

# **Visualizing the Evolution of Evidence: Cumulative Network Meta-Analyses of New Generation Antidepressants in the Last 40 Years**

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## 1 Assessment of the confidence in the evidence through CINeMA

The confidence in the evidence provided by NMA at each time point was assessed using the CINeMA (Confidence in Network Meta-Analysis) framework<sup>1,2</sup> through the dedicated software<sup>3</sup>. The confidence in each NMA  $OR_{AB}$  between two given drugs A and B was evaluated for six domains. The software required some input in each domain in order to recommend whether there were “major concerns”, “some concerns” or “no concerns” for the particular domain.

- (1) **Within-trial bias:** we estimated it as the weighted average of the overall risk of bias of all the trials contributing information to the estimation of  $OR_{AB}$ .
- (2) **Reporting bias:** also known as “publication bias”. We considered comparisons that involved amitriptyline, clomipramine, fluvoxamine, milnacipran and trazadone to have “suspected” publication bias. This is because, for these drugs, neither FDA nor company reports were available. Other drugs were rated as “undetected bias”.
- (3) **Indirectness:** since the included studies matched the clinical question of the review, we had “no concern” about any of the evaluated  $OR_{AB}$ .
- (4) **Imprecision:** which was rated based on whether the 95% CI of OR was allowing recommendations to be made. We set the margin of equivalent effects (where none of the drugs is favored) to be between OR 0.8 and 1.25<sup>4</sup>. These values were motivated by the fact that assuming 50% response rate for drug B, then an  $OR_{AB}$  of 1.25 indicated a response rate more than 56% for drug A, which we considered as clinically meaningful. Then, the degree of overlap between the 95% CI of  $OR_{AB}$  and the margin of equivalent effects suggests the judgement. For details see the manuscript of Nikolakopoulou et al<sup>5</sup>.
- (5) **Heterogeneity:** this was evaluated by monitoring the agreement between confidence intervals (CIs) and prediction intervals (PIs). CINeMA judges whether the two intervals and their overlap with the margin of equivalent effects provide similar conclusions.
- (6) **Incoherence:** this was evaluated by monitoring the level of disagreement between confidence intervals (CIs) of the direct and indirect  $OR_{AB}$  and their overlap with the margin of equivalent effects<sup>5</sup>.

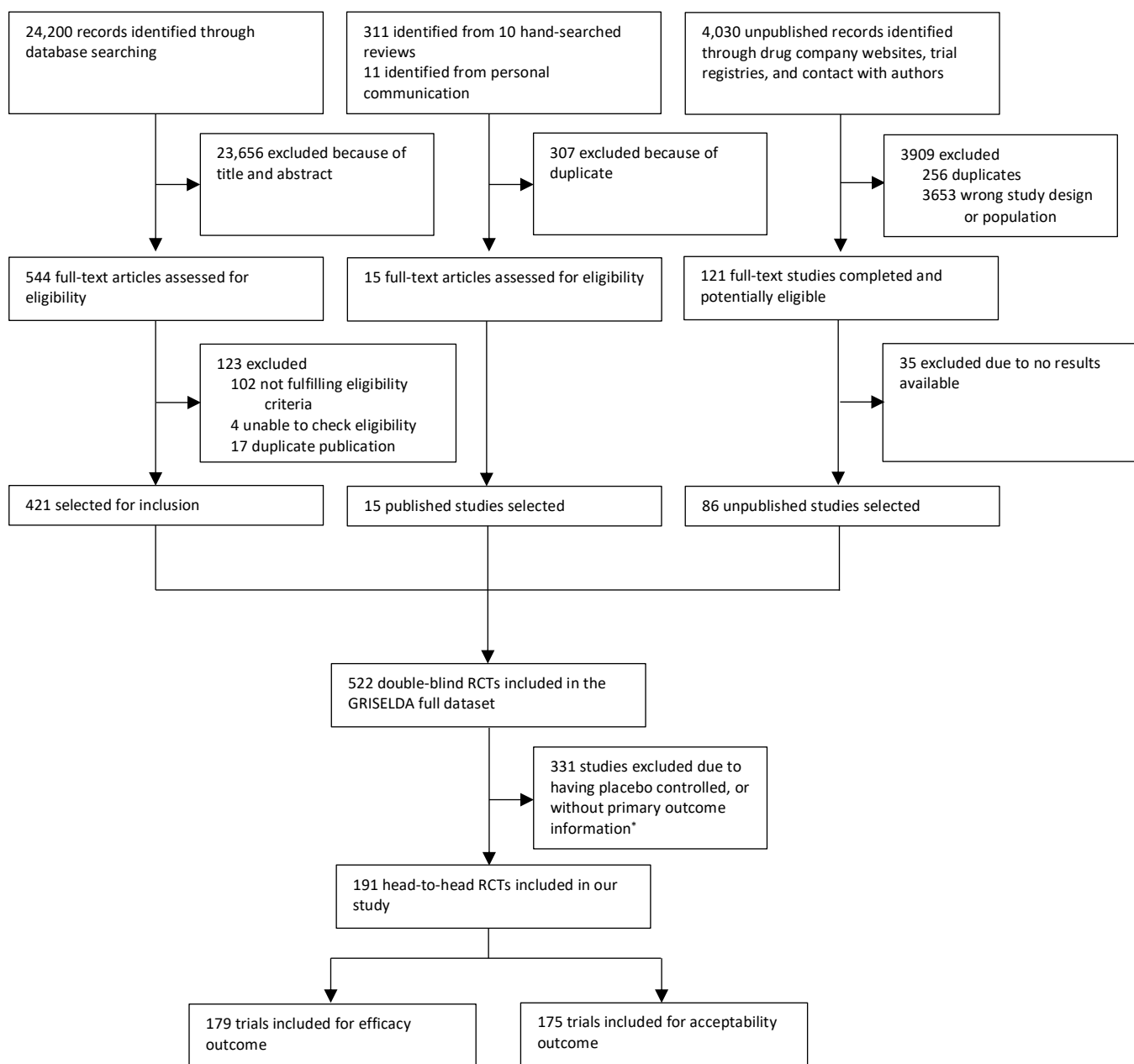
After the judgement for all the six domains, we summarized the overall confidence in evidence for each OR between any two drugs into high, moderate, low and very low. Starting with high confidence, we went one level down for each ‘major concern’ in any of the six domains; then two thirds level down for ‘some concerns’ in ‘within-study bias’; one third level down for each ‘some concerns’ in any of the other five domains. To obtain the final level, we rounded the number of downgradings to their nearest integer. For each drug, we calculated the percentage of the four levels based on all comparisons including that drug, combining both efficacy and acceptability.

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## 2 Study selection process



**eFigure 1. Flow chart for study selection process.** \*Primary outcome refers to efficacy in terms of response rate and acceptability in terms of all-cause discontinuation rate. Please refer to the main text for more information.

### 3 Reference list of included studies

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**164. Studie032 (M2020/0032)**

- [https://www.iqwig.de/download/Studie\\_032.pdf](https://www.iqwig.de/download/Studie_032.pdf)

**165. Study 043**

- [https://www.iqwig.de/download/Studie\\_043.pdf](https://www.iqwig.de/download/Studie_043.pdf)

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**174. Van Moffaert 1995a**

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## 4 Characteristics of included studies

*eTable 1. Characteristics of included studies.*

Study Name	Year	No. of arms included in NMA	No of total study arms	Drug	Sponsored	No. randomized	Mean age (SD)	% Female	Dose (min-max, mg daily)	Dosing Schedule	Mean Dose Delivered	Baseline Severity Scale	Mean Baseline Severity	Length of trial (weeks)	Diagnostic Criteria	Recruitment	Multi/Single Centre	Treatment Setting	Patient Status	Placebo Run in	Rescue Medication	
Aberg-Wisted 2000	2000	2	2	paroxetine	No	177	*	*	20-40	Flexible	*	MADRS	30.70	8	DSM-III-R	Europe	Multi-center	Unclear	Outpatients only	No	Unclear	
				sertraline	No	176	*	*	50-150	Flexible	*	MADRS	30.30									
Aguglia 1993	1993	2	2	sertraline	No	52	57.5 (15.5)	*	50-150	Flexible	72	HAMD 17	24.80	8	DSM-III-R	Europe	Multi-center	Unclear	Outpatients only	Yes	Unclear	
				fluoxetine	No	56	58.9 (17.3)	*	20-60	Flexible	28	HAMD 17	25.10									
Allard 2004	2004	2	2	citalopram	No	75	72.5 (5.7)	*	20-30	Flexible	26	MADRS	27.00	8	DSM-IV	Europe	Multi-center	Unclear	Outpatients only	No	Unclear	
				venlafaxine	Yes	76	73.6 (5.9)	*	75-150	Flexible	116	MADRS	27.60									
Altamura 1989b	1989	2	3	amitriptyline	Unclear	37	66.43 (5.6)	0.57	75-75	Fixed	75	HAMD 21	29.03	5	DSM-III	Europe	Multi-center	Unclear	Inpatients only	Unclear	Unclear	
				trazodone	Unclear	36	64.61 (5.7)	0.61	150-150	Fixed	150	HAMD 21	29.68									
Alves 1999	1999	2	2	fluoxetine	No	47	42.3 (12.2)	*	20-40	Flexible	*	HAMD 21	26.90	12	DSM-IV	Europe	Multi-center	Unclear	Outpatients only	No	Unclear	
				venlafaxine	Yes	40	45.4 (12)	*	75-150	Flexible	*	HAMD 21	27.90									
Amini 2005	2005	2	2	mirtazapine	No	18	35 (10.6)	*	30-30	Fixed	30	HAMD 17	25.80	6	DSM-IV	Asia	Single center	Secondary/Tertiary care	Both	No	Unclear	
				fluoxetine	No	18	37.7 (11.3)	*	20-20	Fixed	20	HAMD 17	24.80									
Andersen 1986	1986	2	2	citalopram	Unclear	57	*	0.70	40-40	Fixed	40	HAMD 17	22.5	5	*	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Yes	
				clomipramine	Unclear	57	*	0.69	150-150	Fixed	150	HAMD17	22									
Anseau 1989a	1989	3	3	milnacipran	Unclear	47	48.6 (10.9)	0.66	50-50	Fixed	50	HAMD 17	25.10	4	RDC	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Yes	
				milnacipran	Unclear	48	48.6 (10.9)	0.66	100-100	Fixed	100	HAMD 17	24.40									
				amitriptyline	No	49	48.6(10.9)	0.66	150-150	Fixed	150	HAMD 17	24.80									
Anseau 1989b	1989	2	2	milnacipran	Unclear	44	49.6 (11.6)	*	200-200	Fixed	200	HAMD 24	37.30	4	RDC	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Yes	
				amitriptyline	No	43	49.6 (11.6)	*	150-150	Fixed	150	HAMD 24	37.60									

