Supplementary Materials for:

Linde K, Kriston L, Rücker G, Jamil S, Schumann I, Meissner K, Sigterman K, Schneider A. Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. *Ann Fam Med*. 2015;13(1):69-79.

Supplemental material

1. Example electronic literature search

Main search Medline (Ovid) 8.6.2011

# ▲	Searches	Results
1	exp Depressive Disorder/dh, dt, pc, px, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Psychology, Surgery, Therapy]	49739
2	exp Depression/dh, dt, pc, px, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Psychology, Surgery, Therapy]	31599
3	(depress* or antidepress*).tw.	271636
4	1 or 2 or 3	288675
5	exp general practitioners/ or exp physicians, family/ or exp physicians, primary care/	14380
6	exp Primary Health Care/	63530
7	general practice/ or family practice/	58042
8	(primary adj2 care).mp.	79930
9	(general practitioner* or family physician*).mp.	38994
10	(general practice* or family practice* or family medicine).mp.	77213
11	(outpatient* or out-patient*).mp.	106092
12	5 or 6 or 7 or 8 or 9 or 10 or 11	280006
13	(randomised controlled trial or randomized controlled trial).pt.	306533
14	controlled clinical trial.pt.	82376
15	random*.ab.	503544
16	placebo.ab.	124298
17	clinical trials as topic.sh.	154193
18	trial.ti.	91920
19	13 or 14 or 15 or 16 or 17 or 18	828465
20	exp animals/ not humans.sh.	3598584
21	19 not 20	754266
22	4 and 12 and 21	4268

2. References of included primary studies

(only the 65 main publications; Boyer et al. reports two trials)

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3. Characteristics of included studies and assessment of risk of bias

sTable 1

General characteristics of included studies

First author	Year	n	Diagnosis	% Female	Mean Age	Weeks treatm.	Intervention 1	Intervention 2	Intervention 3
Barge-Schaapveld	2002	63	Major depression	73	43	6	Imipramine 100-200 mg	Placebo	
Barge-Schaapveld	1995	21	Major depression		39	6	Amitriptyline 150 mg	Fluvoxamine 100 mg	
Barrett	2001	241	Mixed/unclear	64	44	11	Paroxetine 20-40 mg	Problem-solving**	Placebo
Beaumont	1993	345	Major depression	71	44	6	Dothiepin 75-150 mg	Moclobemide 450 mg	
Beaumont	1984	125	Mixed/unclear	78	42	6	Trazodone 100-200 mg***	Mianserin 60-120 mg	
Bjerkenstedt	2005	170	Major depression	75	50	4	Fluoxetine 20 mg	Hypericum 900 mg	Placebo
Blacker	1988	227	Major depression		44	6	Amitriptyline 100-150 mg*	Trazodone 150 mg***	Mianserin 60 mg
							Dothiepin 100-150 mg*		
Blashki	1971	58	Mixed/unclear	100	37	4	Amitriptyline 75 mg*, ***	Placebo	
							Amitriptyline 150 mg*		
Boyer Teil 1	1996	323	Dysthymia	75	48	12	Amineptine 200 mg	Placebo	Amisulprid**
Boyer Teil 2	1996	219	Dysthymia	55	43	24	Imipramine 100 mg	Placebo	Amisulprid**
Brink	1984	52	Mixed/unclear	54		4	Mianserin 60 mg	Placebo	
Christiansen	1996	144	Mixed/unclear			8	Amitriptyline 75-150 mg	Paroxetine 20-40 mg	
Corne	1989	100	Major depression	70	42	6	Dothiepin 75-100 mg	Fluoxetine 40-60 mg	
Doogan	1994	308	Major depression	70	47	6	Dothiepin 75-150 mg	Sertraline 50-100 mg	Placebo
Fairwheather	1999	84	Major depression	64	44	6	Dothiepin 150 mg	Fluoxetine 20 mg	
Freed	1999	375	Mixed/unclear	75	48	9	Amitriptyline 100 mg	Paroxetine 20 mg	
Gachoud	1994	130	Major depression	67	48	4	Maprotiline 75-100 mg	Moclobemide 300-400 mg	
Gastpar	2005	241	Major depression	74	49	12	Sertraline 50 mg	Hypericum STW3 612 mg	
Gastpar	2006	388	Major depression	68	50	6	Citalopram 20 mg	Hypericum STW3-VI 900 mg	Placebo
GSK-2906	1991	134	Major depression	73	76	6	Dothiepin 75 mg	Paroxetine 20 mg	

GSK-PAR2906	1985	162	Major depression	76	39	6	Amitriptyline 75-150 mg	Paroxetine 30 mg	
GSK-PARMDUK	1986	59	Major depression	73	42	6	Amitriptyline 100-150 mg	Paroxetine 30 mg	
Guelfi	1999	237	Major depression	83	78	12	Tianeptine 25-37.5 mg	Fluoxetine 20 mg	
Harrer	1991	120	Mixed/unclear	61	48	6	Hypericum Psychotonin M	Placebo	
Harrer	1999	161	Major depression	87	69	6	Fluoxetine 20 mg	Hypericum Lo-Hyp 57 800 mg	
Hollyman	1988	178	Mixed/unclear	83		6	Amitriptyline 125-175 mg	Placebo	
Huebner	1993	40	Minor depression	56	51	4	Hypericum LI 160 900 mg	Placebo	
Hutchinson	1992	90	Major depression	77	72	6	Amitriptyline 100 mg	Paroxetine 30 mg	
König	1993	112	Mixed/unclear	75	45	6	Hypericum Z-90017 500-1000 mg	Placebo	
Kragh-Sorensen	1995	142	Major depression	70	48	6	Clompiramine 150 mg	Moclobemide 400 mg	
Kyle	1998	365	Major depression	73	74	8	Amitriptyline 50-100 mg***	Citalopram 20-40 mg	
Laakmann	1998	98	Major depression	80	49	6	Hypericum WS 5572 900 mg*	Placebo	
							Hypericum WS 5573 900 mg*		
Lecrubier	1997	229	Major depression	67	40	13	Imipramine 150 mg	Venlafaxine 150 mg	Placebo
Lepola	2003	468	Major depression	72	43	8	Citalopram 20-40 mg*	Placebo	
							Escitalopram 10-20 mg*		
Lingyesrde	1995	53	Mixed/unclear	66	43	6	Doxepine 150-250 mg	Moclobemide 400-600 mg	
Malt	1999	372	Mixed/unclear	72	48	24	Sertraline 100-200 mg	Mianserin 60-120 mg	Placebo
McPartlin	1998	361	Major depression	68	45	12	Paroxetine 20 mg	Venlafaxine 75 mg	
Montgomery	2004	293	Major depression	72	48	8	Escitalopram 10-20 mg	Venlafaxine 75-150 mg	
Moon	1994	106	Depression+anxiety	52	44	6	Clomipramine 50 mg***	Sertraline 50 mg	
Moon	1996	138	Major depression	71	44	6	Lofepramine 140 mg	Paroxetine 20 mg	
Moon	1990	228	Depression+anxiety	79	42	6	Dothiepin 75 mg	Trazodone 150 mg***	
Moon	1988	40	Major depression	51	52	6	Trazodone 150 mg***	Mianserin 30-60 mg***	
Moon	1991	62	Major depression	68	42	6	Fluvoxamine 100-300 mg	Mianserin 60-180 mg	
Murphy	1976	105	Mixed/unclear			6	Imipramine 100 mg	Mianserin 40 mg***	Placebo
Mynor-Wallis	1995	91	Major depression	77	37	12	Amitriptyline 150 mg	Problem-solving**	Placebo
Peveler	2005	327	Mixed/unclear	67		52	Individualized TCA	Individualized SSRI	

Philipp	1999	263	Mixed/unclear	75	47	8	Imipramine 100 mg	Hypericum 1050 mg	Placebo
Ravindran	1997	1019	Depression+anxiety	73	43	12	Clomipramine 75-150 mg	Paroxetine 30-40 mg	
Richards	1982	83	Mixed/unclear	73		6	Trazodone 100-200 mg***	Mianserin 60-120 mg	Diazepam**
Rosenberg	1994	472	Mixed/unclear	69	48	6	Imipramine 50-150 mg	Citalopram 10-60 mg	
Schmidt	1989	40	Mixed/unclear	50	46	4	Hypericum Psychotonin M	Placebo	
Schrader	2000	240	Major depression	65	46	6	Fluoxetine 20 mg	Hypericum Ze 117 500 mg	
Serrano-Blanco	2006	103	Mixed/unclear	73	43	12	Imipramine mean 58 mg***	Fluoxetine mean 21 mg	
Simon	1996	536	Mixed/unclear	72	41	26	Imipramine flexible*	Fluoxetine flexible	
							Desipramine flexible*		
Thase	2011	1385	Major depression	78	42	26	SSRIs	Venlaflaxine 75-225 mg	
Trick	2004	88	Major depression	70	71	26	Dothiepin 75 mg	Venlafaxine 75 mg	
Tylee	1997	341	Major depression	71	44	12	Fluoxetine 20 mg	Venlafaxine 75 mg	
van Gurp	2002	90	Major depression	60	39	12	Setraline 50-100 mg	Hypericum 900-1800 mg	
Wade	2002	380	Major depression	76	41	8	Escitalopram 10 mg	Placebo	
Wade	2003	197	Major depression	73	40	24	Paroxetine 20-30 mg	Mirtazapine 30-45 mg	
Wheatley	1992	144	Major depression	66	47	6	Amitriptyline 150 mg	Minaprine 100 mg*	
								Minaprine 200 mg*	
Wheatley	1989	117	Mixed/unclear	80	55	6	Mianserin 60 mg	Minaprine 200 mg*	
								Minaprine 300 mg*	
Wheatley	1997	165	Major depression	81	40	6	Amitriptyline 75 mg	Hypericum 900 mg	
Wiles	2012	601	Mixed/unclear	68	39	12	Citalopram 20 mg	Reboxetine 8 mg	
Williams	2000	415	Mixed/unclear	41	71	11	Paroxetine 10-40 mg	Problem-solving**	Placebo
Witte	1995	97	Major depression	66	43	6	Hypericum Psychotonin forte 240 mg	Placebo	

