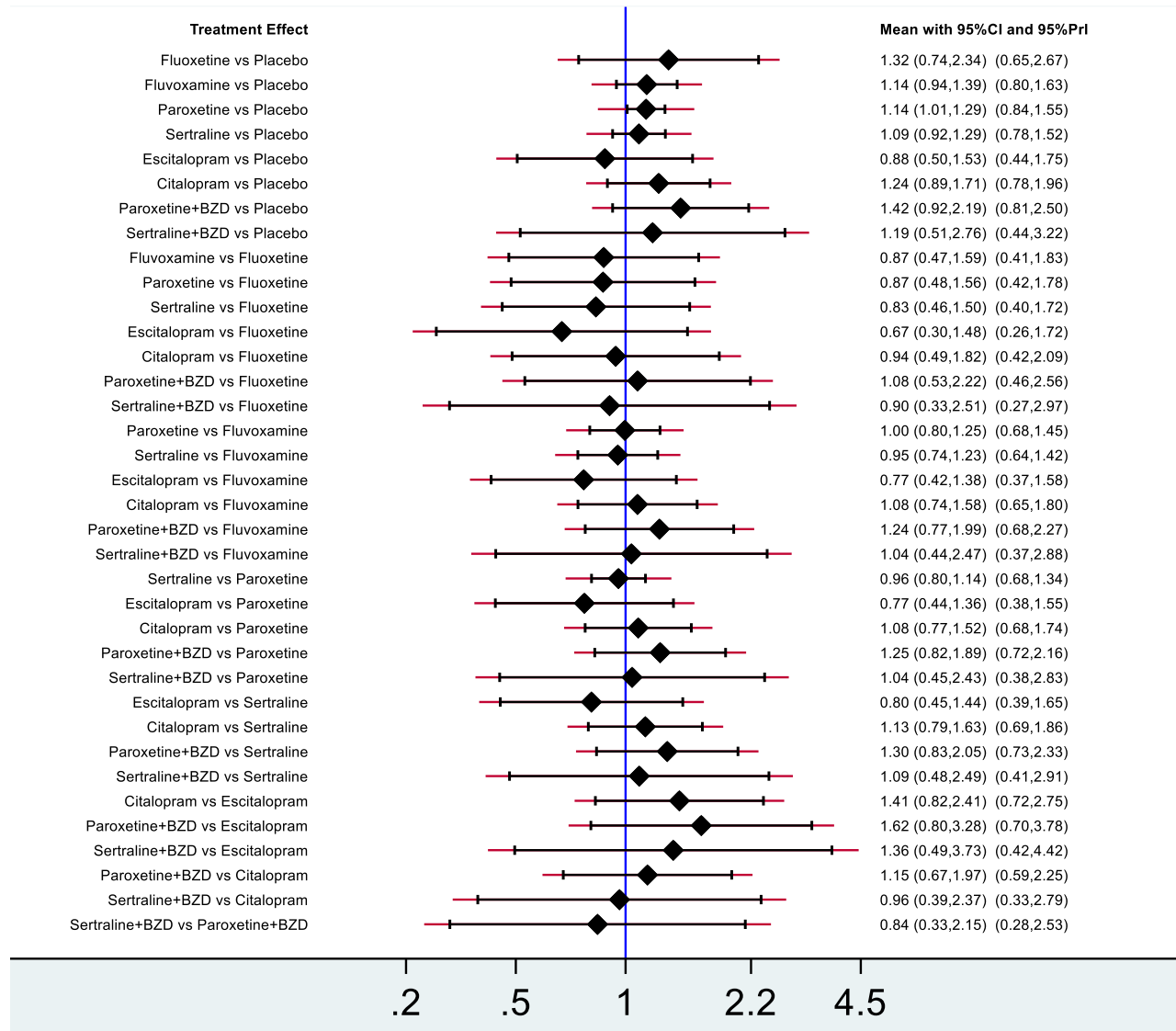
eAppendix Figure 8. Predictive interval plot of network meta-analysis of adverse drug events for drug classes



eAppendix Figure 9. Predictive interval plot of network meta-analysis of remission for individual SSRIs



eAppendix Figure 10. Predictive interval plot of network meta-analysis of adverse drug events for individual SSRIs



eAppendix Figure 11. Node splitting test of network meta-analysis of remission for drug classes

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
01 02	.3066091	.0642539	.3738307	.0948273	-.0672216	.1170379	0.566
01 03 *	.4009427	.045897	.3166396	.1048867	.0843031	.1143463	0.461
01 04 *	-.1718503	.421837	-.4807048	.5162151	.3088545	.6516806	0.636
01 06 *	.1861867	.2615864	-.0909123	.3833323	.277099	.4689174	0.555
01 07	.3199309	.0487922	.3266679	.1033117	-.006737	.1131578	0.953
01 08 *	.2285219	.0724533	.3273478	.1923296	-.0988259	.2108245	0.639
01 09	.7738826	.3418802	-.2206187	.3284754	.9945014	.4741077	0.036
02 03	-.014377	.0627485	.178609	.0838784	-.192986	.104733	0.065
02 06	.0170062	.30979	-.4625609	.2987048	.4795671	.4313231	0.266
02 07	.068518	.0975109	-.0563852	.0750093	.1249032	.123715	0.313
03 04 *	-.7108468	.3380177	-.4019923	.676424	-.3088545	.6516806	0.636
03 06	-.6576799	.3256777	-.0758223	.2572023	-.5818576	.388643	0.134
03 07	-.1281734	.1439913	-.0559417	.0604406	-.0722318	.1561619	0.644
05 07 *	.0587509	.127591	.6401453	57.28854	-.5813944	57.28867	0.992
07 08	-.0035806	.0897655	-.1763945	.1046038	.1728138	.1379157	0.210
07 09	-.5306162	.325647	.4638422	.3445718	-.9944585	.4741027	0.036
07 10 *	.0953102	.6417394	-.6366902	130.3595	.7320003	130.3611	0.996

eAppendix Figure 12. Node splitting test of network meta-analysis of drop-out for drug classes