Anseau 1991	1991	3	3	fluvoxamine	Unclear	41	46.6 (11.6)	*	200-200	Fixed	200	HAMD 24	32.69	4	RDC	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Yes		
				milnacipran	Unclear	42	49.9 (12.4)	*	150-150	Fixed	150	HAMD 24	33.94										
				milnacipran	Unclear	43	46.5 (13.3)	*	200-200	Fixed	200	HAMD 24	31.89										
Anseau 1994a (MY-1005/BRL-029060/1/CPM S-112)	1994	2	2	paroxetine	Yes	55	43.7 (11.5)	0.46	20-30	Flexible	*	HAMD 21	26.00	6	DSM-III-R	Europe	Multi-center	Other/Unclear	Other/Unclear	Yes	Unclear		
				fluvoxamine	No	65	43.4 (9.9)	0.67	100-200	Flexible	*	HAMD 21	26.50										
Anseau 1994b	1994	2	2	milnacipran	Yes	97	44.8 (11.2)	*	100-100	Fixed	100	HAMD 24	30.60	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes		
				fluoxetine	No	93	45 (12.3)	*	20-20	Fixed	20	HAMD 24	32.40										
Armitage 1997	1997	2	2	nefazodone	Yes	22	37.1 (8.4)	0.50	400-500	Flexible	433	HAMD 17	23.50	8	DSM-III-R	North America	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear		
				fluoxetine	No	21	37.2 (10.5)	0.76	20-40	Flexible	31	HAMD 17	23.60										
Baldwin 1996	1996	2	2	nefazodone	Yes	105	38.3 (*)	0.60	200-600	Flexible	472	HAMD 17	24.60	8	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Yes		
				paroxetine	No	101	37.9 (*)	0.50	20-40	Flexible	33	HAMD 17	24.80										
Baldwin 2006a (97-CRBX-052 - Study 052)	2006	2	2	reboxetine	Yes	159	42.4 (12.1)	0.63	8-10	Flexible	9	HAMD 17	24.20	8	DSM-IV	Europe	Multi-center	Other/Unclear	Other/Unclear	Unclear	Yes		
				paroxetine	No	166	45.1 (11)	0.62	20-40	Flexible	27	HAMD 17	24.10										
Baldwin 2006b (Study 99505)	2006	2	2	paroxetine	No	159	45.1 (13.2)	*	20-40	Flexible	26	MADRS	29.70	8	DSM-III-R	Europe	Multi-center	Other/Unclear	Other/Unclear	Yes	Unclear		
				escitalopram	Yes	166	44.9 (14.7)	*	10-20	Flexible	14	MADRS	29.60										
Battegay 1985 (PAR 29060.309 HP/81/162A)	1985	2	2	paroxetine	Yes	11	41.5 (11.3)	0.55	30-30	Fixed	30	*	*	7	*	Europe	Single center	Unclear	Unclear	Unclear	Unclear		
				amitriptyline	No	10	36.9 (10.8)	0.60	100-100	Fixed	100	*	*										
Beasley 1991	1991	2	2	trazodone	No	61	40 (10.8)	0.69	50-400	Flexible	244	HAMD 21	24.30	6	DSM-III	North America	Multi-center	Unclear	Outpatients only	Yes	Yes		
				fluoxetine	Yes	65	40 (11.3)	0.65	20-60	Flexible	21	HAMD 21	23.40										
Behnke 2003 (E-1690, Kjernisted 2002)	2003	2	2	mirtazapine	Yes	176	42 (11)	*	30-45	Flexible	38	HAMD 17	*	8	DSM-IV	Cross-Continental	Multi-center	Both	Unclear	No	Unclear		
				sertraline	No	170	41 (12)	*	50-150	Flexible	93	HAMD 17	*										
Benkert 2000 (E-1559)	2000	2	2	mirtazapine	Yes	139	47.2 (11.1)	*	15-45	Flexible	33	HAMD 17	22.40	6	DSM-IV	Europe	Multi-center	Both	Outpatients only	Yes	Unclear		
				paroxetine	No	136	47.3 (10.3)	*	20-40	Flexible	23	HAMD 17	22.40										
Benkert 2006(C-1763)	2006	2	2	mirtazapine	Yes	140	46.4 (11.1)	0.56	45-45	Fixed	45	HAMD 17	24.60	6	DSM-IV	Europe	Multi-center	Unclear	Outpatients only	No	Unclear		
				venlafaxine	No	135	45.1 (12.7)	0.59	225-225	Fixed	225	HAMD17	24.90										



Bennie 1995	1995	2	2	sertraline	Yes	142	49.9 (*)	*	50-100	Flexible	62	HAMD 17	23.20	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				fluoxetine	No	144	49.9 (*)	*	20-40	Flexible	25	HAMD 17	23.40								
Berlanga 1997	1997	2	2	nefazodone	Yes	37	41.5 (12.8)	0.78	400-500	Flexible	400	HAMD 17	25.10	8	DSM-III-R	South America	Multi-center	Unclear	Outpatients only	Unclear	Yes
				fluoxetine	No	37	39.9 (13.4)	0.76	20-40	Flexible	24	HAMD 17	23.70								
Bersani 1994	1994	2	2	sertraline	Unclear	34	47.2 (12)	0.63	50-150	Flexible	88	HAMD 21	33	8	DSM-III-R	Europe	Unclear	Unclear	Outpatients only	Unclear	No
				amitriptyline	Unclear	34	46.9 (12)	0.63	50-150	Flexible	84	HAMD 21	32								
Bielski 2004 (SCT-MD-12)	2004	2	2	escitalopram	Yes	101	37.3 (12.3)	*	20-20	Fixed	20	HAMD 24	28.60	8	DSM-IV	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Unclear
				venlafaxine	No	101	37.5 (11.6)	*	225-225	Fixed	225	HAMD 24	27.40								
Bignamini 1992 (PAR 29060/078)	1992	2	2	paroxetine	Yes	156	49.1 (13.8)	*	20-30	Flexible	*	HAMD 21	30.50	6	DSM-III	Europe	Multi-center	Unclear	Outpatients only	Unclear	Unclear
				amitriptyline	No	153	49.8 (11.9)	*	75-150	Flexible	*	HAMD 21	30.90								
Blacker 1988	1988	2	4	amitriptyline	No	44	42 (12.5)	*	100-100	Fixed	100	HAMD 21	26.70	6	DSM-III	Europe	Multi-center	Primary care	Outpatients only	Unclear	Unclear
				trazodone	Unclear	112	45 (12.8)	*	150-150	Fixed	150	HAMD 21	26.30								
Bosc 1997b (Study 016 - Massana 1999)	1997	2	2	reboxetine	Yes	79	44 (12.6)	0.72	8-10	Flexible	8	HAMD 21	28.60	8	DSM-III-R	Cross-Continental	Multi-center	Unclear	Both	Unclear	Yes
				fluoxetine	No	89	43.6 (11.8)	0.72	20-40	Flexible	23	HAMD 21	27.40								
Bougerol 1997 (Study 91302 - FDA)	1997	2	2	fluoxetine	No	158	41 (*)	*	20-20	Fixed	20	MADRS	31.80	8	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Other/Unclear	No	Yes
				citalopram	Yes	158	43 (*)	*	40-40	Fixed	40	MADRS	31.20								
Boulenger 2006 (Study 10351)	2006	2	2	escitalopram	Yes	232	43.8 (12.5)	*	20-20	Fixed	20	MADRS	35.20	24	DSM-IV	Europe	Multi-center	Both	Outpatients only	No	Unclear
				paroxetine	Yes	227	44.7 (13)	*	40-40	Fixed	40	MADRS	34.80								
Boulenger 2014 (13267A, NCT01140906)	2014	4	4	placebo	No	158	48.1 (13.1)	0.70	0-0	Fixed	0	MADRS	31.50	8	DSM-IV	Cross-Continental	Multi-center	Secondary/Tertiary care	Both	Unclear	Yes
				vortioxetine	Yes	152	47 (14.6)	0.64	15-15	Fixed	15	MADRS	31.80								
				vortioxetine	Yes	151	46.2 (13.4)	0.60	20-20	Fixed	20	MADRS	31.20								
				duloxetine	No	147	45.6 (13.6)	0.69	60-60	Fixed	60	MADRS	31.20								
Bueno 1997	1997	2	2	nefazodone	Unclear	19	46.7 (10.5)	0.79	200-500	Flexible	*	HAMD unspecified	*	8	DSM-III-R	South America	Unclear	Unclear	Outpatients only	Yes	Unclear

				amitriptyline	Unclear	18	45.2 (12.2)	0.89	50-125	Flexible	*	HAMD unspecified	*								
Caligiuri 2003	2003	2	3	bupropion	No	7	42 (9.8)	*	*	Flexible	400	HAMD 17	18.40	9	DSM-IV	North America	Single center	Secondary /Tertiary care	Outpatients only	Unclear	Unclear
				sertraline	No	9	42 (9.8)	*	50-*	Flexible	165	HAMD 17	18.40	8							
Casabona 2002 (0600B 428)	2002	2	2	paroxetine	No	56	*	*	20-20	Fixed	20	*	*	8	DSM-IV	Europe	Multi- center	Unclear	Outpatients only	Unclear	Unclear
				venlafaxine	Yes	58	*	*	75-75	Fixed	75	*	*								
Cassano 2002 (29060/421)	2002	2	2	paroxetine	Yes	123	75.61 (6.99)	*	20-40	Flexible	*	HAMD unspecified	22.95	6	ICD-10	Europe	Multi- center	Unclear	Outpatients only	Yes	Unclear
				fluoxetine	No	119	74.85 (6.67)	*	20-60	Flexible	*	HAMD unspecified	23.41								
Chang 2015	2015	2	2	fluoxetine	No	58	41.7 (12)	0.76	20-80	Flexible	21	HAMD 21	24.30	6	DSM-IV	Asia	Unclear	Other/Unclear	Outpatients only	Unclear	Yes
				venlafaxine	No	54	37.5 (12.5)	0.70	75-225	Flexible	80	HAMD 21	25.90								
Chouinard 1983a	1983	2	2	amitriptyline	Unclear	41	35.1 (*)	*	75-150	Flexible	119	HAMD 21	26.10	13	Other operati onalize d	North America	Multi- center	Unclear	Outpatients only	Yes	Yes
				bupropion	Unclear	77	38.9 (*)	*	300-450	Flexible	374	HAMD 21	26.50								
Chouinard 1985	1985	2	2	fluoxetine	Unclear	25	41 (*)	*	40-80	Flexible	69	HAMD 21	27.60	5	RDC	North America	Multi- center	Secondary /Tertiary care	Outpatients only	Yes	Yes
				amitriptyline	Unclear	28	39 (*)	*	150-300	Flexible	163	HAMD 21	25.90								
Chouinard 1999 (29060/131)	1999	2	2	paroxetine	Yes	102	40.6 (10.7)	*	20-50	Flexible	26	HAMD 21	25.91	12	DSM- III-R	North America	Multi- center	Unclear	Unclear	Yes	Unclear
				fluoxetine	No	101	41.2 (10.7)	*	20-80	Flexible	28	HAMD 21	25.45								
Christiansen 1996	1996	2	2	paroxetine	Unclear	71	*	*	20-40	Flexible	*	HAMD 17	23.8	8	*	Europe	Multi- center	Unclear	Outpatients only	Unclear	Unclear
				amitriptyline	Unclear	73	*	*	100-150	Flexible	*	HAMD 17	24.2								
CL3-20098-036	2004	2	2	agomelatine	Yes	137	39.6 (10.3)	0.72	50-50	Fixed	50	MADRS	27.90	24	DSM-IV	Cross- Continental	Multi- center	Primary care	Outpatients only	No	No
				venlafaxine	No	140	42.1 (10)	0.72	75-150	Flexible	*	MADRS	27.90								
CL3-20098-048	2008	2	2	agomelatine	Yes	213	68.6 (6.2)	*	25-50	Flexible	*	HAMD 17	26.30	24	DSM-IV	Cross- Continental	Multi- center	Primary care	Outpatients only	No	No
				paroxetine	No	199	68.3 (6.2)	*	20-30	Flexible	*	HAMD 17	26.20								
CL3-20098-062	2010	2	2	agomelatine	Yes	202	43 (12.3)	*	25-50	Flexible	*	HAMD 17	26.20	25	DSM-IV	Cross- Continental	Multi- center	Primary care	Outpatients only	No	No
				duloxetine	No	216	42.5 (11.9)	*	60-60	Fixed	60	HAMD 17	26.30								