*Groups pooled for meta-analysis; **treatment excluded from our review; ***dosage below recommended standard dosages (assessment of adequacy of dosages according to recommendations in the German National guideline DGPPN, BÄK, KBV, AWMF, AkdÄ, PPtK, et al. S3-Leitlinie/Nationale Versorgungsleitlinie Unipolare Depression - Langfassung. Berlin, Düsseldorf: DGPPN, ÄZQ, AWMF; 2009; http://www.depression.versorgungsleitlinien.de/) – studies were not excluded from analysis

sTable 2

Data used for meta-analyses for the outcomes response (RS) and remission (RE)

		Outcome data used					
First author	Year	RS after treatment	RS ≤ 13 w	RS > 13 w	RE after treatment	RE ≤ 13 w	RE > 13 w
Included in drug network							
Barge-Schaapveld	2002	7	7		15	15	
Barge-Schaapveld	1995						
Barrett	2001				12	12	
Beaumont	1993	1	1		18	18	
Beaumont	1984	8	8		18	18	
Bjerkenstedt	2005	1	1		12	12	
Blacker	1988	7	7		15	15	
Blashki	1971	7	7		15	15	
Boyer Teil 1	1996	5	5		19	19	
Boyer Teil 2	1996	8		8	19		19
Brink	1984	7	7		15	15	
Christiansen	1996	5	5		11	11	
Corne	1989	8	8		18	18	
Doogan	1994	3	3				
Fairwheather	1999	1	1				
Freed	1999	5	5		11	11	
Gachoud	1994	7	7		15	15	
Gastpar	2005	2	2	2	15	15	15
Gastpar	2006	2	2		15	15	
GSK-2906	1991	2	2		11	11	
GSK-PAR2906	1985	1	1		18	18	
GSK-PARMDUK	1986	8	8		15	15	
Guelfi	1999	3	3		16	16	
Harrer	1991	2	2		18	18	
Harrer	1999	2	2		21	21	
Hollyman	1988	6	6		15	15	
Huebner	1993	2	2		15	15	
Hutchinson	1992	1	1		149	149	
König	1993	6	6				
Kragh-Sorensen	1995				12	12	
Kyle	1998	5	5		19	19	
Laakmann	1998	1	1		15	15	
Lecrubier	1997	4	4				
Lepola	2003	3	3		13	13	
Lingyesrde	1995	3	3		19	19	
Malt	1999	6	6	6			
McPartlin	1998	1	1		12	12	
Montgomery	2004	3	3		19	19	

Moon	1994	1					
Moon	1996	3	3		19	19	
Moon	1990	9	9		21	21	
Moon	1988	9	9		21	21	
Moon	1991	5	5		149	149	
Murphy	1976						
Mynor-Wallis	1995	7	7		12	12	
Peveler	2005	9	9	9	21	21	21
Philipp	1999	1	1		15	15	
Ravindran	1997	3	3		16	16	
Richards	1982	1	1				
Rosenberg	1994	1	1				
Schmidt	1989	1	1		12	12	
Schrader	2000	2	2		18	18	
Serrano-Blanco	2006	7	7	7	17	17	17
Simon	1996	8	8	8	12	12	12
Thase	2011	7		7	12	12	12
Trick	2004	7	7	7	15	15	15
Tylee	1997	6	6		19	19	
van Gurp	2002	2	2		15	15	
Wade	2002	3	3		16	16	
Wade	2003	1	1	1	12	12	12
Wheatley	1992				12	12	
Wheatley	1989	8	8		12	12	
Wheatley	1997	2	2		11	11	
Wiles	2012	6	6		6	6	
Williams	2000	8	8		12	12	
Witte	1995	2	2		15	15	

Preference strategy for extraction/imputation of response data

1 HAMD (Hamilton Tating Scale for Depression) Response
2 HAMD Response or Remission
3 MADRS (Montogomery-Asberg Depression Rating Scale) Response
4 MADRS Response or Remission
5 CGI (Clinical Global Impression) at least much improved
6 other response measures based on validated scales/instruments
7 imputation based on complete score data (following preference 1 to 4 and 6)
8 imputation based on imputation (mostly missing SD) score data (following preference 1 to 4 and 6)
9 other response measure

Preference strategy for extraction/imputation of remission data

11 CGI-S = 1 (normal, not ill)/CIDI and other validated diagnostic instrument = no depression)
12 HAMD ≤ 7 (cut-offs ± 1 point accepted)
13 MADRS ≤ 10 (cut-offs ± 1 point accepted)
14 BDI (Beck depression Index) ≤ 8 (cut-offs ± 1 point accepted)
149 CGI-S = 1 or 2 and HAMD cut-off > 9
15-17 if 12 to 14 imputable without problems from score data (as 7) imputation if remission cut-offs clearly higher as stated in 12 to 14
18-20 HAMD, MADRS, BDI with other cut-offs but 15 to 17 not applicable
21 other remission criteria

sTable 3

Assessment of risk of bias: + indicates low risk of bias, ? unclear risk of bias and – high risk of bias

First author	Year	Seq. gener	Conceal-ment	Double blinding	Attrition ≤ 16 w	Attrition > 16 w	Selective report.	Overall*
Included in drug network								
Barge-Schaapveld	2002	?	?	?	?	?	-	-
Barge-Schaapveld	1995	?	?	-	-		+	-
Barrett	2001	+	?	?	?		?	?
Beaumont	1993	?	?	+	+		?	?
Beaumont	1984	?	?	+	-		+	-
Bjerkenstedt	2005	+	+	+	?		+	+
Blacker	1988	?	?	+	-		+	-
Blashki	1971	?	+	+	?		+	?
Boyer Teil 1	1996	?	?	+	+		+	?
Boyer Teil 2	1996	?	?	+	+	+	+	?
Brink	1984	?	?	+	-		+	-
Christiansen	1996	?	?	+	+		+	?
Corne	1989	?	?	+	-		?	-
Doogan	1994	+	?	+	+		+	+
Fairwheather	1999	?	?	+	-		-	-
Freed	1999	+	?	+	-		+	-
Gachoud	1994	?	?	+	+		+	?
Gastpar	2005	+	+	+	+	+	+	+
Gastpar	2006	+	?	+	+		+	+
GSK-2906	1991	?	?	+	?		+	?
GSK-PAR2906	1985	?	?	+	-		+	-
GSK-PARMDUK	1986	?	?	+	?		+	?
Guelfi	1999	?	?	?	+		+	?
Harrer	1991	?	?	+	-		?	-
Harrer	1999	?	?	+	?		+	?
Hollyman	1988	?	?	+	-		+	-
Huebner	1993	+	+	+	+		?	+
Hutchinson	1992	?	?	+	-		?	-
König	1993	?	+	+	-		+	-
Kragh-Sorensen	1995	?	?	+	-		-	-
Kyle	1998	?	?	+	?		+	?
Laakmann	1998	+	+	+	+		+	+
Lecrubier	1997	?	?	+	?		-	-
Lepola	2003	?	?	+	+		-	-
Lingyesrde	1995	?	?	+	?		-	-
Malt	1999	?	?	+	-	-	-	-
McPartlin	1998	?	?	+	?		+	?
Montgomery	2004	?	?	+	+		+	?
Moon	1994	?	?	+	+		+	?