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
01 02	-.3840532	.1203571	-.1932824	.2048346	-.1907708	.2356979	0.418
01 03 *	-.8019813	.1160786	-.5181595	.2853159	-.2838218	.301101	0.346
01 04 *	-.3631896	.645197	3.343396	2.918264	-3.706586	2.972219	0.212
01 05	.5093175	.7049695	-.1873112	.4192343	.6966287	.8204056	0.396
01 06	.6732057	.3741942	.3073766	.7045868	.3658291	.8365781	0.662
01 07	-.0401522	.0988867	-.4011763	.2627539	.3610241	.2807014	0.198
01 08 *	-.2470563	.1999801	.1423313	.5645784	-.3893877	.5939622	0.512
01 09	-.7467106	.455594	.4906681	.6795714	-1.237379	.8181584	0.130
02 03	-.3893006	.1790872	-.4820494	.1951391	.0927488	.2643353	0.726
02 05	2.34e-07	.465693	.8002848	.5555852	-.8002846	.7249438	0.270
02 06	.3653211	.443429	1.553485	.4773402	-1.188164	.6691594	0.076
02 07	.2039758	.1842755	.2912814	.1692245	-.0873056	.249845	0.727
02 11 *	-.3220835	.5622725	.3492383	200.0335	-.6713218	200.0333	0.997
03 04 *	2.246015	1.498554	-1.460571	1.740145	3.706586	2.972219	0.212
03 06	2.473539	.7633601	1.017876	.3817613	1.455663	.8943098	0.104
03 07	.7931704	1.260488	.6802304	.1410845	.1129399	1.268359	0.929
05 07	-.4418284	.8635132	-.0010456	.4038262	-.4407828	.9532761	0.644
07 08	-.0771509	.3106545	-.1552434	.2668093	.0780925	.4089418	0.849
07 09	.5596043	.6731968	-.6777556	.4649582	1.23736	.8181545	0.130
07 10 *	-.4795731	.8982386	-.3099307	199.9793	-.1696424	199.9779	0.999
07 12 *	-.1167288	.352637	.0529095	141.468	-.1696384	141.468	0.999

eAppendix Figure 13. Node splitting test of network meta-analysis of adverse drug events for drug classes

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
01 02	.4653046	.1324698	.7468313	.1594452	-.2815267	.2097907	0.180
01 03	.6488292	.0711593	-.1503031	.2177677	.7991323	.2314449	0.001
01 05 *	-.0764402	.3867037	-.7797858	.5283325	.7033456	.6308159	0.265
01 06	.1303979	.0920063	.3913688	.2032337	-.260971	.2233296	0.243
01 07 *	.1856924	.1731707	.4506294	.4938896	-.2649371	.5235252	0.613
01 08	.1053605	.2887677	.0067437	.3083601	.0986169	.4224603	0.815
02 03	-.1215846	.1269493	.183074	.1740997	-.3046586	.2133446	0.153
02 04	-.2162932	.2693582	-.5332008	.2946143	.3169075	.3991876	0.427
02 05	-.7945138	.4359444	-.9953005	.4330742	.2007867	.5767956	0.728
02 06	-.2815371	.1890743	-.4826183	.1465494	.2010812	.2392025	0.401
02 10 *	.0833816	.6173676	-1.162528	123.2957	1.245909	123.2973	0.992
03 05	-1.352612	.4725807	-.5573719	.3978467	-.79524	.578016	0.169
04 06	.0961688	.2681242	-.2205329	.2957297	.3167018	.3991824	0.428
06 07	.0729335	.2657192	.0136304	.2320625	.0593031	.3530177	0.867
06 08	-.1648219	.2956725	-.0662253	.3017762	-.0985966	.422461	0.815
06 09 *	.5136787	.4768446	-.4342608	60.947	.9479395	60.95024	0.988
06 11 *	.1812591	.2585754	-.3474463	32.72969	.5287054	32.73094	0.987

eAppendix Figure 14. Node splitting test of network meta-analysis of remission for individual SSRIs

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
1 2	.4083816	.2197744	.3266564	.3141324	.0817252	.3834069	0.831
1 3
1 4	.3480545	.0956334	.2204289	.3182572	.1276255	.3293882	0.698
1 5
1 6 *	.2898193	.2213807	.634108	.5772529	-.3442887	.6288498	0.584
1 7 *	.0406891	.2343824	.2128334	.2095899	-.1721443	.3144249	0.584
2 7	-.2076386	.2590119	-.2893612	.2826921	.0817225	.3834084	0.831
4 7	-.1276365	.2530624	-.2552576	.214327	.1276211	.3293921	0.698
4 8 *	.0953102	.6538807	-.5740372	199.9789	.6693473	199.978	0.997
6 7 *	-.2491302	.2198277	.0951584	.5790307	-.3442887	.6288498	0.584

eAppendix Figure 15. Node splitting test of network meta-analysis of adverse drug events for individual SSRIs

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
1 2
1 3
1 4	.1185611	.0753261	.2104908	.1751237	-.0919297	.1911992	0.631
1 5	.0972994	.1246468	.0707496	.1562154	.0265498	.2008756	0.895
1 6 *	.0324537	.3231439	-.7433646	.6337577	.7758183	.7183316	0.280
1 7 *	.291436	.1922509	-.0414147	.3416185	.3328506	.3919102	0.396
4 5	-.0593906	.1381571	-.032842	.1444301	-.0265486	.2008751	0.895
4 7	-.163971	.3358989	.1688776	.2019042	-.3328486	.3919097	0.396
4 8 *	.2204733	.2127626	-.0406354	199.1334	.2611087	199.1334	0.999
5 9 *	.0870114	.4220321	-.0836537	200.1376	.170665	200.1372	0.999
6 7 *	.4444703	.2887025	-.331348	.6818116	.7758183	.7183314	0.280

eAppendix Table 1. Transitivity assessment for network meta-analysis of drug classes