Clerc 1994	1994	2	2	fluoxetine	No	34	53.6 (*)	*	40-40	Fixed	40	HAMD 21	29.70	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Unclear
				venlafaxine	Yes	34	49 (*)	*	200-200	Fixed	200	HAMD 21	29.10								
Clerc 2001	2001	2	2	fluvoxamine	No	56	52.2 (12.6)	*	200-200	Fixed	200	HAMD 24	31.40	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Both	Yes	Yes
				milnacipran	Yes	57	48.7 (15.1)	*	100-100	Fixed	100	HAMD 24	32.80								
Cohn 1990	1990	2	2	sertraline	Unclear	161	70.2 (*)	0.50	50-200	Flexible	116	HAMD 17	23.7	8	DSM-III	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				amitriptyline	No	80	70.6 (*)	0.46	50-150	Flexible	88	HAMD 17	25.2								
Colonna 2005 (Study 99022)	2005	2	2	escitalopram	Yes	175	46 (12)	*	10-10	Fixed	10	MADRS	29.50	8	DSM-IV	Europe	Multi-center	Primary care	Outpatients only	Yes	Unclear
				citalopram	No	182	46 (11)	*	20-20	Fixed	20	MADRS	30.20								
Corruble 2013 (CL3-20098-063)	2008	2	2	agomelatine	Yes	164	43.6 (12.9)	0.73	25-50	Flexible	*	HAMD 17	26.80	25	DSM-IV	Cross-Continental	Multi-center	Primary care	Outpatients only	No	No
				escitalopram	No	160	42.8 (11.8)	0.69	10-20	Flexible	*	HAMD 17	26.60								
Costaesilva 1998	1998	2	2	fluoxetine	No	186	39.8 (10.3)	*	20-40	Flexible	*	HAMD 17	29.70	8	DSM-III-R	South America	Multi-center	Unclear	Outpatients only	No	Unclear
				venlafaxine	Yes	196	40.5 (10.7)	*	75-150	Flexible	*	HAMD 17	30.40								
Dalery 2003	2003	2	2	fluvoxamine	Yes	90	42 (*)	*	100-100	Fixed	100	HAMD 17	22.30	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				fluoxetine	No	94	42.1 (*)	*	20-20	Fixed	20	HAMD 17	22.20								
Debonnel 2000 (Blier 2009, iQWIG E-1639)	2009	2	3	mirtazapine	Yes	21	45.9 (9.1)	0.29	30-45	Flexible	*	HAMD 17	24.00	6	DSM-IV	North America	Single center	Unclear	Unclear	Yes	Yes
				paroxetine	No	21	39.7 (11.8)	0.48	20-30	Flexible	*	HAMD 17	24.20								
Debus 1988	1988	2	2	fluoxetine	Yes	22	35.4 (8.6)	*	20-60	Flexible	31	HAMD 21	23.40	6	DSM-III	North America	Multi-center	Both	Outpatients only	Yes	No
				trazodone	No	21	39.3 (8.3)	*	50-400	Flexible	305	HAMD 21	25.20								
Demyttenaere 1998	1998	2	2	amitriptyline	No	31	42.1 (8.1)	*	150-150	Fixed	150	HAMD unspecified	23.90	9	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Unclear
				fluoxetine	Yes	35	41.4 (8.9)	*	20-20	Fixed	20	HAMD unspecified	24.90								
DeRonchi 1998	1988	2	2	fluoxetine	Unclear	32	69.1 (5.92)	*	20-20	Fixed	20	HAMD 17	25.60	10	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				amitriptyline	Unclear	33	68.6 (7.64)	*	50-100	Fixed	100	HAMD 17	26.50								
Deushle 2003 (NCT01049347)	2003	2	2	amitriptyline	No	14	49.5 (17.5)	0.64	150-150	Fixed	150	HAMD unspecified	21.64	5	DSM-IV	Europe	Unclear	Unclear	Inpatients only	Unclear	Yes

				paroxetine	No	21	61.2 (13)	0.67	40-40	Fixed	40	HAMD unspecified	23.62								
DeWilde 1983a	1983	2	2	fluvoxamine	Yes	22	*	*	100-300	Flexible	300	HAMD 17	23.40	6	Feighner	Europe	Single center	Secondary /Tertiary care	Outpatients only	Unclear	Yes
				clomipramine	No	21	*	*	50-150	Flexible	144	HAMD 17	24.20								
DeWilde 1993	1993	2	2	paroxetine	Yes	49	43.9 (13.2)	*	20-40	Flexible	*	HAMD 21	27.00	6	DSM-III	Europe	Multi- center	Other/Unclear	Other/Unclear	Yes	Unclear
				fluoxetine	No	50	44.3 (12)	*	20-60	Flexible	*	HAMD 21	28.20								
Dierick 1996	1996	2	2	fluoxetine	No	161	43.2 (13)	0.64	20-20	Fixed	20	HAMD 17	26.60	8	DSM-III-R	Europe	Multi- center	Unclear	Outpatients only	Unclear	Unclear
				venlafaxine	Yes	153	43.7 (12.5)	0.65	75-150	Flexible	112	HAMD 17	27.00								
DUAG 1990	1990	2	2	paroxetine	Unclear	62	*	*	30-30	Fixed	30	HAMD 17	23.12	6	DSM-III	Europe	Multi- center	Secondary /Tertiary care	Inpatients only	Yes	Yes
				clomipramine	Unclear	58	*	*	150-150	Fixed	150	HAMD 17	23.36								
E-1569	unpublished	2	2	mirtazapine	Yes	73	46.5 (12.5)	0.68	30-45	Flexible	*	HAMD 17	24.60	6	DSM-IV	Europe	Multi- center	Other/Unclear	Outpatients only	Yes	Unclear
				paroxetine	No	75	43 (12.5)	0.69	20-40	Flexible	*	HAMD 17	25.70								
Ekselius 1997	1997	2	2	citalopram	No	200	48.1 (12)	*	20-60	Flexible	34	MADRS	28.30	12	DSM-III-R	Europe	Multi- center	Primary care	Outpatients only	Yes	No
				sertraline	Yes	200	47.3 (13.3)	*	50-150	Flexible	82	MADRS	28.30								
Falk 1989	1989	2	2	trazodone	No	13	67.5 (4)	*	50-400	Flexible	350	HAMD 21	26.17	6	DSM-III	North America	Single center	Secondary /Tertiary care	Outpatients only	Yes	Unclear
				fluoxetine	Yes	14	69.1 (6.2)	*	20-60	Flexible	48	HAMD 21	23.77								
Fava 2002	2002	3	3	sertraline	No	96	44 (14.7)	*	50-200	Flexible	108	HAMD 17	21.00	10	DSM-IV	North America	Multi- center	Secondary /Tertiary care	Outpatients only	Yes	Yes
				fluoxetine	Yes	92	42.1 (13.5)	*	20-60	Flexible	42	HAMD 17	20.50								
				paroxetine	No	96	42.5 (14.7)	*	20-60	Flexible	37	HAMD 17	20.60								
Fawcett 1989	1989	2	2	amitriptyline	No	20	44.5 (10.3)	*	50-200	Flexible	*	HAMD 21	23.50	6	DSM-III	North America	Multi- center	Secondary /Tertiary care	Outpatients only	Yes	Yes
				fluoxetine	Yes	20	39.9 (10.6)	*	20-60	Flexible	*	HAMD 21	23.60								
Feiger 1996	1996	2	2	nefazodone	Yes	78	44.5 (11.5)	0.55	100-600	Flexible	456	HAMD 17	23.30	6	DSM-III-R	North America	Multi- center	Other/Unclear	Outpatients only	Unclear	Yes
				sertraline	No	82	43.1 (10)	0.48	50-200	Flexible	148	HAMD 17	23.30								
Feighner 1991	1991	2	2	fluoxetine	No	62	42.9 (*)	*	20-80	Flexible	38	HAMD 17	26.10	6	DSM-III-R	North America	Multi- center	Unclear	Outpatients only	Yes	Unclear
				bupropion	Yes	61	40.9 (*)	*	225-450	Flexible	382	HAMD 17	25.30								