Moon	1996	?	?	+	?		+	?
Moon	1990	?	?	+	-		+	-
Moon	1988	?	?	?	+		+	?
Moon	1991	?	?	+	?		-	-
Murphy	1976	?	?	+	?		+	?
Mynor-Wallis	1995	?	?	?	-		+	-
Peveler	2005	?	+	-	-		+	-
Philipp	1999	+	+	+	+		+	+
Ravindran	1997	+	?	+	?		+	?
Richards	1982	?	?	+	-		+	-
Rosenberg	1994	?	?	+	?		+	?
Schmidt	1989	?	?	+	-		+	-
Schrader	2000	?	?	+	+		+	?
Serrano-Blanco	2006	+	+	-	?	?	+	+
Simon	1996	+	?	-	?	?	-	-
Thase	2011	?	?	-	-	-	+	-
Trick	2004	?	?	+	-	-	+	-
Tylee	1997	+	?	+	+		+	+
van Gurp	2002	+	+	+	?		+	+
Wade	2003	?	?	+	-	-	+	-
Wheatley	1992	?	?	+	?		+	?
Wheatley	1989	?	?	+	-		?	-
Wheatley	1997	+	+	+	-		+	-
Wiles	2012	+	+	-	+		+	+
Witte	1995	?	+	+	-		+	-
Williams	2000	+	+	-	+		-	-

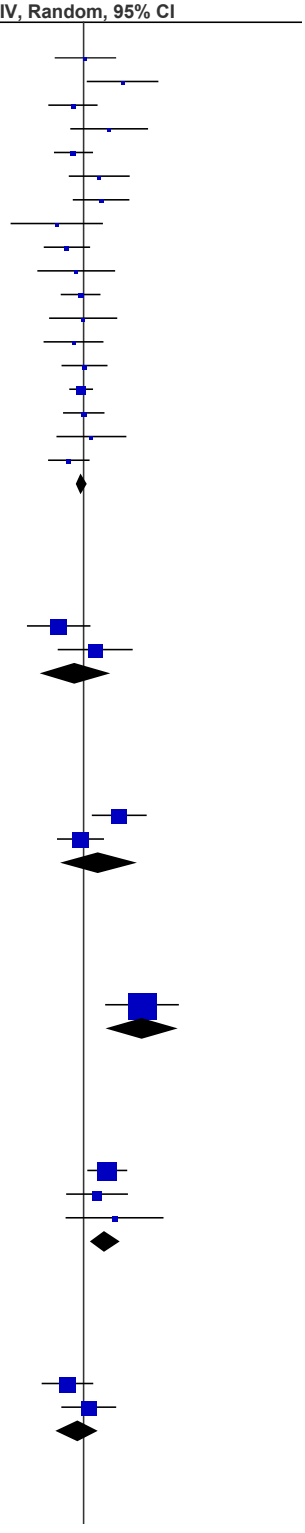
*For assessing the overall risk of bias the following four items were used: sequence generation, concealment, attrition ≤ 16 weeks, selective reporting (blinding was not included to keep assessment identical with the parallel review on psychological treatment [16]). Overall risk of bias was considered high if one or more items were rated 'high'; low if at least three items were considered 'low', and unclear in the remaining trials.

4. Forest plots for direct comparisons

sFigure 1

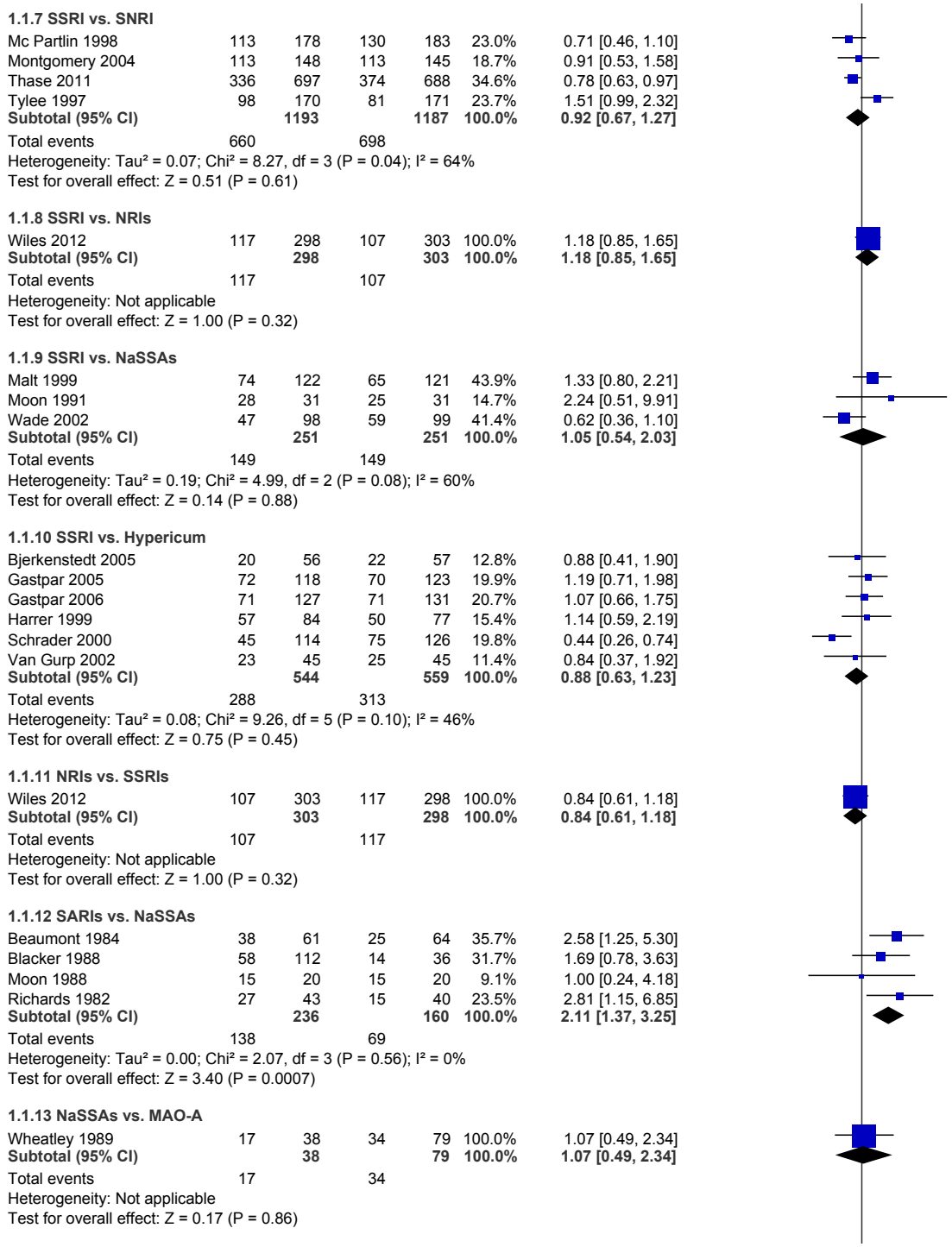
Response (part 1)

Study or Subgroup	Intervention 1 Events	Total	Intervention 2 Events	Total	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 TCAs vs. SSRIs						
Christiansen 1996	48	73	46	71	3.3%	1.04 [0.53, 2.07]
Corne 1989	31	51	19	49	2.4%	2.45 [1.10, 5.47]
Doogan 1994	48	108	50	99	5.2%	0.78 [0.45, 1.35]
Fairweather 1999	21	42	15	42	2.1%	1.80 [0.75, 4.31]
Freed 1999	122	191	127	184	8.5%	0.79 [0.52, 1.22]
GSK-2906 1991	35	67	29	67	3.4%	1.43 [0.73, 2.83]
GSK-PAR290 1985	36	80	29	82	3.9%	1.50 [0.80, 2.81]
GSK-PARMD 1986	11	30	15	29	1.4%	0.54 [0.19, 1.53]
Guelfi 1999	57	115	72	122	5.9%	0.68 [0.41, 1.14]
Hutchinson 1992	18	32	35	58	2.0%	0.84 [0.35, 2.03]
Kyle 1998	124	186	122	179	8.1%	0.93 [0.60, 1.45]
Moon 1994	29	55	27	51	2.7%	0.99 [0.46, 2.13]
Moon 1996	33	68	38	70	3.5%	0.79 [0.41, 1.55]
Peveler 2005	63	218	31	109	6.0%	1.02 [0.61, 1.70]
Ravindran 1997	317	506	328	513	23.9%	0.95 [0.73, 1.22]
Rosenberg 1994	49	92	202	380	7.5%	1.00 [0.64, 1.58]
Serrano-Blanco 2006	22	50	21	53	2.5%	1.20 [0.55, 2.62]
Simon 1996	59	363	37	173	7.5%	0.71 [0.45, 1.13]
Subtotal (95% CI)		**2327**		**2331**	**100.0%**	**0.95 [0.84, 1.08]**
Total events	1123		1243			
Heterogeneity: Tau² = 0.00; Chi² = 17.04, df = 17 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.1.2 TCAs vs. SNRIs						
Lecrubier 1997	49	75	60	78	53.8%	0.57 [0.28, 1.15]
Trick 2004	21	43	19	45	46.2%	1.31 [0.56, 3.03]
Subtotal (95% CI)		**118**		**123**	**100.0%**	**0.83 [0.37, 1.89]**
Total events	70		79			
Heterogeneity: Tau² = 0.19; Chi² = 2.22, df = 1 (P = 0.14); I² = 55%						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.1.3 TCAs vs. SARIs						
Blacker 1988	56	79	58	112	48.3%	2.27 [1.23, 4.18]
Moon 1990	52	114	54	114	51.7%	0.93 [0.55, 1.57]
Subtotal (95% CI)		**193**		**226**	**100.0%**	**1.43 [0.60, 3.42]**
Total events	108		112			
Heterogeneity: Tau² = 0.31; Chi² = 4.71, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.1.4 TCAs vs. NaSSAs						
Blacker 1988	56	79	14	36	100.0%	3.83 [1.67, 8.75]
Subtotal (95% CI)		**79**		**36**	**100.0%**	**3.83 [1.67, 8.75]**
Total events	56		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.18 (P = 0.001)						
1.1.5 TCAs vs. MAO-A						
Beaumont 1993	120	175	95	170	63.9%	1.72 [1.11, 2.67]
Gachoud 1994	35	64	31	66	26.0%	1.36 [0.68, 2.72]
Lingjarde 1995	14	23	13	30	10.1%	2.03 [0.67, 6.15]
Subtotal (95% CI)		**262**		**266**	**100.0%**	**1.65 [1.16, 2.34]**
Total events	169		139			
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 2.79 (P = 0.005)						
1.1.6 TCAs vs. Hypericum						
Philipp 1999	70	110	76	106	52.4%	0.69 [0.39, 1.23]
Wheatley 1997	40	78	42	87	47.6%	1.13 [0.61, 2.08]
Subtotal (95% CI)		**188**		**193**	**100.0%**	**0.87 [0.54, 1.41]**
Total events	110		118			
Heterogeneity: Tau² = 0.03; Chi² = 1.31, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.56 (P = 0.58)						