Comparison	No of studies	Diagnostic criteria	Duration of treatment	No. of participants	%Female	Mean age (years)	Duration of panic disorder (years)	%Agoraphobia
<i>Remission</i>								
TCA vs placebo	1	DSM-III-R	12	56	-	-	-	-
BZD vs placebo	10	DSM-III (5), DSM-III-R (4), DSM-IV (1)	4 – 15	2020	65.36	36.46	8.57	77.54
SSRI vs placebo	12	DSM-III-R (9), DSM-IV (3)	6 – 12	2270	61.99	37.31	8.34	74.03
SNRI vs placebo	2	DSM-IV (2)	10	680	59.01	37.76	7.18	-
NRI vs placebo	1	DSM-III-R	8	75	67	35.8	1.8	-
TCA vs BZD	1	DSM-III-R	12	257	64	34.8	-	-
TCA vs SSRI	2	DSM-III-R (1), DSM-IV (1)	10-24	59	45.58	37.06	5.6	55
BZD vs SSRI	1	DSM-IV (1)	8	120	69	34.9	-	93
MAOI vs SSRI	1	DSM-III (1)	8	366	67	35.0	6	-
SSRI vs NRI	1	DSM-IV	12.8	68	68	30.8	-	-
SSRI vs SSRI plus BZD	1	DSM-IV	8	60	60	-	-	83
TCA vs SSRI vs placebo	4	DSM-III-R (4)	8-12	1083	57.27	34.87	7.59	75.77
TCA vs BZD vs placebo	5	DSM-III (5)	8	1511	61.32	34.16	7.06	40.52

TCA vs buspirone vs placebo	2	DSM-III (2)	8	106	64.64	32.80	11.10	-
SSRI vs SNRI vs placebo	2	DSM-IV (2)	12	1113	75.79	36.75	3.39	-
BZD vs beta-blocker vs placebo	1	DSM-III (1)	5	55	69	31.0	6.4	25
BZD vs buspirone vs placebo	1	DSM-III-R (1)	8	92	80	36.7	15.2	17
SSRI vs SSRI vs placebo	1	DSM-IV (1)	10	351	58	37.7	-	-
<i>Drop-out</i>								
TCA vs placebo	5	DSM-III (1), DSM-III-R (4)	8-12	431	54.43	34.71	7.90	97.27
BZD vs placebo	14	DSM-III (8), DSM-III-R (5), DSM-IV (1)	4 – 15	2770	53.58	36.23	8.63	59.77
SSRI vs placebo	12	DSM-III-R (10), DSM-IV (2)	8-14	2309	62.35	37.53	8.42	44.2
SNRI vs placebo	3	DSM-III-R (2), DSM-IV (1)	8-10	705	57.63	37.72	7.18	-
NRI vs placebo	1	DSM-III-R (1)	8	75	67	35.8	1.8	-
MAOI vs placebo	2	DSM-III-R (2)	8-12	57	90	32	9.6	98.42
TCA vs BZD	1	DSM-III-R (2)	12-24	572	63.45	35.57	-	-
BZD vs buspirone	1	DSM-III (1)	4	16	69	35	-	-
BZD vs SSRI	1	DSM-IV (1)	8	120	69	34.9	-	93
MAOI vs SSRI	1	DSM-III-R (1)	16	32	-	-	-	-

SSRI vs NRI	1	DSM-IV (1)	12.8	68	68	30.8	-	66
SSRI vs SSRI plus BZD	2	DSM-IV (2)	8 – 12	107	57.8	38.2	6.8	82.12
TCA vs SSRI vs placebo	7	DSM-III-R (5), DSM-IV (2)	8-26	1363	59.23	36.31	7.35	46.41
TCA vs BZD vs placebo	7	DSM-III (5), DSM-III-R (1)	8-16	1662	62.59	34.52	7.06	45.10
TCA vs buspirone vs placebo	3	DSM-III (3)	8	197	65.73	32.75	11.1	-
TCA plus BZD vs TCA	1	DSM-III-R (1)	8	135	59	35.5	5.7	-
SSRI vs SNRI vs placebo	2	DSM-IV (2)	12	1113	75.79	36.75	3.39	-
BZD vs beta-blocker vs placebo	1	DSM-III (1)	5	55	69	31	6.4	25
BZD vs buspirone vs placebo	1	DSM-III-R (1)	8	92	80	36.7	15.2	17
SSRI vs SSRI vs placebo	1	DSM-IV (1)	10	351	58	37.7	-	-
NaSSA vs SSRI	1	DSM-IV (1)	8	27	77	36.2	3	73
TCA vs MAOI	1	DSM-III-R (1)	8	135	59	35.5	5.7	-
<i>Adverse drug events</i>								

BZD vs placebo	12	DSM-III (6), DSM-III-R (5), DSM-IV (1)	4-9	2237	49.89	35.96	8.44	77.41
SSRI vs placebo	7	DSM-III-R (6), DSM-IV (1)	6-12	1703	60.58	37.16	8.55	71.85
SNRI vs placebo	3	DSM-III-R (1), DSM-IV (2)	8-10	705	57.63	37.72	7.18	-
NRI vs placebo	1	DSM-III-R (1)	8	75	67	35.8	1.8	-
TCA vs BZD	1	DSM-III-R (2)	12-24	572	63.45	35.57	-	-
TCA vs MAOI	1	DSM-III-R (1)	8	135	59	35.5	5.7	-
TCA vs SSRI	1	DSM-IV (1)	26	207	74	40.3	7.4	60
TCA vs TCA plus BZD	1	DSM-III-R (1)	4	48	54	36.2	10	69
MAOI vs SSRI	1	DSM-III (1)	8	366	67	35	6	-
SSRI vs NRI	2	DSM-III (1), DSM-IV (1)	8 – 12.8	85	66	31.74	-	66
SSRI vs SSRI plus BZD	2	DSM-IV (2)	8 – 12	107	57.8	38.2	6.8	82.12
TCA vs BZD vs placebo	3	DSM-III (3)	8	1351	60.83	34.13	8	37.93
TCA vs SSRI vs placebo	2	DSM-III-R (2)	8	183	53.28	34.46	7.9	50.63
SSRI vs SNRI vs placebo	2	DSM-IV (2)	12	1113	75.79	36.75	3.39	-
TCA plus BZD vs TCA	1	DSM-III-R (1)	4	48	54	36.2	10	69

TCA vs buspirone vs placebo	1	DSM-III	8	52	57	30.3	-	-
BZD vs buspirone vs placebo	1	DSM-III-R	8	92	80	36.7	15.2	17
SSRI vs NaSSA	1	DSM-III-R	8	75	67	35.8	1.8	-