Fudge 1990	1990	2	2	fluoxetine	Unclear	21	*	*	20-60	Flexible	*	HAMD unspecified	23.20	6	DSM-III	North America	Single center	Secondary/Tertiary care	Outpatients only	Yes	Unclear
				trazodone	Unclear	17	*	*	50-400	Flexible	*	HAMD unspecified	23.60								
Gagliano 1993	1993	2	2	paroxetine	Yes	45	37.8 (12.5)	*	20-40	Flexible	*	HAMD 21	25.00	6	DSM-III	Africa	Single center	Unclear	Outpatients only	Yes	Unclear
				fluoxetine	No	45	39.6 (11.7)	*	20-60	Flexible	*	HAMD 21	24.50								
Gentil 2000	2000	2	2	venlafaxine	Yes	57	37.9 (10.1)	*	75-150	Flexible	103	HAMD 21	23.90	8	DSM-IV	South America	Multi-center	Unclear	Outpatients only	Yes	Yes
				amitriptyline	No	59	39.1 (8.7)	*	75-150	Flexible	103	HAMD 21	24.50								
Geretsegger 1995 (MY-060/BRL-029060/1)	1995	2	2	paroxetine	Yes	44	71 (*)	*	20-30	Flexible	*	HAMD 21	26.80	6	DSM-III	Europe	Multi-center	Unclear	Inpatients only	No	Unclear
				amitriptyline	No	47	71.3 (*)	*	100-150	Flexible	*	HAMD 21	28.30								
Gerner 1980	1980	2	3	trazodone	Yes	19	68.4 (*)	0.62	100-400	Flexible	305	HAMD unspecified	27.38	4	RDC	North America	Unclear	Unclear	Outpatients only	Unclear	Unclear
				placebo	No	20	68.4 (*)	0.62	0-0	Flexible	0	HAMD unspecified	25.00								
Gillin 1997	1997	2	2	nefazodone	Yes	24	35.3 (8.8)	0.67	400-500	Flexible	435	HAMD 17	22.90	8	DSM-III-R	North America	Multi-center	Unclear	Outpatients only	Unclear	Unclear
				fluoxetine	No	20	36.7 (8.5)	0.70	20-40	Flexible	34	HAMD 17	23.20								
Ginestet 1989	1989	2	2	fluoxetine	Unclear	28	46.5 (10.8)	0.71	20-80	Flexible	58	HAMD 21	33.10	8	DSM-III	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Unclear	Yes
				clomipramine	No	26	51.6 (11)	0.73	50-200	Flexible	148	HAMD 21	33.70								
Guelfi 1998	1998	3	3	milnacipran	Yes	100	45.6 (12.4)	*	100-100	Fixed	100	HAMD 17	27.90	12	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Yes
				milnacipran	Yes	100	45.2 (12.5)	*	200-200	Fixed	200	HAMD 17	27.70								
				fluoxetine	No	100	45.8 (12.8)	*	20-20	Fixed	20	HAMD 17	27.40								
Guillibert 1989 (PAR 290 MDF 29060 1727 M)	1989	2	2	clomipramine	No	39	68.1 (6.1)	*	75-75	Fixed	75	HAMD 21	27.50	6	DSM-III	Europe	Multi-center	Unclear	Unclear	Yes	Yes
				paroxetine	Yes	40	69.3 (5.3)	*	30-30	Fixed	30	HAMD 21	27.90								
Hackett 1998	1998	2	2	fluvoxamine	No	34	*	*	200-200	Fixed	200	MADRS	31.60	6	DSM-III-R	Europe	Multi-center	Unclear	Outpatients only	No	Unclear
				venlafaxine	Yes	77	*	*	150-150	Fixed	150	MADRS	32.20								
Hale 2010 (CL3-20098-045)	2008	2	2	agomelatine	Yes	252	41.8 (11.2)	0.77	25-50	Flexible	*	HAMD 17	28.50	24	DSM-IV	Cross-Continental	Multi-center	Primary care	Outpatients only	No	No
				fluoxetine	No	263	42.7 (11.9)	0.78	20-40	Flexible	*	HAMD 17	28.70								
Hao 2014	2014	2	2	duloxetine	Yes	140	38.4 (13)	0.56	60-60	Fixed	60	HAMD 17	23.70	6	DSM-IV	Asia	Multi-center	Both	Both	No	Yes
				paroxetine	No	141	38.5 (1.6)	0.62	20-20	Fixed	20	HAMD 17	23.70								

Harris 1991	1991	2	2	fluvoxamine	Unclear	35	38.6 (12.1)	0.63	50-150	Flexible	115	HAMD 17	22.70	6	DSM-III	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				amitriptyline	Unclear	34	48.1 (12.3)	0.82	50-150	Flexible	99	HAMD 17	22.80								
Heller 2009 (NCT00909155)	2009	2	2	venlafaxine	Yes	15	30.74 (11.5)	0.53	75-300	Flexible	118	HAMD 21	20.07	24	DSM-IV	North America	Unclear	/Unclear	Other/Unclear	Unclear	Unclear
				fluoxetine	No	14	33.14 (10.7)	0.57	20-80	Flexible	37	HAMD 21	21.36								
Hicks 2002	2002	2	2	nefazodone	Yes	20	42.8 (11.9)	0.40	400-600	Flexible	495	HAMD unspecified	21.60	24	DSM-IV	Europe	Single center	Secondary/Tertiary care	Outpatients only	Unclear	No
				paroxetine	No	20	43 (10.1)	0.45	20-40	Flexible	30	HAMD unspecified	22.30								
Hong 2003 (22521)	2003	2	2	mirtazapine	Yes	66	47.2 (14.7)	*	30-45	Flexible	34	HAMD 17	23.10	6	DSM-IV	Asia	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Unclear
				fluoxetine	No	66	47.1 (15.5)	*	20-40	Flexible	31	HAMD 17	24.30								
Hosseini 2015 (IRCT201203048513N1.)	2015	2	2	venlafaxine	No	28	37.12 (10.9)	0.75	37.5-150	Other/Unclear	*	HAMD unspecified	19.88	8	DSM-IV	Asia	Single center	Secondary/Tertiary care	Outpatients only	Unclear	Unclear
				citalopram	No	25	35.6 (8.72)	0.91	10-40	Other/Unclear	*	HAMD unspecified	17.63								
Hsu 2011	2011	2	2	citalopram	No	25	43.4 (11.4)	*	20-*	Flexible	23	MADRS	36.60	6	DSM-IV	Asia	Single center	Secondary/Tertiary care	Other/Unclear	No	Yes
				sertraline	No	26	38 (13.8)	*	50-*	Flexible	57	MADRS	38.20								
Hu 2009	2009	2	2	escitalopram	Unclear	25	30.92 (8.04)	0.52	10-20	Flexible	*	HAMD 17	21.30	6	Other operationalized	Asia	Single center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				citalopram	Unclear	23	30.61 (8.61)	0.57	20-40	Flexible	*	HAMD 17	20.78								
Hutchinson 1992	1992	2	2	amitriptyline	No	32	71.5 (9.5)	*	100-100	Fixed	100	HAMD 21	20.28	6	DSM-III	Europe	Multi-center	Primary care	Outpatients only	Yes	Yes
				paroxetine	Yes	58	72 (5.6)	*	30-30	Fixed	30	HAMD 21	21.56								
Jiang 2009	2009	2	2	escitalopram	Unclear	32	38.62 (11.54)	0.56	10-20	Flexible	*	HAMD 17	23.82	6	Other operationalized	Asia	Single center	Secondary/Tertiary care	Both	Unclear	Yes
				citalopram	Unclear	32	39.23 (11.9)	0.53	20-60	Flexible	*	HAMD 17	23.46								
Judd 1993	1993	2	2	fluoxetine	Yes	30	41.7 (9.8)	0.66	20-20	Fixed	20	HAMD 17	24.40	6	DSM-III-R	Australia	Multi-center	Unclear	Unclear	Yes	Yes
				amitriptyline	No	28	41.7 (9.8)	0.66	150-200	Flexible	171	HAMD 17	23.70								
Kamijima 2013 (japicCTI-090733)	2013	3	3	milnacipran	Yes	303	35.9 (10.4)	0.53	100-100	Fixed	100	HAMD 17	22.10	9	DSM-IV	Asia	Multi-center	Unclear	Both	Yes	Yes
				milnacipran	Yes	301	36.7 (10.5)	0.51	200-200	Fixed	200	HAMD 17	22.30								

				paroxetine	No	301	36.6 (11.1)	0.55	30-40	Flexible	*	HAMD 17	22.10								
Kasper 2005b	2005	2	2	paroxetine	Unclear	53	44.3 (11.3)	0.68	20-40	Flexible	22	HAMD 17	20.90	6	DSM-IV	Europe	Multi-center	Unclear	Outpatients only	Yes	Yes
				trazodone	Unclear	55	43.5 (12.2)	0.58	150-450	Flexible	305	HAMD 17	21.00								
Keegan 1991	1991	2	2	fluoxetine	Yes	20	39.5 (13.6)	0.67	20-80	Flexible	53	HAMD 21	*	6	DSM-III	North America	Multi-center	Unclear	Unclear	Yes	Yes
				amitriptyline	No	22	47.8 (14.2)	0.67	100-250	Flexible	171	HAMD 21	*								
Keller 2007 (NCT00046020)	2007	2	2	fluoxetine	Unclear	275	40 (11.6)	*	20-60	Flexible	50	HAMD 17	23.00	10	DSM-IV	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	No
				venlafaxine	Yes	821	39.6 (11.2)	*	75-300	Flexible	208	HAMD 17	22.60								
Kennedy 2005 (SCT-MD-16)	unpublis hed	2	2	escitalopram	Yes	102	37.1 (11.4)	*	10-20	Flexible	*	HAMD unspecified	25.90	8	DSM-IV	North America	Multi-center	Unclear	Outpatients only	Unclear	Unclear
				fluoxetine	No	103	37 (11.8)	*	20-40	Flexible	*	HAMD unspecified	26.50								
Kerkhofs 1990	1990	2	2	fluoxetine	Yes	16	45.3 (12.7)	0.69	60-60	Fixed	60	HAMD unspecified	21.90	6	RDC	Europe	Unclear	Unclear	Other/Unclear	Yes	Yes
				amitriptyline	No	18	46.2 (11.4)	0.61	150-150	Fixed	150	HAMD unspecified	21.80								
Khan 2007 (SCT-MD-23, NCT00108979)	2007	2	2	escitalopram	Yes	140	41.8 (12.7)	*	10-20	Flexible	*	HAMD 24	26.60	8	DSM-IV	North America	Multi-center	Unclear	Outpatients only	Unclear	Unclear
				duloxetine	No	138	43 (13.4)	*	60-60	Fixed	60	HAMD 24	26.90								
Kiev 1997	1997	2	2	fluvoxamine	Yes	30	42.7 (*)	*	50-150	Flexible	102	HAMD 21	24.40	7	DSM-III-R	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				paroxetine	No	30	39.9 (*)	*	20-50	Flexible	36	HAMD 21	24.40								
Kuhs 1989 (MDUK_29060_III_85_043)	1989	2	2	paroxetine	Yes	12	39.2 (11.8)	0.9	30-30	Fixed	30	HAMD 21	24.60	6	DSM-III	Europe	Single center	Other/Unclear	Other/Unclear	Yes	Unclear
				amitriptyline	No	12	39.1 (11.5)	1.0	150-150	Fixed	150	HAMD 21	25.00								
Laakman 1988	1988	2	2	fluoxetine	Unclear	63	*	*	20-60	Flexible	*	HAMD unspecified	26.7	5	Other operationalized	Europe	Unclear	Other/Unclear	Outpatients only	Yes	Yes
				amitriptyline	Unclear	65	*	*	50-150	Flexible	*	HAMD unspecified	23.8								
Lalit 2004	2004	3	3	escitalopram	Yes	69	33 (8)	*	10-20	Flexible	*	HAMD 17	26.00	4	ICD-10	Asia	Multi-center	Other/Unclear	Outpatients only	No	Yes
				citalopram	Yes	74	33 (9)	*	20-40	Flexible	*	HAMD 17	25.00								
				sertraline	No	71	37 (11)	*	100-150	Flexible	*	HAMD 17	25.00								
Lapierre 1980	1980	2	2	amitriptyline	Unclear	20	*	*	150-150	Fixed	150	*	*	4	Feighner	North America	Unclear	Secondary/Tertiary care	Both	Yes	Unclear
				trazodone	Unclear	20	*	*	150-150	Fixed	150	*	*								