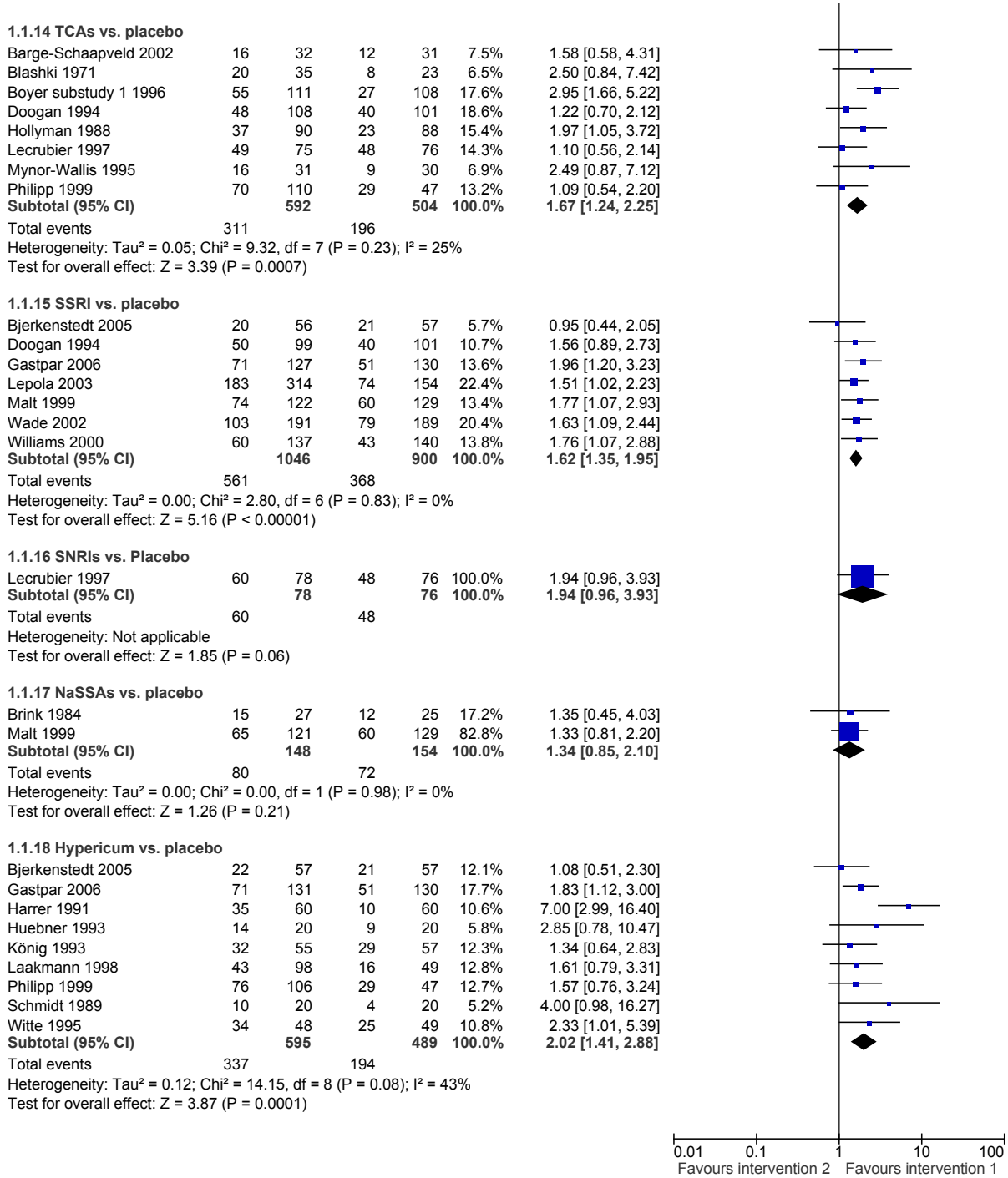
sFigure 1

Response (part 2)



sFigure 1

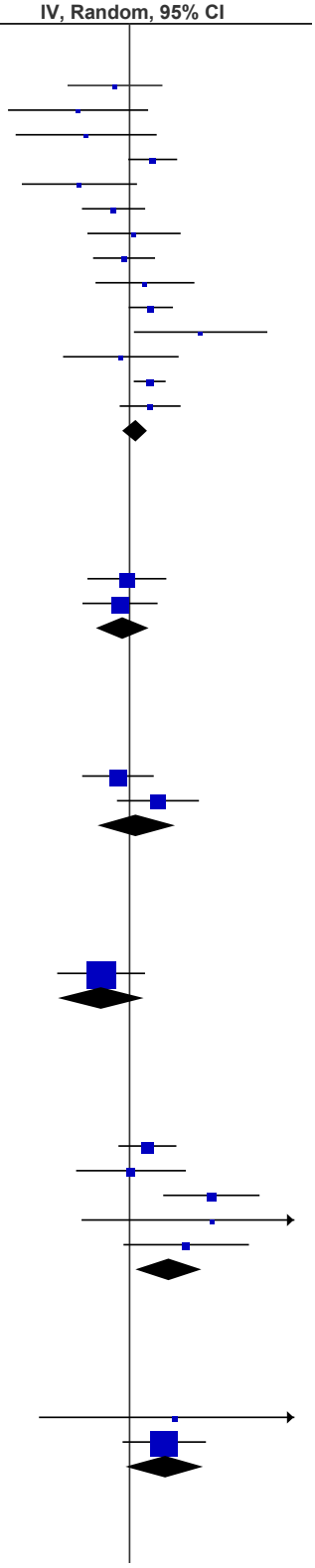
Response (part 3)