BZDs, benzodiazepines; DSM, Diagnostic and Statistical Manual of Mental Disorders; MAOIs, monoamine oxidase inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants NRI, norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitors; TCAs, tricyclic anti-depressants

eAppendix Table 2. Transitivity assessment for network meta-analysis of individual SSRIs

Comparison	No of studies	Diagnostic criteria	Duration of treatment	No. of participants	%Female	Mean age is (years)	Duration of panic disorder (years)	%Agoraphobia
Remission								
Fluvoxamine vs placebo	5	DSM-III-R (5)	6-8	392	62.93	35.48	4.7	66.9
Fluoxetine vs placebo	2	DSM-III-R (1), DSM-IV ()	10-12	333	65.22	36.8	-	78
Paroxetine vs placebo	7	DSM-III-R (3), DSM-IV (4)	9-12	1961	63.87	37.09	6.85	80.4
Sertraline vs placebo	3	DSM-III-R (3)	10-12	521	56.31	37.57	9.46	70
Escitalopram vs citalopram vs placebo	1	DSM-IV (1)	10	351	59	37.7	-	-
Paroxetine vs citalopram	2	DSM-IV (2)	8-52	152	67.63	34	4.2	71
Paroxetine+clonazepam vs paroxetine	1	DSM-IV (1)	8	42	60	-	-	83
Fluoxetine vs citalopram	1	DSM-IV (1)	24	42	60	37	5.8	69
Adverse drug events								
Fluvoxamine vs placebo	5	DSM-III-R (5)	6-8	378	61.6	35.09	5.3	61.7
Fluoxetine vs placebo	1	DSM-III-R (1)	10	153	69	36.8	-	78.0
Paroxetine vs placebo	6	DSM-III-R (3), DSM-IV (3)	10-12	2014	64.18	37.07	7.4	77.5
Sertraline vs placebo	3	DSM-III-R (3)	10-12	521	56.31	37.57	9.5	70.0
Escitalopram vs citalopram vs placebo	1	DSM-IV (1)	10	351	59	37.7	-	-
Paroxetine vs citalopram	1	DSM-IV (1)	8	52	65	31.3	-	79.0
Paroxetine and clonazepam vs paroxetine	1	DSM-IV (1)	8	42	60	-	-	83.0
Sertraline and clonazepam vs sertraline	1	DSM-IV (1)	12	47	55	38.2	6.8	81.0
Paroxetine vs sertraline	2	DSM-IV (1), ICD-10 (1)	12	544	67.1	38.9	3.9	65.0
Citalopram vs placebo	1	DSM-III-R (1)	8	193	79	-	-	75.0

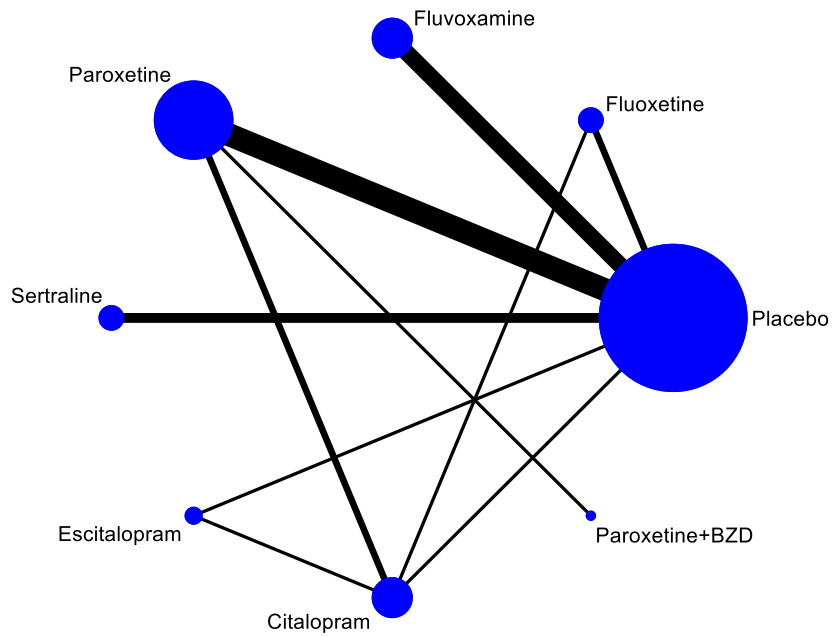
eAppendix 3: Network meta-analysis of individual selective serotonin reuptake inhibitors

Remission rate

Twenty-two studies with 8 interventions (i.e., fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram, paroxetine plus benzodiazepine (BZD), and placebo) were included in the network meta-analysis (NMA) of remission (eAppendix Figure 16 and eAppendix Table 3). Global test indicated the consistency results (Global Chi-square = 0.28, p-value=0.8715). Fluoxetine, fluvoxamine, paroxetine, and sertraline significantly increased remission rate, when compared to placebo with risk ratios (RR) of 1.46 (95% CI: 1.04,2.06), 1.45 (95% CI: 1.10,1.91), 1.40 (95% CI: 1.18,1.66), and 1.31 (95% CI: 1.02,1.68), respectively (eAppendix Table 4).

SUCRA suggested fluoxetine (68.4%), fluvoxamine (65.4%), and escitalopram (62.7%) as the top three best SSRIs for remission (eAppendix Figure 17). The comparison-adjusted funnel plot was symmetry, indicating no publication bias (eAppendix Figure 18).

eAppendix Figure 16. Network map of disease remission for individual selective serotonin reuptake inhibitors