Lee 2007 (F1J-AA-HMCV) (NCT00489775)	2007	2	2	duloxetine	Yes	238	39 (13.9)	*	60-60	Fixed	60	HAMD 17	21.10	8	DSM-IV	*	Multi-center	Secondary/Tertiary care	Both	No	Unclear
				paroxetine	No	240	38 (15.3)	*	20-20	Fixed	20	HAMD 17	21.20								
Leinonen 1997	1997	2	2	milnacipran	Yes	52	49.2 (9.8)	*	100-200	Flexible	*	HAMD 17	23.70	26	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Both	Unclear	Yes
				clomipramine	No	55	47.1 (10.6)	*	75-150	Flexible	*	HAMD 17	23.10								
Leinonen 1999 (Agren1995)	1999	2	2	mirtazapine	Yes	137	42.1 (12.3)	*	15-60	Flexible	35	MADRS	29.60	8	DSM-IV	Europe	Multi-center	Secondary/Tertiary care	Both	Yes	Yes
				citalopram	No	133	41.1 (10.8)	*	20-60	Flexible	37	MADRS	29.10								
Lemoine 2007 (CL3-20098-035)	2004	2	4	agomelatine	Yes	165	40.7 (10.7)	0.75	25-50	Fixed	50	HAMD 17	25.90	24	DSM-IV	Europe	Multi-center	Primary care	Outpatients only	No	No
				venlafaxine	No	167	39.6 (10.3)	0.67	75-150	Fixed	150	HAMD 17	26.00								
Lepine 2000	2000	2	2	sertraline	Yes	82	42.3 (*)	0.71	50-200	Flexible	114	HAMD 17	29.8	8	DSM-III-R	Cross-Continental	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				clomipramine	No	84	41.8 (*)	0.69	50-150	Flexible	98	HAMD 17	29.6								
Li 2006	2006	2	2	escitalopram	Unclear	28	36.5 (12.8)	0.55	10-20	Flexible	*	HAMD 17	23.70	6	Other operationalized	Asia	Single center	Secondary/Tertiary care	Outpatients only	Unclear	Yes
				citalopram	Unclear	28	34.4 (11.9)	0.53	20-40	Flexible	*	HAMD 17	23.80								
Li 2010	2010	2	2	escitalopram	Yes	24	*	*	10-20	Flexible	*	HAMD unspecified	*	6	Other operationalized	Asia	Multi-center	Other/Unclear	Other/Unclear	Unclear	Unclear
				citalopram	Yes	24	*	*	20-40	Flexible	*	HAMD unspecified	*								
Manna 1989	1989	2	2	fluoxetine	Unclear	15	47.7 (10)	0.63	20-20	Fixed	20	HAMD 17	25.7	5	DSM-III	Europe	Unclear	Secondary/Tertiary care	Inpatients only	Unclear	Unclear
				clomipramine	Unclear	15	48.5 (8.36)	0.63	75-75	Fixed	75	HAMD 17	25								
Mao 2008	2008	2	2	fluoxetine	No	117	40.7 (13.9)	0.74	20-20	Fixed	20	HAMD 17	24.10	8	DSM-IV	Asia	Multi-center	Secondary/Tertiary care	Both	No	Yes
				escitalopram	Yes	123	37.1 (14.1)	0.61	10-10	Fixed	10	HAMD 17	24.70								
Marchesi 1998	1998	2	2	fluoxetine	Yes	67	43.6 (11.9)	0.73	20-20	Fixed	20	HAMD 17	25.50	10	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes
				amitriptyline	No	75	43.6 (11.9)	0.75	75-225	Flexible	115	HAMD 17	25.30								
McPartlin 1998	1998	2	2	paroxetine	No	178	44 (14)	*	20-20	Fixed	20	HAMD 17	23.00	12	DSM-IV	Europe	Multi-center	Primary care	Outpatients only	Unclear	Yes



				venlafaxine	Yes	183	45 (15)	*	75-75	Fixed	75	HAMD 17	23.00								
MDF/29060/III/ 070/88/MC	unpublis hed	2	2	paroxetine	Yes	32	73 (*)		20-30	Flexible	*	MADRS	30.88	5	Feighne r	Europe	Multi- center	Other/Unc lear	Outpatients only	Yes	Yes
				clomipramin e	No	30	73 (*)		60-75	Flexible	*	MADRS	29.00								
Mehtonen 2000	2000	2	2	sertraline	No	72	41 (10.7)	*	50-100	Flexible	*	HAMD 21	25.80	8	DSM-IV	Europe	Multi- center	Other/Unc lear	Outpatients only	No	Unclear
				venlafaxine	Yes	75	44.1 (11.4)	*	75-150	Flexible	*	HAMD 21	25.50								
Miura 2000	2000	2	2	paroxetine	Yes	109	45.9 (13.9)	*	20-40	Flexible	32	HAMD 17	23.80	6	DSM-IV	Asia	Multi- center	Secondary /Tertiary care	Both	No	Yes
				amitriptyline	No	119	47.1 (13.8)	*	50-150	Flexible	109	HAMD 17	23.90								
Moller 1998 (Hegerl 1997)	1998	2	2	amitriptyline	No	79	49.5 (12.9)	0.71	75-225	Flexible	141	HAMD 21	29.1	6	DSM- III-R	Europe	Multi- center	Secondary /Tertiary care	Inpatients only	No	Yes
				sertraline	Yes	81	47.7 (13)	0.69	50-150	Flexible	105	HAMD 21	28.3								
Moller 2000	2000	2	2	sertraline	Yes	116	47.7 (13.2)	*	50-100	Flexible	55	HAMD 21	27.10	6	DSM- III-R	Europe	Multi- center	Both	Outpatients only	No	Yes
				amitriptyline	No	124	48.1 (14)	*	75-150	Flexible	87	HAMD 21	27.50								
Montgomery 2004a (Study 99067)	2004	2	2	escitalopram	Yes	148	49 (15)	*	10-20	Flexible	12	HAMD 17	19.99	8	DSM-IV	Europe	Multi- center	Primary care	Other/Unclea r	No	Unclear
				venlafaxine	No	145	47 (14)	*	75-150	Flexible	95	HAMD 17	20.44								
Montgomery 2004b (CL3- 20098-030)	2001	2	2	agomelatine	Yes	167	42.8 (13.5)	*	25-25	Fixed	25	MADRS	23.10	12	DSM-IV	Cross- Continental	Multi- center	Primary care	Outpatients only	No	No
				paroxetine	No	168	42.1 (13.4)	*	20-20	Fixed	20	MADRS	23.00								
Moon 1994	1994	2	2	sertraline	Yes	51	42 (*)	0.41	50-150	Flexible	64	HAMD 17	23.9	6	DSM-III	Europe	Multi- center	Primary care	Outpatients only	Yes	Yes
				clomipramin e	No	55	45 (*)	0.60	50-150	Flexible	61	HAMD 17	22.7								
Moore 2005	2005	2	2	escitalopram	Yes	142	44.1 (10.9)	*	20-20	Fixed	20	MADRS	36.30	8	DSM-IV	Europe	Multi- center	Both	Outpatients only	No	Unclear
				citalopram	No	152	46.2 (11.1)	*	40-40	Fixed	40	MADRS	35.70								
Munizza 2006	2006	2	2	sertraline	No	60	46.9 (10.6)	0.70	50-100	Flexible	59	HAMD 17	21.9	6	DSM-IV	Europe	Multi- center	Other/Unc lear	Outpatients only	Unclear	Yes
				trazodone	Yes	62	45 (11.5)	0.60	150-450	Flexible	297	HAMD 17	21.7								
Murasaki 1998	1998	2	2	fluvoxamine	Yes	113	40.5 (*)	*	50-150	Flexible	87	HAMD 21	22.90	4	DSM- III-R	Asia	Multi- center	Both	Both	No	Yes
				amitriptyline	No	122	45.3 (*)	*	50-150	Flexible	76	HAMD 21	23.60								
Murasaki 2010a (IQWIG22532, Schoemaker 2002)	2002	2	2	mirtazapine	Yes	104	42 (12.1)	0.68	15-45	Flexible	23	HAMD 17	25.10	6	DSM-IV	Europe	Multi- center	Both	Outpatients only	No	Yes
				fluvoxamine	No	105	39.4 (12.7)	0.64	50-150	Flexible	78	HAMD 17	25.10								

Murasaki 2010b (iQWIG9902, Schoemaker 2002)	2002	2	2	mirtazapine	Yes	101	40.7 (11.8)	0.50	15-45	Flexible	*	HAMD 17	22.90	6	DSM-IV	Asia	Multi-center	Both	Outpatients only	No	Yes	
				fluvoxamine	No	102	42.2 (12.9)	0.39	50-150	Flexible	*	HAMD 17	22.50									
Nemeroff 1995	1995	2	2	fluvoxamine	Yes	49	38.5 (*)	*	50-150	Flexible	124	HAMD 21	24.57	7	DSM-III-R	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes	
				sertraline	No	48	41.2 (*)	*	50-200	Flexible	137	HAMD 21	23.15									
Nemeroff 2007	2007	3	3	fluoxetine	Unclear	104	37.9 (11.5)	*	20-60	Flexible	41	HAMD 21	23.70	6	DSM-IV	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Unclear	
				venlafaxine	Yes	102	40.1 (11.1)	*	75-225	Flexible	142	HAMD 21	23.50									
				placebo	No	102	40.4 (11.7)	*	0-0	Flexible	0	HAMD 21	23.70									
Newhouse 2000	2000	2	2	sertraline	Yes	117	68 (5.3)	*	50-100	Flexible	72	HAMD 24	25.10	12	DSM-III-R	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes	
				fluoxetine	No	119	67 (5.9)	*	20-40	Flexible	29	HAMD 24	25.00									
Noguera 1991	1991	2	2	clomipramine	No	60	46 (*)	*	100-100	Fixed	100	HAMD unspecified	24.60	6	DSM-III	Europe	Multi-center	Secondary/Tertiary care	Other/Unclear	Yes	Yes	
				fluoxetine	Yes	60	46.3 (*)	*	20-40	Flexible	*	HAMD unspecified	24.30									
Ontiveros 1994 (MY-0144/BRL 29060/1/CPMS-135, PAR135)	1994	2	2	paroxetine	No	60	43.1 (11)	*	20-20	Fixed	20	HAMD 21	26.20	6	DSM-III-R	North America	Multi-center	Other/Unclear	Outpatients only	Yes	No	
				fluoxetine	No	62	38.7 (10.7)	*	20-20	Fixed	20	HAMD 21	26.40									
Ontiveros Sanchez 1998	1998	2	2	fluoxetine	Yes	21	38.6 (11.5)	0.43	20-20	Fixed	20	HAMD 17	23.50	6	DSM-III-R	South America	Single center	Secondary/Tertiary care	Outpatients only	Yes	Unclear	
				amitriptyline	No	21	36.5 (9.34)	0.62	150-250	Flexible	160	HAMD 17	23.10									
Ottevanger 1995	1995	2	2	fluvoxamine	Yes	20	51.3 (15.39)	*	100-300	Flexible	204	HAMD 17	26.40	4	Feighner	Europe	Multi-center	Other/Unclear	Inpatients only	Unclear	Yes	
				clomipramine	No	20	47.05 (12.4)	*	50-150	Flexible	106	HAMD 17	25.70									
Ou 2010	2010	2	2	citalopram	Unclear	120	36.4 (12.3)	0.54	20-40	Flexible	28	HAMD 17	22.9	6	DSM-IV	Asia	Multi-center	Secondary/Tertiary care	Both	Unclear	Yes	
				escitalopram	Unclear	120	36.7 (12.5)	0.58	10-20	Flexible	14	HAMD 17	23.4									
PAR 29060.308 (HP/81/74A)	unpublished	2	2	paroxetine	Yes	10	43.3 (12.6)	0.60	30-30	Fixed	30	*	*	6	*	Europe	Single center	Secondary/Tertiary care	Inpatients only	Yes	Unclear	
				amitriptyline	No	12	45.3 (12.5)	0.58	150-150	Fixed	150	*	*									
PAR 29060.310 (HP 81/85A)	unpublished	2	2	paroxetine	Yes	10	39.1 (11.9)	0.67	30-30	Fixed	30	*	*	7	*	Europe	Single center	Other/Unclear	Other/Unclear	Yes	Unclear	