sFigure 2

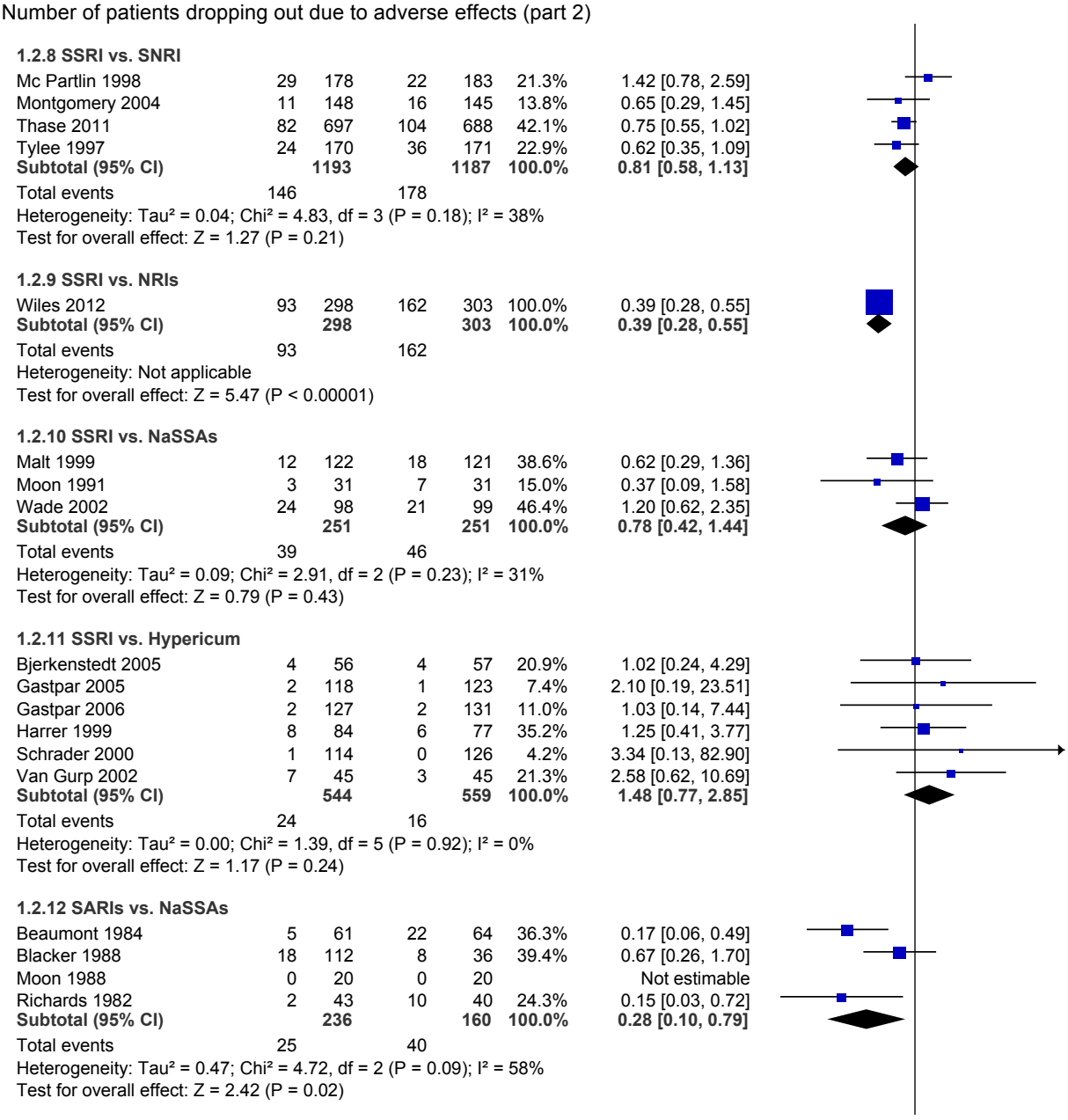
Number of patients dropping out due to adverse effects (part 1)

Study or Subgroup	TCA Events	TCA Total	Comparator Events	Comparator Total	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 TCAs vs. SSRIs						
Barge-Schaapveld 1995	0	10	0	11		Not estimable
Christiansen 1996	6	73	8	71	5.3%	0.71 [0.23, 2.15]
Corne 1989	2	51	6	49	2.8%	0.29 [0.06, 1.53]
Doogan 1994	2	108	5	99	2.8%	0.35 [0.07, 1.87]
Freed 1999	38	191	23	184	11.7%	1.74 [0.99, 3.05]
GSK-2906 1991	3	67	9	67	3.9%	0.30 [0.08, 1.17]
GSK-PAR290 1985	16	80	22	82	9.1%	0.68 [0.33, 1.42]
GSK-PARMD 1986	10	30	9	29	5.5%	1.11 [0.37, 3.32]
Guelfi 1999	16	115	19	122	9.3%	0.88 [0.43, 1.80]
Hutchinson 1992	6	32	8	58	5.0%	1.44 [0.45, 4.60]
Kyle 1998	48	186	31	179	12.7%	1.66 [1.00, 2.76]
Moon 1994	10	55	2	51	3.1%	5.44 [1.13, 26.20]
Moon 1996	4	68	5	70	3.9%	0.81 [0.21, 3.16]
Ravindran 1997	85	506	57	513	15.4%	1.62 [1.13, 2.32]
Rosenberg 1994	12	92	32	380	9.5%	1.63 [0.80, 3.31]
Subtotal (95% CI)		**1664**		**1965**	**100.0%**	**1.15 [0.85, 1.55]**
Total events	258		236			
Heterogeneity: Tau² = 0.12; Chi² = 22.69, df = 13 (P = 0.05); I² = 43%						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.2.2 TCAs vs. SNRIs						
Lecrubier 1997	10	75	11	78	47.5%	0.94 [0.37, 2.36]
Trick 2004	14	43	17	45	52.5%	0.80 [0.33, 1.91]
Subtotal (95% CI)		**118**		**123**	**100.0%**	**0.86 [0.46, 1.62]**
Total events	24		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.2.3 TCAs vs. SARIs						
Blacker 1988	10	79	18	112	53.2%	0.76 [0.33, 1.74]
Moon 1990	13	114	7	114	46.8%	1.97 [0.75, 5.13]
Subtotal (95% CI)		**193**		**226**	**100.0%**	**1.18 [0.46, 3.01]**
Total events	23		25			
Heterogeneity: Tau² = 0.25; Chi² = 2.17, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 0.35 (P = 0.72)						
1.2.4 TCAs vs. NaSSAs						
Blacker 1988	10	79	8	36	100.0%	0.51 [0.18, 1.42]
Subtotal (95% CI)		**79**		**36**	**100.0%**	**0.51 [0.18, 1.42]**
Total events	10		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
1.2.5 TCAs vs. MAO-A						
Beaumont 1993	24	175	16	170	33.9%	1.53 [0.78, 2.99]
Gachoud 1994	5	64	5	66	20.2%	1.03 [0.28, 3.76]
Kragh-Sorens 1995	21	71	4	71	23.2%	7.04 [2.27, 21.78]
Lingjarde 1995	2	23	0	30	5.6%	7.09 [0.32, 155.28]
Wheatley 1992	5	46	3	98	17.2%	3.86 [0.88, 16.92]
Subtotal (95% CI)		**379**		**435**	**100.0%**	**2.57 [1.18, 5.60]**
Total events	57		28			
Heterogeneity: Tau² = 0.35; Chi² = 7.61, df = 4 (P = 0.11); I² = 47%						
Test for overall effect: Z = 2.38 (P = 0.02)						
1.2.7 TCAs vs. Hypericum						
Philipp 1999	1	110	0	106	8.4%	2.92 [0.12, 72.42]
Wheatley 1997	13	78	7	87	91.6%	2.29 [0.86, 6.06]
Subtotal (95% CI)		**188**		**193**	**100.0%**	**2.33 [0.92, 5.93]**
Total events	14		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.78 (P = 0.08)						



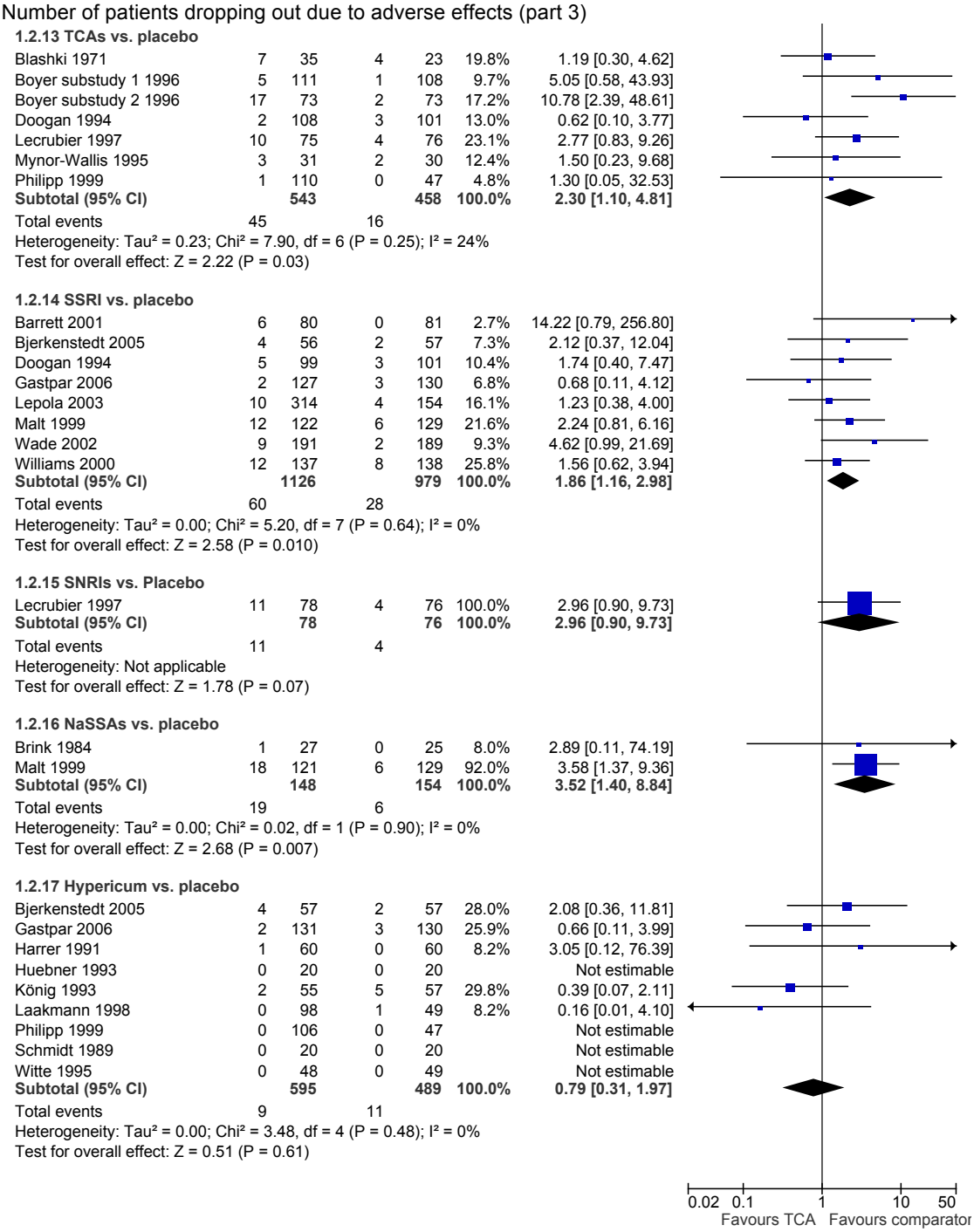
sFigure 2

Number of patients dropping out due to adverse effects (part 2)