The size of each node represents the number of participants randomly assigned to the treatment comparison. The width of each line represents the number of studies comparing the two connected treatments. The number provided over each line indicates the number of studies comparing the two connected treatments

eAppendix Table 3. Data used for pooling disease remission for individual SSRIs

Author	Year	Duration of treatment (weeks)	Intervention	Remission	Non- remission
Black	1993	8	Fluvoxamine	18	7
			Placebo	6	19
Hoehn-Saric	1993	8	Fluvoxamine	11	7
			Placebo	4	14
Sandmann	1998	6	Fluvoxamine	8	9
			Placebo	6	12
Asnis	2001	8	Fluvoxamine	60	27
			Placebo	42	50
Londborg	1998	12	Sertraline	72	55
			Placebo	18	26
Pohl	1998	10	Sertraline	49	30
			Placebo	40	47
Pollack	1998	10	Sertraline	50	38
			Placebo	41	47
Michelson	1998	10	Fluoxetine	18	62
			Placebo	11	61
Michelson	2001	12	Fluoxetine	38	52
			Placebo	25	65
Oehrberg	1995	12	Paroxetine	19	41
			Placebo	8	52
Sheehan	2005	10	Paroxetine	236	141
			Placebo	208	187
Bergink	2005	9	Paroxetine	3	6
			Placebo	5	5
Stahl	2003	10	Escitalopram	63	62
			Placebo	43	71
Nair	1996	8	Fluvoxamine	19	31
			Placebo	24	26
Bakker	1999	12	Paroxetine	21	11
			Placebo	11	21
Lecrubier	1997	12	Paroxetine	56	67
			Placebo	37	86
Pollack	2007	12	Paroxetine	98	63
			Placebo	55	101
Pollack	2007	12	Paroxetine	88	63
			Placebo	75	82
Pollack	2003	8	Paroxetine+BZD	4	16

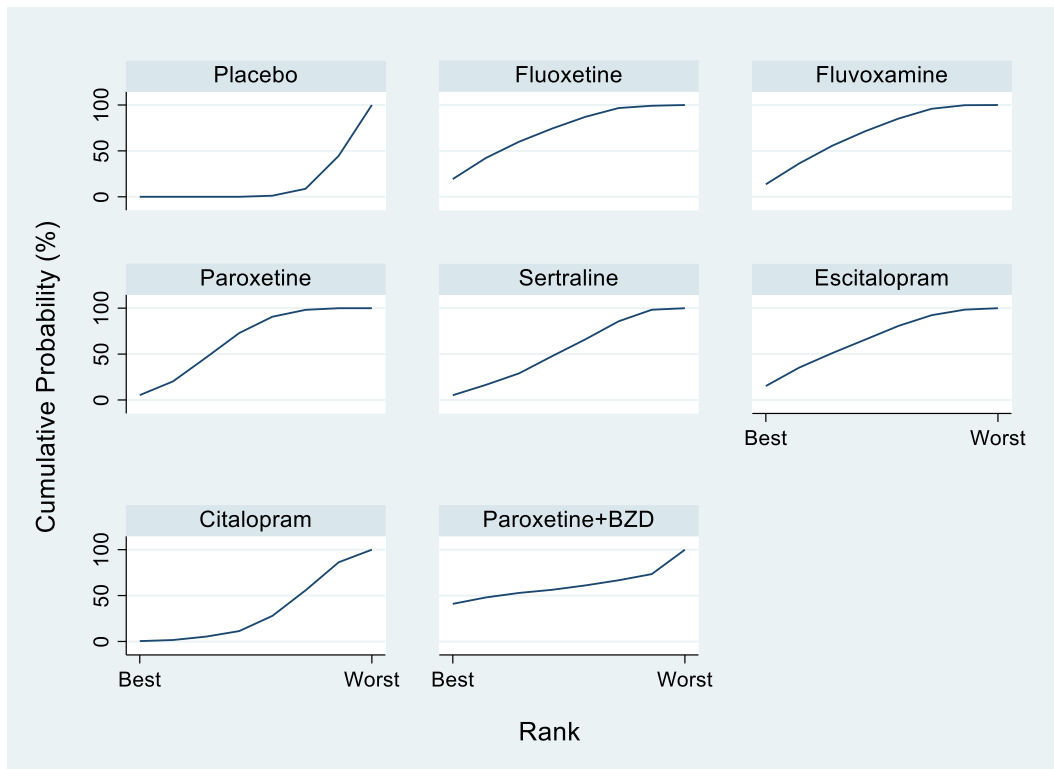
Author	Year	Duration of treatment (weeks)	Intervention	Remission	Non- remission
			Paroxetine	4	18
Amore	1999	24	Fluoxetine	16	4
			Citalopram	13	7
Marchesi	2006	52	Paroxetine	16	21
			Citalopram	17	1
Perna	2001	8	Paroxetine	10	10
			Citalopram	6	19

eAppendix Table 4. Estimation of the relative treatment effects (95% confidence intervals) on disease remission for individual selective serotonin reuptake inhibitors

Placebo	1.54 (0.42,5.60)	1.15 (0.85,1.54)	1.40 (0.96,2.06)	1.31 (1.02,1.68)	1.40 (1.18,1.66)	1.45 (1.10,1.91)	1.46 (1.04,2.06)
	Paroxetine+BZD	0.74 (0.20,2.79)	0.91 (0.24,3.50)	0.85 (0.23,3.18)	0.91 (0.25,3.27)	0.94 (0.25,3.53)	0.95 (0.25,3.62)
		Citalopram	1.22 (0.84,1.79)	1.14 (0.77,1.69)	1.22 (0.89,1.67)	1.27 (0.85,1.89)	1.28 (0.89,1.84)
			Escitalopram	0.93 (0.59,1.48)	1.00 (0.66,1.50)	1.03 (0.65,1.65)	1.04 (0.65,1.68)
				Sertraline	1.07 (0.79,1.45)	1.11 (0.76,1.60)	1.12 (0.73,1.71)
					Paroxetine	1.04 (0.75,1.42)	1.05 (0.72,1.52)
						Fluvoxamine	1.01 (0.65,1.56)
							Fluoxetine