				amitriptyline	No	13	43.7 (10.2)	0.50	150-150	Fixed	150	*	*								
PAR 29060.314 (HP 82/134)	unpublis hed	2	2	paroxetine	Yes	10	46.8 (13.1)	0.30	30-30	Fixed	30	*	*	6	*	Europe	Single center	Other/Unc lear	Other/Unclea r	Yes	Unclear
				amitriptyline	No	8	41.8 (11.7)	0.75	150-150	Fixed	150	*	*								
PAR 29060.316 (HP/82/47A)	unpublis hed	2	2	paroxetine	Yes	9	47.2 (14.8)	0.78	30-30	Fixed	30	*	*	7	RDC	Europe	Multi- center	Secondary /Tertiary care	Inpatients only	Yes	Unclear
				amitriptyline	No	8	41 (11.7)	1.00	150-150	Fixed	150	*	*								
PAR 29060.318 (HP/82/64A)	unpublis hed	2	2	paroxetine	Yes	9	47.3 (10.1)	1.00	30-30	Fixed	30	*	*	7	*	Europe	Single center	Secondary Tertiary care	Inpatients only	Yes	Unclear
				amitriptyline	No	12	50.1 (8.2)	1.00	150-150	Fixed	150	*	*								
PAR 29060/281	unpublis hed	2	2	paroxetine	Yes	82	39.5 (13.1)	0.78	30-30	Fixed	30	HAMD 21	27.80	6	Feighne r	Europe	Single center	Primary care	Other/Unclea r	Yes	Unclear
				amitriptyline	No	80	38.1 (13.1)	0.75	75-150	Flexible	*	HAMD 21	26.60								
PAR MDUK 032	unpublis hed	2	2	paroxetine	Yes	29	42.6 (11.7)	*	20-30	Flexible	*	HAMD 17	24.00	6	DSM-III	*	Multi- center	Primary care	Outpatients only	Unclear	Unclear
				amitriptyline	No	30	46.2 (11.8)	*	100-150	Flexible	*	HAMD 17	23.20								
Patris 1996 (Study 91301 - FDA)	1996	2	2	fluoxetine	No	184	43 (*)	*	20-20	Fixed	20	MADRS	29.40	8	DSM- III-R	Europe	Multi- center	Primary care	Outpatients only	Yes	Unclear
				citalopram	Yes	173	44 (*)	*	20-20	Fixed	20	MADRS	29.70								
Pelicier 1993 (PAR MDED/29060/II I/86/1728M291 )	1993	2	2	clomipramin e	No	42	70.2 (8.9)		60-60	Fixed	60	MADRS	30.00	5	Feighne r	Europe	Multi- center	Other/Unc lear	Outpatients only	Unclear	Unclear
				paroxetine	Yes	41	71.1 (8)		20-20	Fixed	20	MADRS	29.50								
Perahia 2008a (HMBU) (NCT00071695)	2008	2	2	duloxetine	Yes	166	45.42 (13)	0.72	60-60	Fixed	60	HAMD 17	23.10	6	DSM-IV	Cross- Continental	Multi- center	Other/Unc lear	Outpatients only	Unclear	Unclear
				venlafaxine	No	166	42.62 (13.1)	0.69	150-150	Fixed	150	HAMD 17	23.10								
Perahia 2008b (HMCQ, NCT00067912)	2008	3	3	duloxetine	Yes	164	43.07 (12.6)	0.67	60-60	Fixed	60	HAMD 17	22.21	6	DSM-IV	Cross- Continental	Multi- center	Other/Unc lear	Outpatients only	Unclear	Unclear
				venlafaxine	No	169	42.46 (12.4)	0.68	75-75	Fixed	75	HAMD 17	22.51								
				venlafaxine	No	171	40.64 (11.4)	0.62	150-150	Fixed	150	HAMD 17	22.24								
Preskorn 1991	1991	2	2	fluoxetine	Yes	30	*	*	20-60	Flexible	*	HAMD unspecified	23.8	6	DSM-III	North America	Multi- center	Other/Unc lear	Outpatients only	Yes	Yes
				amitriptyline	No	31	*	*	50-200	Flexible	*	HAMD unspecified	23.5								
Quera-Salva 2010 (CL3- 20098-056)	2010	2	2	agomelatine	Yes	71	41.3 (12.4)	*	25-50	Flexible	*	HAMD 17	26.10	25	DSM-IV	Cross- Continental	Multi- center	Primary care	Outpatients only	No	No
				escitalopram	No	67	41.4 (10.7)	*	10-20	Flexible	*	HAMD 17	26.10								

Rapaport 1996	1996	2	2	fluvoxamine	Yes	51	40 (*)	*	100-150	Flexible	102	HAMD 21	25.20	7	DSM-III-R	North America	Multi-center	Other/Unclear	Outpatients only	Yes	Yes
				fluoxetine	No	49	38.6 (*)	*	20-80	Flexible	34	HAMD 21	25.60								
Ravindran 1997 (MY-1055/BRL-029060/1/CPMS-245 PAR 245)	1997	2	2	paroxetine	Yes	513	43.3 (13)	0.73	20-40	Flexible	*	MADRS	29.7	12	Other operationalized	Cross-Continental	Multi-center	Primary care	Other/Unclear	Yes	Yes
				clomipramine	No	506	42 (12.5)	0.73	75-150	Flexible	*	MADRS	29.1								
Remick 1994	1994	2	2	amitriptyline	No	17	41 (*)	*	50-300	Flexible	135	HAMD 17	23.50	7	DSM-III	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Unclear
				fluvoxamine	Yes	16	41.7 (*)	*	50-300	Flexible	175	HAMD 17	23.80								
Ropert 1989	1989	2	2	fluoxetine	Unclear	71	42.7 (11)	0.60	20-20	Fixed	20	HAMD 21	23.00	6	DSM-III	Europe	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear
				clomipramine	No	72	44.8 (12.6)	0.69	75-75	Fixed	75	HAMD 21	23.00								
Rossini 2005	2005	2	2	fluvoxamine	Unclear	40	67.8 (*)	*	200-200	Fixed	200	HAMD 21	31.23	7	DSM-IV	Europe	Single center	Secondary/Tertiary care	Inpatients only	Unclear	Yes
				sertraline	Unclear	48	68.2 (*)	*	150-150	Fixed	150	HAMD 21	29.23								
Rouillon 1991 (Limosin 2006, 029060/1/CPMS 069 1991)	1991	2	2	paroxetine	Yes	45	71.8 (7.4)	0.87	20-50	Other/Unclear	*	HAMD 21	27	6	DSM-III	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Unclear	Unclear
				clomipramine	No	47	70.8 (6.5)	0.91	50-150	Other/Unclear	*	HAMD 21	27.6								
Samuelian 1998	1998	2	2	venlafaxine	Yes	52	47 (12)	*	100-150	Flexible	105	HAMD 21	27.80	6	DSM-III-R	Europe	Multi-center	Other/Unclear	Outpatients only	Yes	Yes
				clomipramine	No	50	47 (11)	*	100-150	Flexible	105	HAMD 21	27.80								
Sauer 2003	2003	2	2	venlafaxine	Yes	79	48.5 (10.8)	*	75-150	Flexible	85	HAMD 21	23.60	6	ICD-10	Europe	Multi-center	Both	Outpatients only	Unclear	No
				amitriptyline	No	77	46 (10.9)	*	75-150	Flexible	84	HAMD 21	23.64								
Schatzberg 2002 (003-901)	2002	2	2	mirtazapine	Yes	128	71.7 (5.7)	*	15-45	Flexible	34	HAMD 17	22.20	8	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Unclear	Yes
				paroxetine	No	126	72 (5.1)	*	20-40	Flexible	34	HAMD 17	22.40								
Schoene 1993 (Geretsegger 1994 MY1021/BRC)	1993	2	2	paroxetine	Yes	54	74.3 (6)	*	20-50	Flexible	*	HAMD 21	29.00	6	DSM-III-R	Europe	Multi-center	Other/Unclear	Outpatients only	Yes	Unclear
				fluoxetine	No	52	73.7 (6.4)	*	20-80	Flexible	*	HAMD 21	27.90								
Schwartz 2002 (iQWIG)	2002	2	2	reboxetine	Unclear	80	41.9 (*)	0.71	8-10	Flexible	*	HAMD 17	28.60	8	DSM-IV	Cross-Continental	Multi-center	Other/Unclear	Other/Unclear	Unclear	Unclear
				venlafaxine	Unclear	87	42.2 (*)	0.67	225-375	Flexible	*	HAMD 17	28.80								