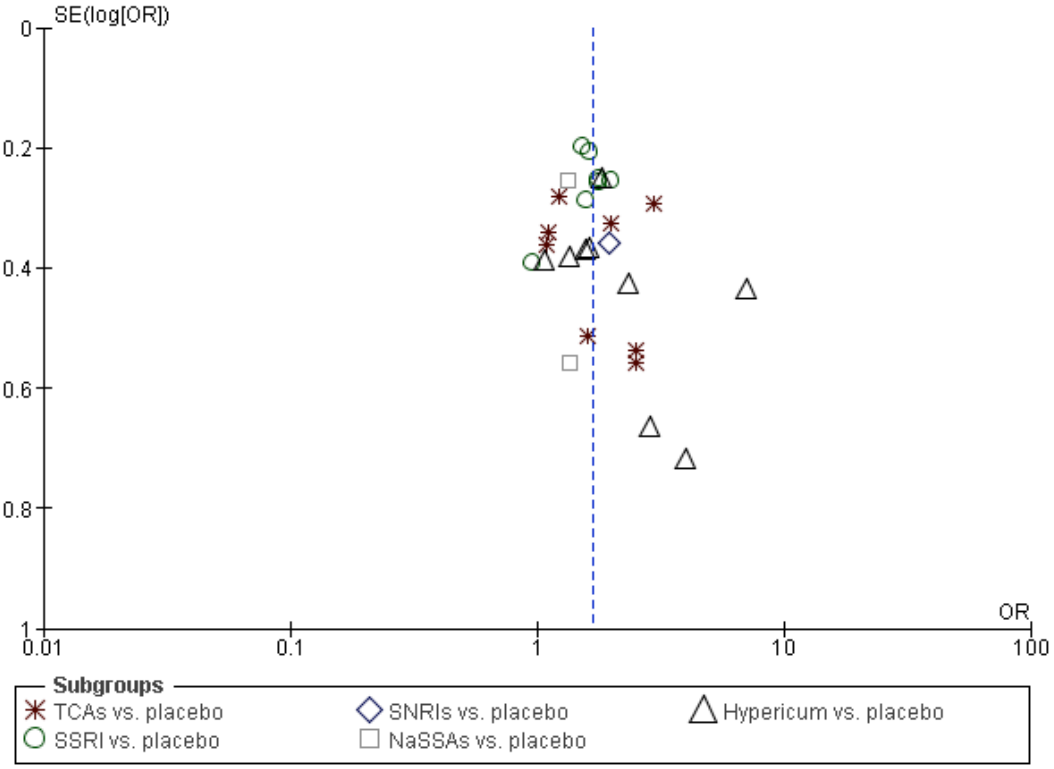


sFigure 2

Number of patients dropping out due to adverse effects (part 3)

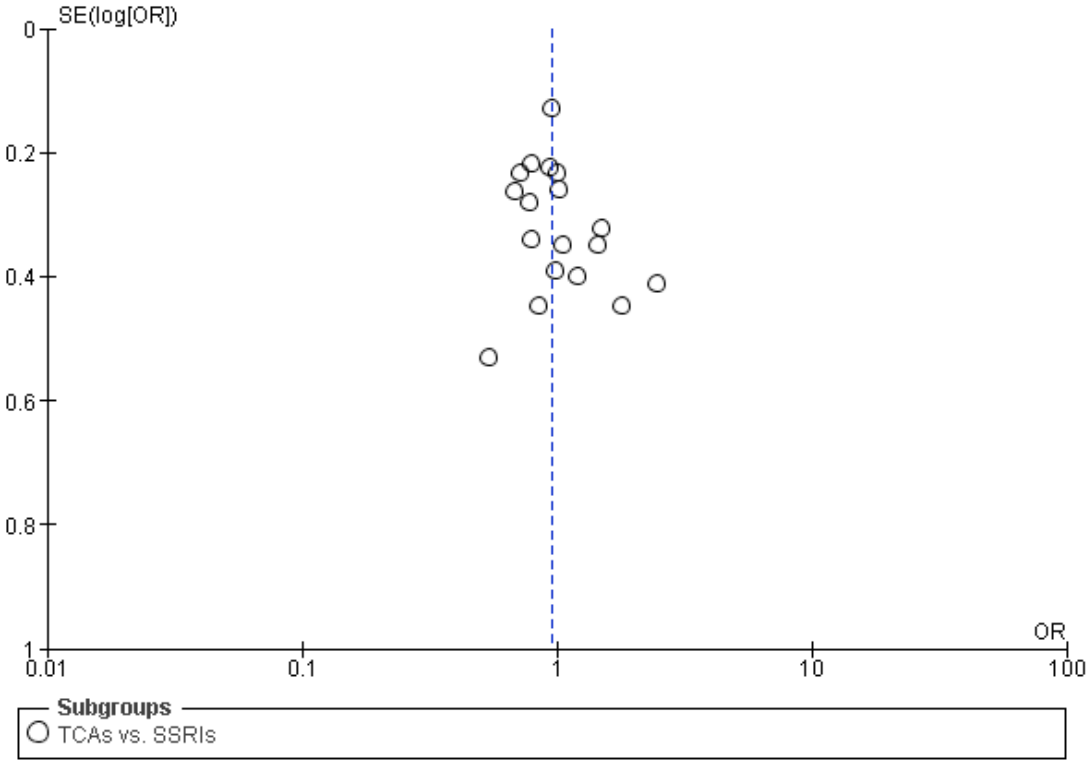


5. Funnel plots



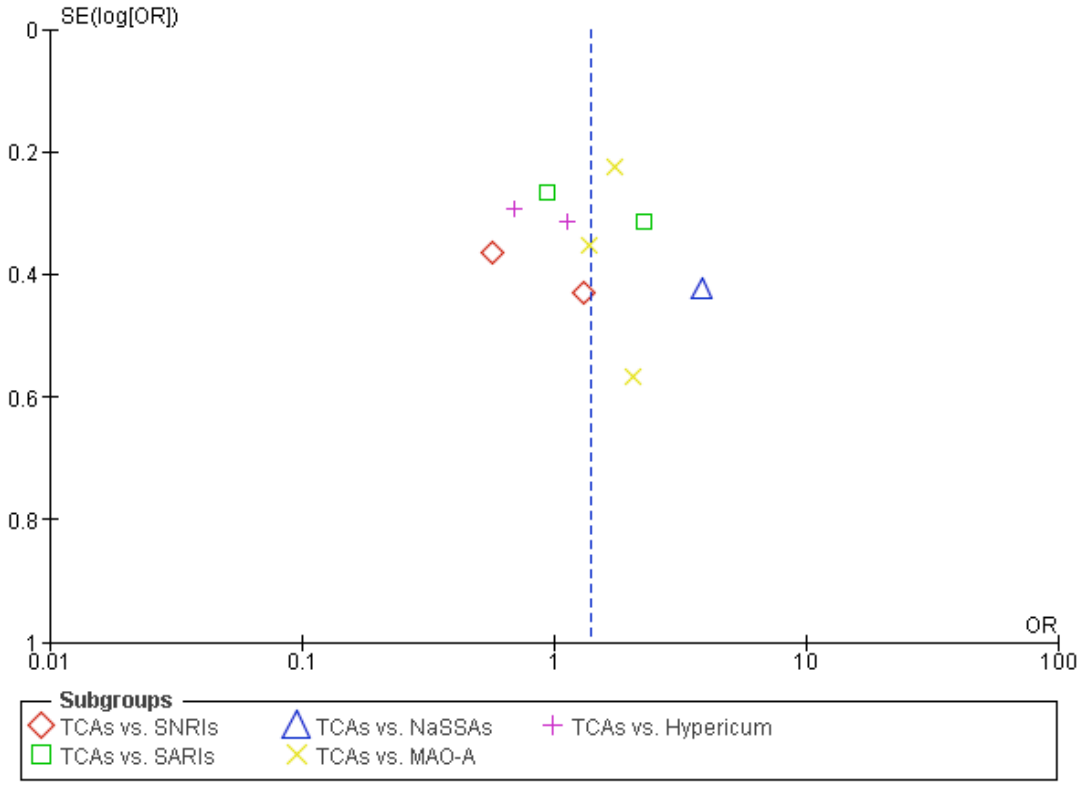
sFigure 3

Funnel plot of trials comparing antidepressants with placebo (outcome response)