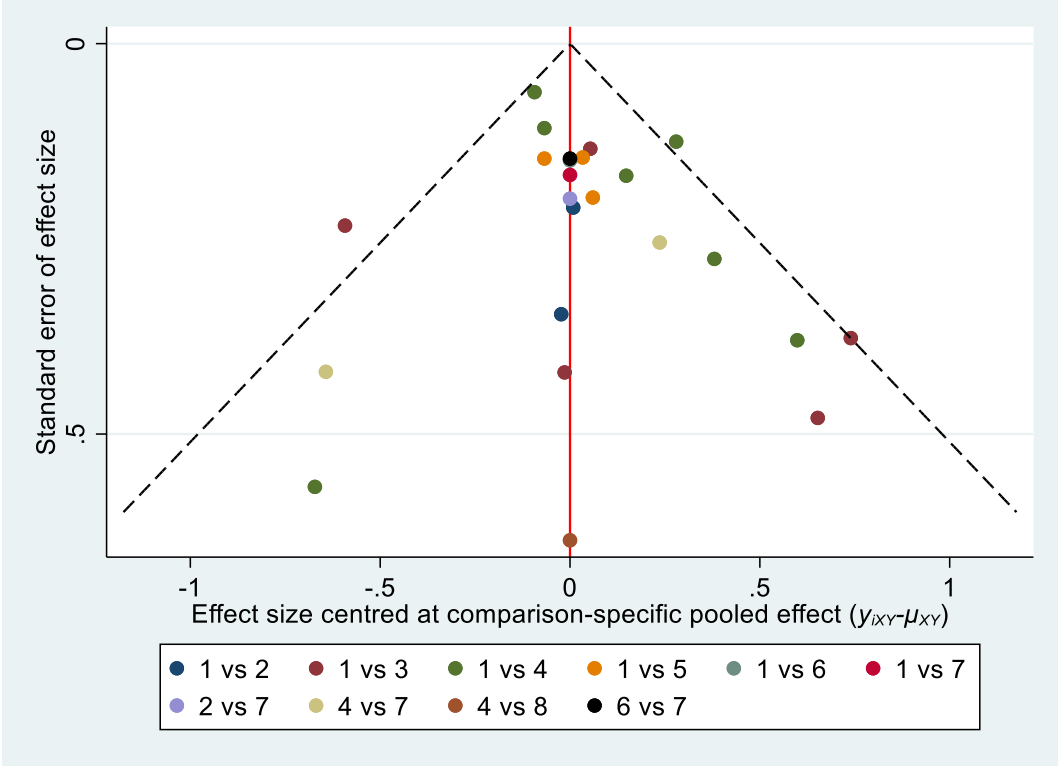
Results are risk ratios (95% confidence intervals) between each pair of treatments from network meta-analysis. Comparisons are read from right to left. Bold font indicates statistical significance. The GRADE certainty of evidence of each comparison is highlighted: Light green, light red, and dark red refer to moderate, low, and very low certainty.

eAppendix Figure 17. Surface under the cumulative ranking curve of remission for individual selective serotonin reuptake inhibitors



Treatment	SUCRA	PrBest	MeanRank
Placebo	7.8	0.0	7.5
Fluoxetine	68.4	19.3	3.2
Fluvoxamine	65.4	13.6	3.4
Paroxetine	61.9	5.3	3.7
Sertraline	49.8	5.2	4.5
Escitalopram	62.7	15.2	3.6
Citalopram	26.9	0.4	6.1
paroxetine+BZD	57.1	41.0	4.0

eAppendix Figure 18. Comparison-adjusted funnel plot of remission for individual selective serotonin reuptake inhibitors

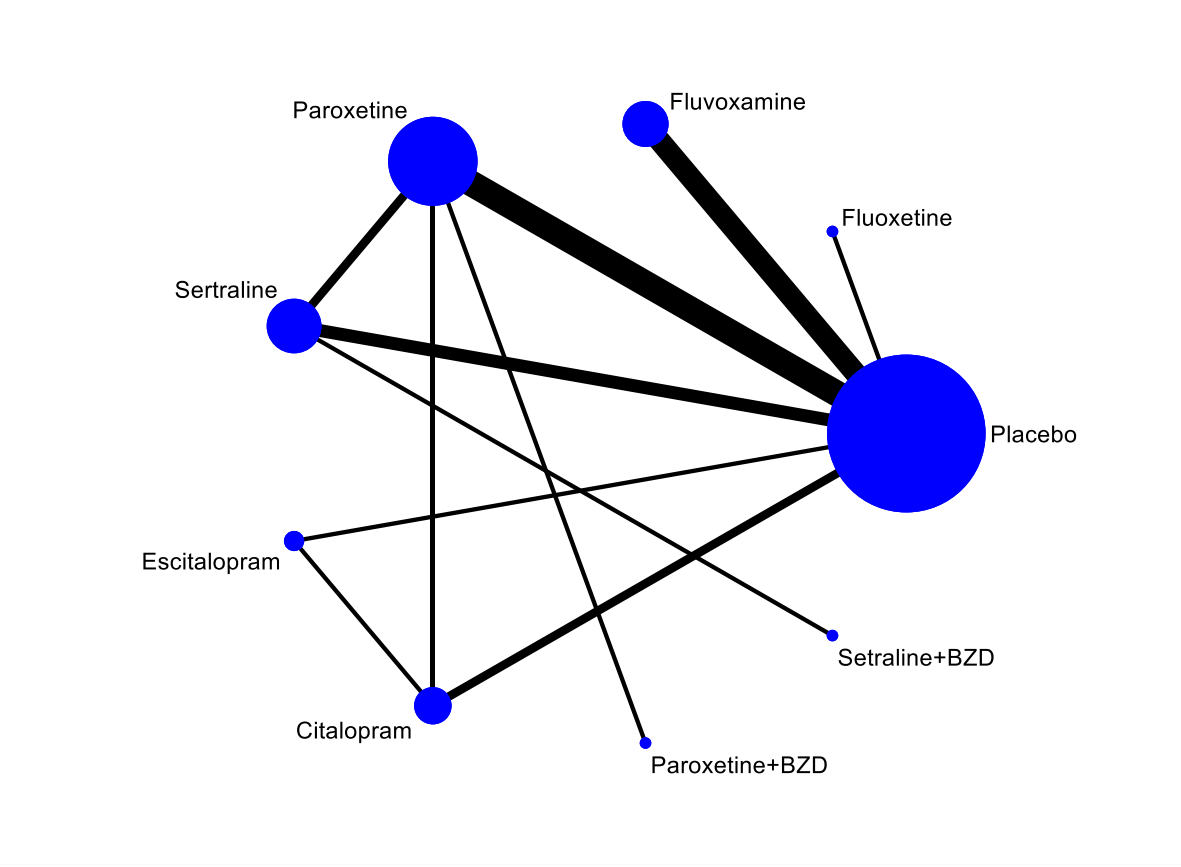


Adverse events

Twenty-two studies with 9 interventions (i.e., fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram, paroxetine plus benzodiazepine (BZD), sertraline plus BZD, and placebo) were considered in NMA of adverse events (eAppendix Figure 19 and eAppendix Table 5). Findings from global test showed inconsistency results (Global Chi-square = 1.3, p-value=0.7292). Only paroxetine had significantly higher risk of adverse events than placebo with RR of 1.14 (95% CI: 1.01,1.29), see eAppendix Table 6. Risk of adverse events in escitalopram group was lower than risk in placebo group but this difference did not reach statistical significance (RR = 0.88; 95% CI: 0.50,1.53).