SCT-MD-09	unpublis hed	2	2	escitalopram	Yes	16	35.9 (10.6)	*	10-20	Fixed	*	*	*	5	DSM-IV	North America	Single center	Other/Unc lear	Outpatients only	Unclear	Unclear	
				fluoxetine	No	14	41.4 (9.8)	*	20-40	Fixed	*	*	*									
Sechter 1999	1999	2	2	sertraline	Yes	118	43.4 (12.3)	*	50-150	Flexible	77	HAMD 17	24.50	8	DSM- III-R	Europe	Multi- center	Secondary /Tertiary care	Outpatients only	No	Unclear	
				fluoxetine	No	120	42.5 (11.1)	*	20-60	Flexible	34	HAMD 17	24.90									
Sechter 2004	2004	2	2	milnacipran	Yes	149	44.8 (11.6)	*	100-100	Fixed	100	HAMD 17	23.70	6	DSM-IV	Europe	Multi- center	Secondary /Tertiary care	Outpatients only	Unclear	Unclear	
				paroxetine	No	153	42.8 (11.2)	*	20-20	Fixed	20	HAMD 17	23.40									
SER-CHN-1	unpublis hed	2	2	paroxetine	Yes	113	40.14 (13.2)	0.55	20-30	Flexible	*	HAMD unspecified	27.10	6	DSM- III-R	Asia	Multi- center	Other/Unc lear	Other/Unclea r	Unclear	Unclear	
				amitriptyline	No	118	40.54 (13.45 )	0.53	150-150	Fixed	150	HAMD unspecified	26.60									
Shelton 2006 (NCT00179283)	2006	2	2	venlafaxine	Unclear	78	37.2 (11.6)	*	75-225	Flexible	*	HAMD 17	22.40	8	DSM-IV	North America	Multi- center	Secondary /Tertiary care	Outpatients only	Unclear	No	
				sertraline	Yes	82	41.2 (12)	*	50-150	Flexible	*	HAMD 17	22.10									
Shu 2014 (CL3- 20098-052, ChiCTR-TRC- 11001668)	2014	2	2	agomelatine	Yes	314	39.2 (12.8)	0.68	25-50	Flexible	*	HAMD 17	26.80	8	DSM-IV	Asia	Multi- center	Primary care	Outpatients only	No	No	
				fluoxetine	No	314	38.9 (12.6)	0.71	20-40	Flexible	*	HAMD 17	26.80									
Sir 2005	2005	2	2	venlafaxine	No	84	36.8 (12.4)	*	75-225	Flexible	161	HAMD 17	23.50	8	DSM-IV	Cross- Continental	Multi- center	Secondary /Tertiary care	Outpatients only	Unclear	Unclear	
				sertraline	Yes	79	37.3 (13.5)	*	50-150	Flexible	105	HAMD 17	23.40									
Smeraldi 1998	1998	3	3	venlafaxine	Unclear	55	71 (6)	*	75-150	Flexible	*	*	*	6	DSM- III-R	Europe	Multi- center	Other/Unc lear	Both	Yes	Unclear	
				clomipramin e	Unclear	58	71 (6)	*	50-100	Flexible	*	*	*									
				trazodone	Unclear	57	71 (6)	*	150-300	Flexible	*	*	*									
Staner 1995 (063)	1995	2	2	paroxetine	Yes	21	41.7 (10.8)	*	30-30	Fixed	30	HAMD 21	26.00	5	RDC	Europe	Single center	Secondary /Tertiary care	Inpatients only	Yes	Yes	
				amitriptyline	No	19	42.5 (11.7)	*	150-150	Fixed	150	HAMD 21	24.00									
Studie032 (M2020/0032)	unpublis hed	2	2	reboxetine	Yes	43	40.65 (14.6)	0.63	8-10	Flexible	8	HAMD 21	27.23	8	DSM-IV	Asia	Multi- center	Secondary /Tertiary care	Both	Yes	Yes	
				fluoxetine	No	42	35.98 (12.7)	0.62	20-40	Flexible	27	HAMD 21	28.33									
Study 043	2006	2	2	reboxetine	Yes	183	42.8 (13.3)	0.69	8-10	Flexible	9	HAMD 21	27.40	24	DSM-IV	Europe	Multi- center	Other/Unc lear	Outpatients only	Unclear	Yes	

				citalopram	No	176	41.5 (12)	0.60	20-40	Flexible	28	HAMD 21	27.40								
Szegedi 2006	2006	2	2	mirtazapine	Yes	130	*	*	45-45	Fixed	45	HAMD 17	24.60	6	DSM-IV	Europe	Multi-center	Other/Unclear	Outpatients only	No	Unclear
				venlafaxine	No	128	*	*	225-225	Fixed	225	HAMD 17	24.90								
Thase 2006 (WELL 100368)	2006	2	2	bupropion	Yes	171	37.1 (12.3)	*	150-450	Flexible	300	HAMD 17	24.90	12	DSM-IV	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Unclear
				venlafaxine	No	177	37.4 (11.6)	*	75-225	Flexible	150	HAMD 17	24.10								
Tignol 1993 (29060/087)	1993	2	2	paroxetine	Yes	89	43 (11.6)	*	20-20	Fixed	20	MADRS	30.74	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Unclear
				fluoxetine	No	87	45 (13.2)	*	20-20	Fixed	20	MADRS	31.60								
Timmerman 1993 (Study 89422 - FDA and Haffmans 1996)	1993	2	2	fluvoxamine	No	109	*	*	100-200	Flexible	*	HAMD 17	24.50	6	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Yes
				citalopram	Yes	108	*	*	20-40	Flexible	*	HAMD 17	24.70								
Tsutsui 2000	2000	2	2	paroxetine	Yes	116	39.1 (13.9)	*	10-40	Flexible	32	HAMD 17	23.60	6	DSM-IV	Asia	Multi-center	Both	Both	No	Yes
				trazodone	No	109	38.5 (12.7)	*	75-200	Flexible	154	HAMD 17	24.40								
Tylee 1997	1997	2	2	fluoxetine	No	170	45.5 (14.3)	0.75	20-20	Fixed	20	HAMD 17	22.50	12	DSM-IV	Europe	Multi-center	Primary care	Outpatients only	Unclear	Unclear
				venlafaxine	Yes	171	43.5 (14)	0.68	75-75	Fixed	75	HAMD 17	22.40								
Tzanakaki 2000	2000	2	2	fluoxetine	No	54	49 (10)	*	20-60	Flexible	*	HAMD 21	27.10	6	DSM-IV	Europe	Multi-center	Secondary/Tertiary care	Both	Yes	Unclear
				venlafaxine	Yes	55	47 (11)	*	75-225	Flexible	*	HAMD 21	27.80								
Upward 1988	1988	2	2	fluoxetine	Yes	13	40 (10.6)	0.55	60-80	Flexible	75	*	*	4	*	Europe	Unclear	Other/Unclear	Outpatients only	Yes	Yes
				amitriptyline	No	14	45 (13.2)	0.58	150-200	Flexible	183	*	*								
VanMoffaert 1995a	1995	2	2	sertraline	Yes	83	46.1 (*)	*	50-100	Flexible	*	HAMD 17	24.50	8	DSM-III-R	Europe	Multi-center	Secondary/Tertiary care	Other/Unclear	Yes	Yes
				fluoxetine	No	82	48.4 (*)	*	20-40	Flexible	*	HAMD 17	23.20								
VanMoffaert 1995b	1995	2	2	mirtazapine	Yes	100	46.1 (10.8)	0.69	24-72	Flexible	*	HAMD 17	29.2	6	DSM-III	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Unclear	Yes
				trazodone	No	100	46.3 (12.6)	0.71	150-450	Flexible	*	HAMD 17	27.5								
Ventura 2007 (SCT-MD-18)	2007	2	2	escitalopram	Yes	107	40.6 (13.7)	*	10-10	Fixed	10	HAMD 24	26.80	8	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear
				sertraline	No	108	38.1 (11.5)	*	50-200	Flexible	*	HAMD 24	26.80								

Versiani 1999	1999	2	2	fluoxetine	Yes	77	41.3 (*)	0.76	20-20	Fixed	20	HAMD 21	28.40	8	DSM-IV	South America	Multi-center	Other/Unclear	Other/Unclear	Yes	No
				amitriptyline	No	80	41.3 (*)	0.76	50-250	Flexible	138	HAMD 21	27.80								
Versiani 2005	2005	2	2	mirtazapine	Yes	145	43 (*)	*	15-60	Flexible	*	HAMD 17	29.00	8	DSM-IV	Cross-Continental	Multi-center	Other/Unclear	Other/Unclear	Yes	No
				fluoxetine	No	149	47 (*)	*	20-40	Flexible	*	HAMD 17	28.00								
Wade 2003 (E-1721)	2003	2	2	mirtazapine	Yes	99	40 (14.3)	*	15-45	Flexible	35	HAMD 17	23.80	12	DSM-IV	Europe	Multi-center	Primary care	Outpatients only	No	No
				paroxetine	No	98	40 (11.7)	*	10-30	Flexible	24	HAMD 17	24.40								
Wade 2007 (Study 10990)	2007	2	2	escitalopram	Yes	144	43.3 (11.6)	*	20-20	Fixed	20	HAMD 17	22.70	8	DSM-IV	Cross-Continental	Multi-center	Primary care	Outpatients only	No	Unclear
				duloxetine	No	151	44.5 (11)	*	60-60	Fixed	60	HAMD 17	22.70								
Wang 2015 (NCT01571453, KCT0000432, 13926A)	2015	2	2	vortioxetine	Yes	213	39.6 (12.4)	0.58	10-10	Fixed	10	MADRS	32.30	8	DSM-IV	Asia	Multi-center	Secondary/Tertiary care	Both	Unclear	Yes
				venlafaxine	No	230	40.7 (12.3)	0.62	150-150	Fixed	150	MADRS	32.30								
Weisler 1994	1994	2	2	bupropion	Yes	63	40.2 (*)	*	225-450	Flexible	345	HAMD 21	25.80	6	DSM-III-R	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Unclear
				trazodone	No	61	40.8 (*)	*	150-400	Flexible	207	HAMD 21	24.90								
WELL AK140016	unpublished	2	2	bupropion	Yes	69	37.6 (10.6)	*	300-300	Fixed	300	HAMD 17	21.90	8	DSM-IV	North America	Multi-center	Other/Unclear	Other/Unclear	Unclear	Unclear
				paroxetine	No	71	37 (10.8)	*	20-20	Fixed	20	HAMD 17	22.30								
Wheatley 1998	1998	2	2	mirtazapine	Yes	66	47.2 (15.3)	*	15-60	Flexible	40	HAMD 17	26.00	6	DSM-III	Europe	Multi-center	Other/Unclear	Both	Yes	No
				fluoxetine	No	67	47.5 (14.8)	*	20-40	Flexible	24	HAMD 17	26.10								
Winokur 2003	2003	2	2	mirtazapine	Yes	8	40.9 (*)	*	15-45	Flexible	*	HAMD 21	25.60	8	DSM-IV	North America	Unclear	Other/Unclear	Other/Unclear	No	No
				fluoxetine	No	12	43.5 (*)	*	20-40	Flexible	*	HAMD 21	26.70								
Yang 2003	2003	2	2	milnacipran	Yes	27	43.5 (10.4)	*	50-100	Flexible	*	HAMD 17	25.20	6	DSM-IV	Asia	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Unclear
				sertraline	No	26	42 (8.9)	*	50-100	Flexible	*	HAMD 17	23.20								
Yevtushenko 2007	2007	2	3	escitalopram	Yes	109	35.2 (6.5)	0.61	10-10	Fixed	10	MADRS	25.67	6	DSM-IV	Europe	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Yes
				citalopram	No	110	35.1 (6.5)	0.56	20-20	Fixed	20	MADRS	35.70								
Young 1987	1987	2	2	fluoxetine	Unclear	32	46.1 (*)	0.68	40-80	Flexible	73	HAMD unspecified	44.00	6	RDC	Europe	Unclear	Secondary/Tertiary care	Outpatients only	Unclear	Yes
				amitriptyline	Unclear	32	46.6 (*)	0.68	50-150	Flexible	122	HAMD unspecified	48.10								