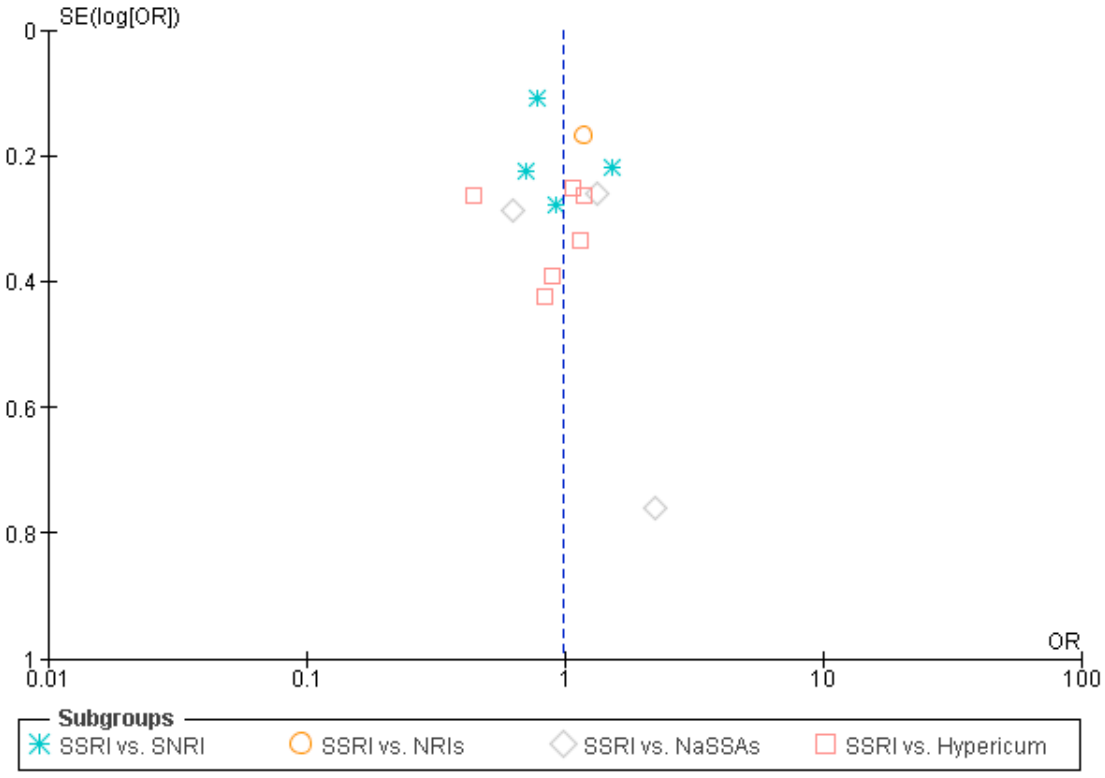
sFigure 4

Funnel plot of trials comparing TCA and SSRI (outcome response)



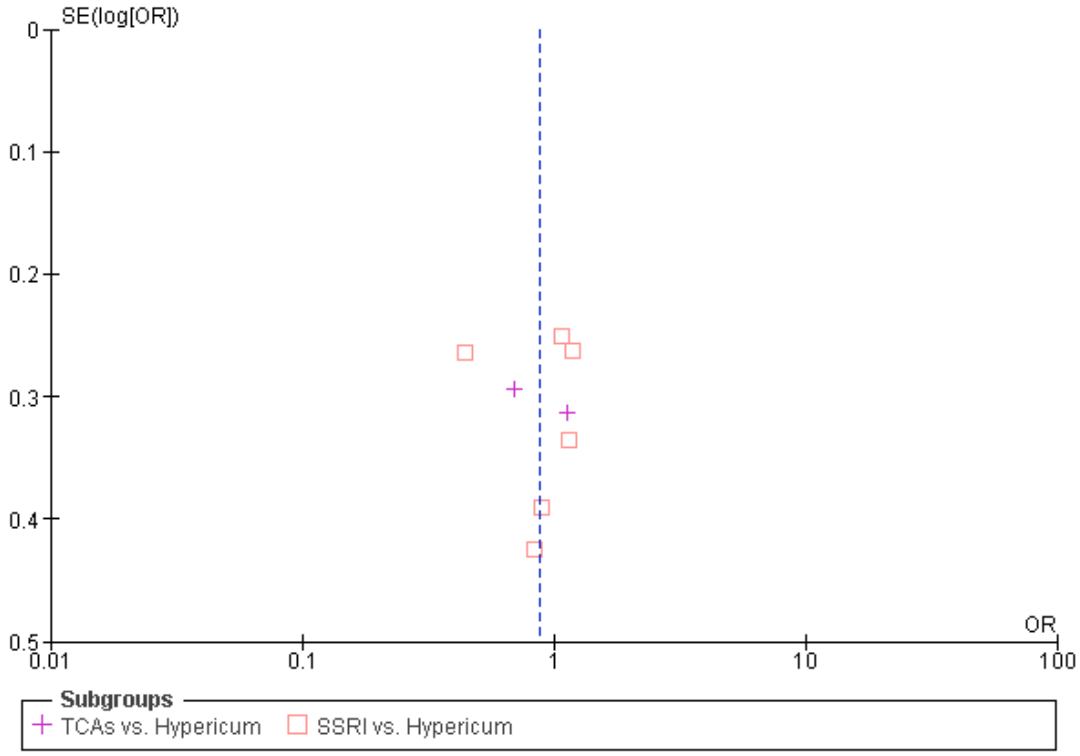
sFigure 5

Funnel plot of trials comparing TCA and other antidepressants (outcome response)



sFigure 6

Funnel plot of trials comparing SSRI and other antideprerssants (outcome response)



sFigure 7

Funnel plot of trials comparing TCA and SSRI with Hypericum extracts (outcome response)

6. Summary tables for direct and network comparisons for secondary outcomes

sTable 4
Secondary analysis efficacy remission ≤ 13 weeks. Figures in black (dark) from direct comparisons, figures in red (bright) from network meta-analysis.

	TCA	SSRI	SNRI	NRI	SARI	NaSSa	MAO-A	Hypericum	Placebo
TCA		0.95 0.81, 1.12 n=13;18%;0.27 1.05 1.23, 0.91	1.19 0.47, 3.01 n=1 0.93 0.72, 1.26	- 1.04 0.59, 1.82	1.36 0.73, 2.51 n=2; 54%; 0.14 1.00 0.65, 1.51	2.97 1.16, 7.60 n=1 1.24 0.81, 1.84	1.11 0.68, 1.80 n=5; 53%; 0.07 1.22 0.89, 1.73	1.17 0.77, 1.77 n=2; 0%; 0.38 0.93 0.74, 1.22	2.19 1.60, 3.01 n=6; 0%, 0.95 1.95 1.52, 2.47
SSRI	1.05 0.89, 1.23 n=13;18%;0.27 0.95 0.81, 1.10		0.84 0.71, 1.00 n=4; 0%; 0.53 0.88 0.70, 1.14	1.00 0.67, 1.49 n=1 0.99 0.58, 1.70	- 0.95 0.59, 1.45	0.78 0.44, 1.39 n=2; 0%; 0.4 1.17 0.78, 1.75	- 1.16 0.81, 1.63	0.95 0.73, 1.24 n=6; 0%; 0.85 0.89 0.70, 1.12	1.54 1.09, 2.18 n=5; 41%; 0.15 1.85 1.47, 2.32
SNRI	0.84 0.33, 2.12 n=1 1.08 0.79, 1.39	1.19 1.00, 1.42 n=4; 0%; 0.53 1.13 0.88, 1.43		- 1.12 0.61, 1.98	- 1.07 0.64, 1.79	- 1.33 0.83, 2.09	- 1.31 0.87, 1.93	- 1.01 0.71, 1.39	- 2.10 1.53, 2.88
NRI	- 0.96 0.55, 1.70	1.00 0.67, 1.49 n=1 1.01 0.59, 1.72	- 0.89 0.50, 1.65		- 0.96 0.47, 1.82	- 1.19 0.61, 2.30	- 0.86 0.43, 1.66	- 0.90 0.50, 1.55	- 1.87 1.05, 3.39
SARI	0.74 0.40, 1.37 n=2; 54%; 0.14 1.00 0.66, 1.55	- 1.06 0.69, 1.69	- 0.93 0.56, 1.54	- 1.05 0.55, 2.14		1.82 1.07, 3.12 n=3; 0%; 0.92 1.24 0.77, 2.02	- 1.22 0.74, 2.06	- 0.94 0.58, 1.53	- 1.95 1.24, 3.20
NaSSa	0.34 0.13, 0.86 n=1 0.81 0.54, 1.23	1.28 0.72, 2.29 n=2; 0%; 0.44 0.85 0.57, 1.29	- 0.75 0.48, 1.20	- 0.84 0.43, 1.63	0.65 0.36, 1.16 n=3; 11%; 0.33 0.81 0.49, 1.29		1.99 0.77, 5.15 n=1 0.99 0.61, 1.63	- 0.76 0.49, 1.19	1.51 0.47, 4.88 n=1 1.57 1.02, 2.48
MAO-A	0.90 0.55, 1.46 n=5, 53%; 0.07 0.82 0.58, 1.13	- 0.86 0.61, 1,23	- 0.76 0.52, 1.15	- 0.86 0.43, 1.66	- 0.82 0.49, 1.36	0.50 0.19, 1.29 n=1 1.02 0.61, 1.63		- 1.17 0.60, 2.31	- 1.87 1.05, 3.39
Hypericum	0.85 0.56, 1.29 n=2; 0%; 0.38 1.07 0.82, 1.35	1.05 0.80, 1.37 n=6; 0%; 0.85 1.13 0.89, 1.43	- 0.99 0.72, 1.40	- 1.12 0.64, 1.99	- 1.07 0.65, 1.73	- 1.32 0.84, 2.03	- 1.30 0.89, 1.95		2.37 1.74, 3.24 n=8; 0%; 0.47 1.08 1.64, 2.70