SUCRA indicated that escitalopram (80.9%) had the highest chance of being the best treatment with lower risk of adverse events, followed by sertraline (58.5%), see eAppendix Figure 20. The comparison-adjusted funnel plot was asymmetry, suggesting possible publication bias for this outcome (eAppendix Figure 21).

eAppendix Figure 19. Network map of adverse events for individual selective serotonin reuptake inhibitors



The size of each node represents the number of participants randomly assigned to the treatment comparison. The width of each line represents the number of studies comparing the two connected treatments. The number provided over each line indicates the number of studies comparing the two connected treatments

eAppendix Table 5. Data used for pooling adverse drug events for individual SSRIs

Author	Year	Most common reported Adverse events	Intervention	Adverse events	No adverse events
SSRIs vs placebo					
Hoehn-Saric	1993	Sedation	Fluvoxamine	5	13
		Dry mouth	Placebo	3	15
Sandmann	1998	Nausea	Fluvoxamine	9	14
		Nausea	Placebo	6	17
Asnis	2001	Nausea	Fluvoxamine	84	9
		Nausea	Placebo	70	25
Oehrberg	1995	Nausea	Paroxetine	46	9
		Nausea	Placebo	33	19
Ballenger	1998	Headache	Paroxetine	19	48
		Headache	Placebo	30	39
Sheehan	2005	Abnormal ejaculation	Paroxetine	120	324
		Nausea	Placebo	76	369
Londborg	1998	Nausea	Sertraline	42	85
		Headache	Placebo	18	26
Pohl	1998	Nausea	Sertraline	26	54
		Nausea	Placebo	15	73
Pollack	1998	Insomnia	Sertraline	83	5
		Headache	Placebo	77	11
Michelson	2001	Not reported	Fluoxetine	25	65
		Not reported	Placebo	19	71
TCAs vs SSRIs					
Nair	1996	Nausea	Fluvoxamine	45	5
		Headache	Placebo	45	5
Bakish	1996	Dry mouth	Fluvoxamine	5	13
		-	Placebo	2	16
Wade	1997	Headache	Citalopram	32	65
		Headache	Placebo	27	69
Lecrubier	1997	Sweating	Paroxetine	90	33
		Headache	Placebo	83	40
SNRIs vs SSRIs					
Pollack	2007	Not reported	Paroxetine	129	32
		Not reported	Placebo	129	33
Pollack	2007	Sedation	Paroxetine	121	40
		Sweating	Placebo	105	51
SSRIs+BZDs vs SSRIs					
Goddard	2001	Sexual dysfunction	Sertraline + BZD	8	14

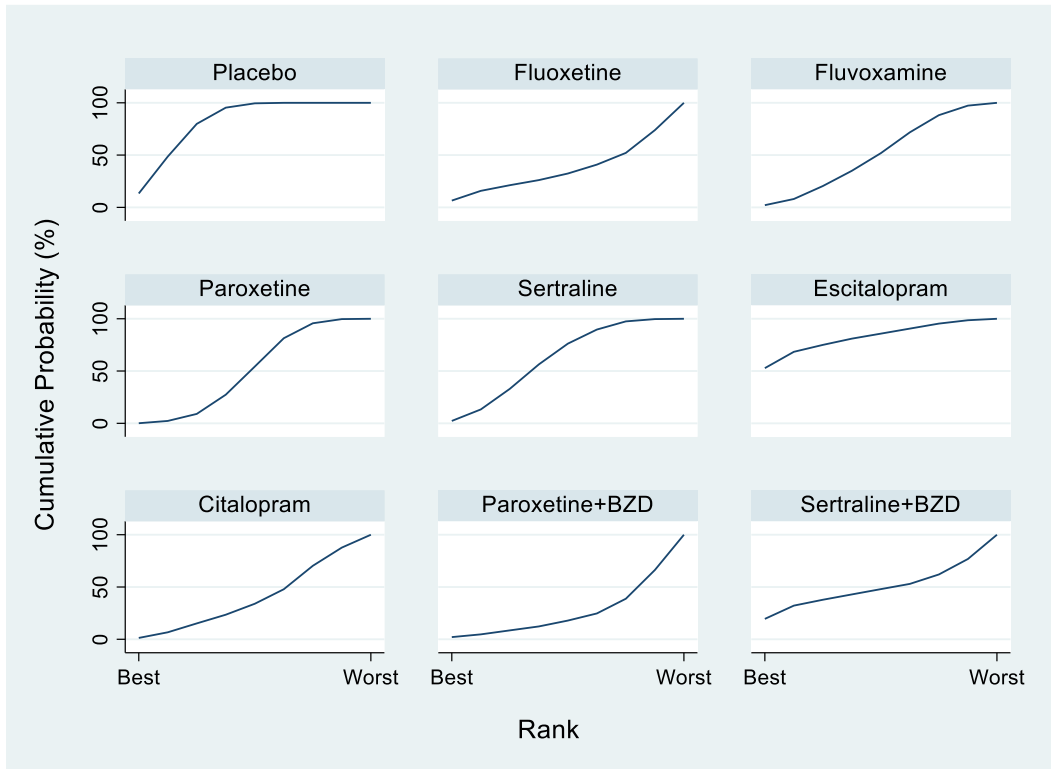
Author	Year	Most common reported Adverse events	Intervention	Adverse events	No adverse events
		Sexual dysfunction	Sertraline	8	16
Pollack	2003	Sedation	Paroxetine + BZD	34	4
		GI	Paroxetine	15	7
Bandelow	2004	Headache	Paroxetine	29	84
		Nausea	Sertraline	24	88
Perna	2001	Sexual dysfunction	Paroxetine	12	13
		Sexual dysfunction	Citalopram	11	16
Stahl	2003	Headache	Escitalopram	20	108
		Headache	Citalopram	29	90
		Headache	Placebo	18	101
Clinicaltrial.gov		Nausea	Paroxetine	134	28
		Dizziness	Sertraline	127	30

eAppendix Table 6. Estimation of the relative treatment effects (95% confidence intervals) on adverse events for individual selective serotonin reuptake inhibitors