1. line: pooled odds ratio (OR) from direct comparisons; 2. line: 95%-confidence interval for pooled OR from direct comparisons; 3. line: number of trials; I^2 and p-value for Chi^2-est for heterogeneity in direct comparisons; 4. line: OR from network meta-analysis; 5. line: 95% credible intervals for pooled OR from network meta-analysis

sTable 5
Secondary analysis acceptability total number of patients dropping out. Figures in black (dark) from direct comparisons, figures in red (bright) from network meta-analysis

	TCA	SSRI	SNRI	NRI	SARI	NaSSa	MAO-A	Hypericum	Placebo
TCA		1.08 0.86, 1.36 n=15;43%;0.04 1.00 0.81, 1.21	0.85 0.50, 1.46 n=2;0%; 0.32 1.00 0.69, 1.40	- 0.57 0.27, 1.17	1.01 0.41, 2.52 n=2; 65%; 0.09 1.56 0.93, 2.71	1.01 0.37, 2.78 n=2;42%; 0.19 0.92 0.59, 1. 50	1.23 0.72; 2.11 n=5; 52%; 0.08 1.10 0.72, 1.71	1.12 0.65;1.92 n=2; 2%; 0.31 1.36 0.94, 1.96	0.91 0.65, 1.28 n=10;38%;0.10 0.98 0.75, 1.26
SSRI	0.92 0.73, 1.16 n=15;43%;0.04 1.00 0.83, 1.23		1.10 0.92, 1.30 n=4; 0%; 0.95 1.01 0.73, 1.35	0.58 0.38, 0.87 n=1 0.57 0.27, 1.19	- 1.56 0.91, 2.72	1.11 0.63, 1.95 n=1 0.93 0.59, 1.55	- 1.10 0.70, 1.84	1.22 0.82, 1.81 n=6; 0%; 0.89 1.36 0.95, 1.93	1.16 0.83; 1.62 n=7; 24%; 0.24 0.98 0.75, 1.28
SNRI	1.18 0.68, 2.02 n=2; 0%; 0.32 1.00 0.71, 1.44	0.95 0.80, 1.13 n=4; 0%; 0.87 0.99 0.74, 1.37		- 0.57 0.25, 1.29	- 1.55 0.84, 2.97	- 0.92 0.53, 1.66	- 1.35 0.85, 2.19	- 1.10 0.62, 2.01	1.25 0.62, 2.56 n=1 0.97 0.66, 1.43
NRI	- 1.77 0.86, 3.74	1.73 1.14, 2.63 n=1 1.76 0.84, 3.70	- 1.77 0.77, 4.05		- 2.75 1.11, 7.06	- 1.63 0.69, 4.04	- 1.94 0.80, 4.52	- 2.39 1.12, 5.81	- 1.72 0.80, 3.71
SARI	0.99 0.40, 2.47 n=2; 65%; 0.09 0.64 0.37, 1.08	- 0.64 0.37, 1.10	- 0.64 0.34, 1.19	- 0.36 0.14, 0.90		0.48 0.23, 1.00 n=4; 45%; 0.14 0.59 0.35, 0.99	- 0.71 0.36, 1.37	- 0.87 0.46, 1.66	- 0.63 0.35, 1.13
NaSSa	0.99 0.36, 2.73 n=2; 42%; 0.19 1.09 0.59, 1.50	0.90 0.51, 1.58 n=1 1.08 0.65, 1.70	- 1.09 0.60, 1.88	- 0.61 0.25, 1.44	2.08 1.00, 4.29 n=4; 45%; 0.14 1.69 1.01, 2.82		0.55 0.17, 1.79 n=1 1.19 0.66, 2.26	- 1.47 0.80, 2.59	1.12 0.46, 2.71 n=2; 0%; 0.41 1.06 0.63, 1.74
MAO-A	0.81 0.47, 1.39 n=5; 52%; 0.08 0.91 0.58, 1.40	- 0.91 0.54, 1.42	- 0.91 0.50, 1.61	- 0.52 0.22, 1.25	- 1.42 0.73, 2.81	1.83 0.56, 5.99 n=1 0.84 0.44, 1.51		- 1.24 0.70, 2.13	- 1.12 0.70, 1.86
Hypericum	0.90 0.52, 1.54 n=2; 2%; 0.31 0.74 0.51, 1.06	0.82 0.55, 1.22 n=6; 0%; 0.89 0.73 0.52, 1.05	- 0.74 0.46, 1.17	- 0.42 0.17, 0.89	- 1.15 0.60, 2.18	- 0.68 0.39, 1.26	- 0.81 0.47, 1.43		0.65 0.43, 0.98 n=9; 3%; 0.41 0.72 0.51, 1.05

Legend see sTable 5

sTable 6
Secondary analysis acceptability number of patients with adverse effects. Figures in black (dark) from direct comparisons, figures in red (bright) from network meta-analysis

	TCA	SSRI	SNRI	NRI	SARI	NaSSa	MAO-A	Hypericum	Placebo
TCA		1.31 1.02, 1.69 n=13;50%;0.02 1.47 1.14, 1.87	- 1.24 0.74, 2.00	-	- 3.46 1.17, 11.48	- 2.34 1.16, 5.23	1.67 1.15, 2.42 n=2; 0%; 0.72 1.68 0.88, 2.99	3.10 2.01, 4.78 n=2; 0%; 0.97 2.27 1.63, 3.28	1.89 1.20, 2.96 n=4; 47%; 0.13 2.05 1.48, 2.80
SSRI	0.76 0.59, 0.98 n=13;50%;0.02 0.68 0.54, 0.88		0.87 0.63, 1.19 n=3; 46%; 0.16 0.84 0.55, 1.27	-	- 2.36 0.74, 7.66	1.57 0.86, 2.87 n=2; 0%; 0.80 1.59 0.78, 3.36	- 1.15 0.59, 2.01	1.34 0.88, 2.03 n=6; 57%; 0.04 1.55 1.14, 2.17	1.36 1.09, 1.69 n=5; 0%; 0.43 1.40 1.06, 1.88
SNRI	- 0.81 0.50, 1.35	1.15 0.84, 1.59 n=3; 46%; 0.16 1.19 0.76, 1.83		-	- 2.80 0.78, 10.17	- 1.89 0.85, 4.57	- 1.36 0.63, 3.04	- 1.84 1.45, 3.23	- 1.55 0.98, 2.90
NRI	-	-	-		-	-	-	-	-
SARI	- 0.29 0.09, 0.90	- 0.42 0.13, 1.35	- 0.36 0.10, 1.28	-		0.79 0.16, 3.88 n=2; 76%; 0.04 0.67 0.29, 1.64	- 0.49 0.12, 1.78	- 0.66 0.19, 2.24	- 0.59 0.17, 1.84
NaSSa	- 0.43 0.19, 0.86	0.64 0.35, 1.16 n=2; 0%; 0.80 0.63 0.30, 1.29	- 0.53 0.22, 1.18	-	2.68 1.09, 6.62 n=1 1.48 0.61, 3.40		- 0.72 0.26, 1.92	- 0.97 0.43, 2.10	- 0.88 0.37, 1.95
MAO-A	0.60 0.41, 0.87 n=2; 0%; 0.72 0.59 0.33, 1.31	- 0.87 0.45, 1.69	- 0.73 0.33, 1.59	-	- 2.06 0.56, 8,25	 1.39 0.52, 3.85		- 1.35 0.69, 2.83	- 1.22 0.63, 2.56
Hypericum	0.32 0.21, 0.50 n=2; 0%; 0.97 0.44 0.31, 0.61	0.75 0.49, 1.14 n=6; 57%; 0.04 0.65 0.46, 0.88	- 0.54 0.31, 0.87	-	- 1.52 0.45, 5.34	- 1.03 0.48, 2.30	- 0.74 0.35, 1.44		0.84 0.61, 1.14 n=7; 0%; 0.60 0.90 0.64, 1.26

Legend see sTable 5