Placebo	1.19 (0.51,2.76)	1.42 (0.92,2.19)	1.24 (0.89,1.71)	0.88 (0.50,1.53)	1.09 (0.92,1.29)	1.14 (1.01,1.29)	1.14 (0.94,1.39)	1.32 (0.74,2.34)
	Sertraline+BZD	1.20 (0.47,3.07)	1.04 (0.42,2.57)	0.74 (0.27,2.03)	0.92 (0.40,2.10)	0.96 (0.41,2.23)	0.96 (0.41,2.29)	1.11 (0.40,3.07)
		Paroxetine+BZD	0.87 (0.51,1.49)	0.62 (0.30,1.25)	0.77 (0.49,1.20)	0.80 (0.53,1.22)	0.81 (0.50,1.29)	0.93 (0.45,1.90)
			Citalopram	0.71 (0.42,1.21)	0.88 (0.61,1.27)	0.92 (0.66,1.29)	0.93 (0.63,1.35)	1.07 (0.55,2.06)
				Escitalopram	1.24 (0.69,2.22)	1.30 (0.74,2.29)	1.31 (0.72,2.36)	1.50 (0.67,3.34)
					Sertraline	1.05 (0.88,1.24)	1.05 (0.81,1.36)	1.21 (0.66,2.20)
						Paroxetine	1.00 (0.80,1.26)	1.15 (0.64,2.07)
							Fluvoxamine	1.15 (0.63,2.11)
								Fluoxetine

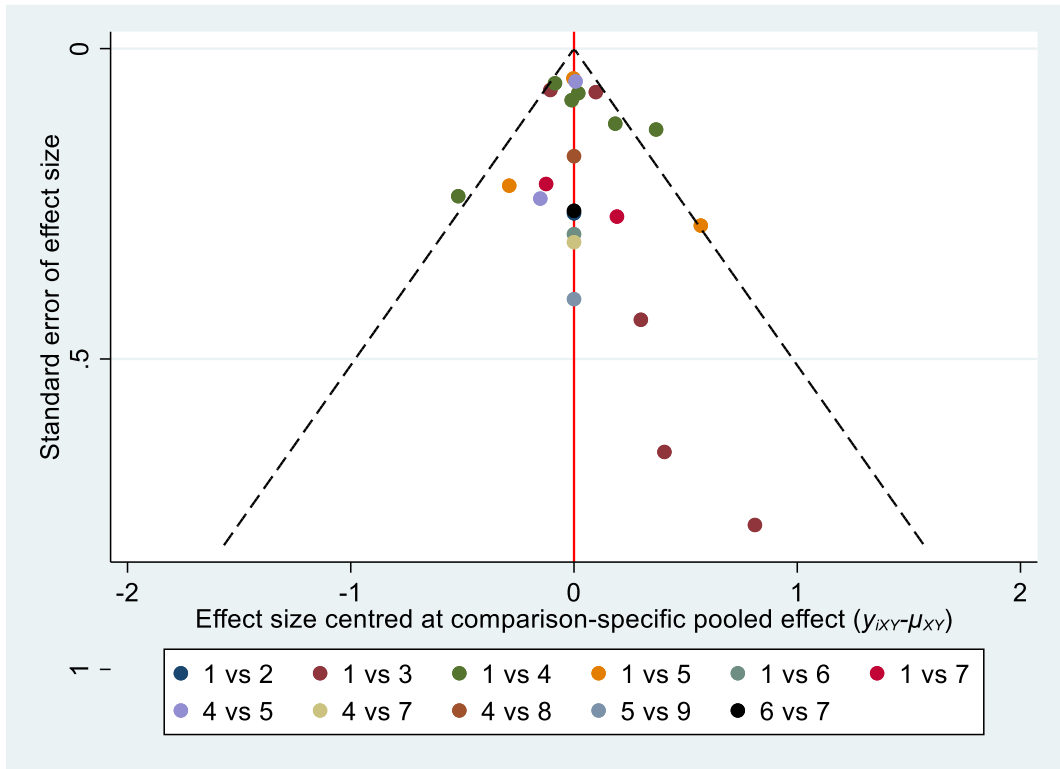
Results are risk ratios (95% confidence intervals) between each pair of treatments from network meta-analysis. Comparisons are read from right to left. Bold font indicates statistical significance. The GRADE certainty of evidence of each comparison is highlighted: Light green and light red refer to moderate and low certainty.

eAppendix Figure 20. Surface under the cumulative ranking curve of adverse events for individual selective serotonin reuptake inhibitors



Treatment	SUCRA	PrBest	MeanRank
Placebo	79.6	13.3	2.6
Fluoxetine	33.6	6.5	6.3
Fluvoxamine	46.8	2.1	5.3
Paroxetine	46.2	0.1	5.3
Sertraline	58.5	2.3	4.3
Escitalopram	80.9	52.8	2.5
Citalopram	35.8	1.3	6.1
paroxetine+BZD	21.9	2.1	7.2
sertraline+BZD	46.5	19.5	5.3

eAppendix Figure 21. Comparison-adjusted funnel plot of adverse events for individual selective serotonin reuptake inhibitors



eAppendix 4. References of included studies

1. Drug treatment of panic disorder. Comparative efficacy of alprazolam, imipramine, and placebo. Cross-National Collaborative Panic Study, Second Phase Investigators. *The British journal of psychiatry: the journal of mental science*. 1992;160:191-202; discussion -5.
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