Zivkov 1995 (Organon 85146, FDA85146)	1997	2	2	mirtazapine	Yes	103	48.5 (10.6)	*	*	Other/U nclear	*	HAMD 17	27.30	6	DSM-III	North America	Multi- center	Other/Unc lear	Other/Unclea r	Unclear	Unclear
				amitriptyline	No	104	47.7 (12.4)	*	*	Other/U nclear	*	HAMD 17	26.20								
0600A-654	unpublis hed	2	2	venlafaxine	Yes	131	*	*	*-150	Flexible	*	MADRS	*	12	DSM-IV	*	Unclear	Other/Unc lear	Other/Unclea r	Unclear	Unclear
				fluoxetine	No	135	*	*	*-40	Flexible	*	MADRS	*								
29060/356	unpublis hed	2	2	paroxetine	Yes	68	42.2 (1.5)	*	20-20	Fixed	20	HAMD 17	24.60	8	DSM- III-R	Australia	Multi- center	Other/Unc lear	Both	Unclear	Unclear
				fluoxetine	No	70	40.6 (1.5)	*	20-20	Fixed	20	HAMD 17	23.80								



## 5 Risk of bias table of included studies

*eTable 2. Risk of bias table of included studies.*

StudyID	Sequence_generation	Allocation_concealment	Blinding_participant	Blinding_therapist	Blinding_assessor	Selective_reporting_bias	Attrition_bias
1. Aberg-Wisted 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias
2. Aguglia 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	High risk of bias
3. Allard 2004	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias
4. Altamura 1989b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
5. Alves 1999	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
6. Amini 2005	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
7. Andersen 1986	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
8. Anseau 1989a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
9. Anseau 1989b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
10. Anseau 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
11. Anseau 1994a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
12. Anseau 1994b	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
13. Armitage 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
14. Baldwin 1996	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
15. Baldwin 2006a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
16. Baldwin 2006b	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
17. Battegay 1985	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
18. Beasley 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
19. Behnke 2003	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
20. Benkert 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
21. Benkert 2006	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
22. Bennie 1995	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
23. Berlanga 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
24. Bersani 1994	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
25. Bielski 2004	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
26. Bignamini 1992	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias

27.	Blacker 1988	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
28.	Bosc 1997b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
29.	Bougerol 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
30.	Boulenger 2006	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
31.	Caligiuri 2003	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
32.	Casabona 2002	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
33.	Cassano 2002	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias
34.	Chang 2015	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias
35.	Chouinard 1983a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
36.	Chouinard 1985	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
37.	Chouinard 1999	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
38.	Christiansen 1996	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
39.	CL3-20098-036	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
40.	CL3-20098-048	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
41.	CL3-20098-062	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
42.	Clerc 1994	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
43.	Clerc 2001	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
44.	Cohn1990	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
45.	Colonna 2005	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
46.	Corruble 2013	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
47.	Costaesilva 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
48.	Dalery 2003	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
49.	Debonnel 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	High risk of bias
50.	Debus 1988	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
51.	Demyttenaere 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
52.	DeRonchi 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
53.	Deushle 2003	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	High risk of bias
54.	DeWilde 1983a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
55.	DeWilde 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
56.	Dierick 1996	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias

57.	DUAG 1990	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
58.	E-1569	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
59.	Ekselius 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias
60.	Falk 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
61.	Fava 2002	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
62.	Fawcett 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
63.	Feiger 1996	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
64.	Feighner 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
65.	Fudge 1990	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
66.	Gagiano 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
67.	Gentil 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
68.	Geretsegger 1995	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
69.	Gillin 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
70.	Ginestet 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
71.	Guelfi 1998	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
72.	Guillibert 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
73.	Hackett 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
74.	Hale 2010	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
75.	Hao 2014	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias
76.	Harris 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
77.	Heller 2009	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
78.	Hicks 2002	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
79.	Hong 2003	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
80.	Hosseini 2015	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
81.	Hsu 2011	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
82.	Hu 2009	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
83.	Hutchinson 1992	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
84.	Jiang 2009	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
85.	Judd 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
86.	Kamijima 2013	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias

87.	Kasper 2005b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
88.	Keegan 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
89.	Keller 2007	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias
90.	Kennedy 2005	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
91.	Kerkhofs 1990	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
92.	Khan 2007	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
93.	Kiev 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
94.	Kuhs 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
95.	Laakman 1988	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
96.	Lalit 2004	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
97.	Lapierre 1980	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Low risk of bias
98.	Lee 2007	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
99.	Leinonen 1997	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
100.	Leinonen 1999	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
101.	Lemoine 2007	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
102.	Lepine 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
103.	Li 2006	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
104.	Li 2010	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
105.	Lv 2013	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
106.	Manna 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
107.	Mao 2008	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
108.	Marchesi 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
109.	McPartlin 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
110.	MDF/29060/III/070/88/ MC	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
111.	Mehtonen 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
112.	Miura 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
113.	Moller 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
114.	Moller 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
115.	Moller 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
116.	Montgomery 2004a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias

117.	Montgomery 2004b	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
118.	Moon 1994	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
119.	Moore 2005	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
120.	Munizza 2006	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
121.	Murasaki 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
122.	Murasaki 2010a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
123.	Murasaki 2010b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
124.	Nemeroff 1995	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
125.	Newhouse 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
126.	Noguera 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
127.	Ontiveros 1994	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
128.	OntiverosSanchez 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
129.	Ottevanger 1995	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
130.	Ou 2010	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
131.	PAR 29060.308	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
132.	PAR 29060.310	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
133.	PAR 29060.314	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
134.	PAR 29060.316	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
135.	PAR 29060.318	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
136.	PAR 29060/281	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
137.	PAR MDUK 032	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
138.	Patris 1996	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
139.	Pelicier 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
140.	Perahia 2008a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
141.	Perahia 2008b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
142.	Preskorn 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
143.	Quera-Salva 2010	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
144.	Rapaport 1996	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
145.	Ravindran 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
146.	Remick 1994	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias

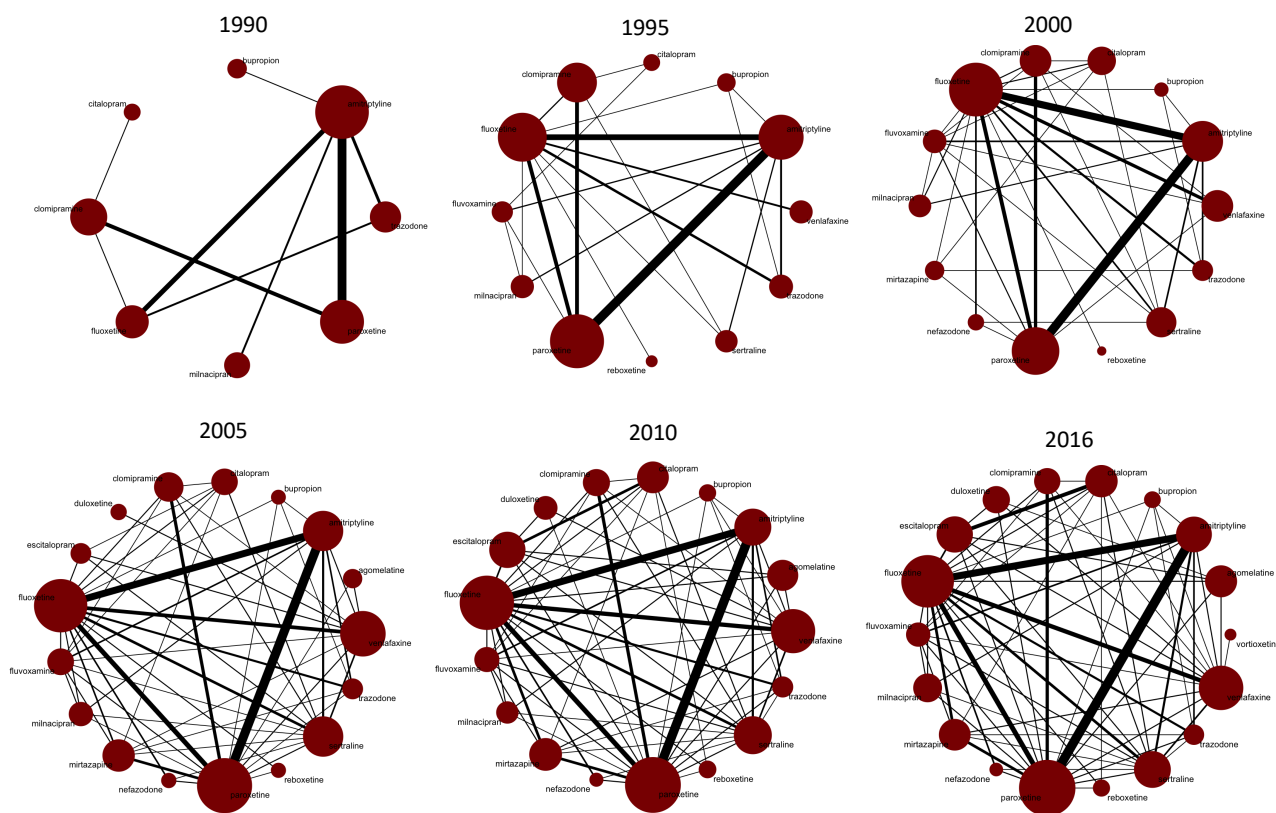
147.	Roport 1989	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
148.	Rossini 2005	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
149.	Rouillon 1991	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
150.	Samuelian 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
151.	Sauer 2003	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
152.	Schatzberg 2002	Low risk of bias	Unclear risk of bias	Low risk of bias	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
153.	Schoene 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
154.	Schwartz 2002	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
155.	SCT-MD-09	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
156.	Sechter 1999	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
157.	Sechter 2004	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
158.	SER-CHN-1	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
159.	Shelton 2006	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
160.	Shu 2014	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
161.	Sir 2005	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
162.	Smeraldi 1998	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
163.	Staner 1995	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
164.	Studie032	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
165.	Study 043	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
166.	Szegedi 2006	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
167.	Thase 2006	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
168.	Tignol 1993	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
169.	Timmerman 1993	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
170.	Tsutsui 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
171.	Tylee 1997	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
172.	Tzanakaki 2000	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
173.	Upward 1988	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
174.	vanMoffaert 1995a	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
175.	vanMoffaert 1995b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
176.	Ventura 2007	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias

177.	<b>Versiani 1999</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Low risk of bias
178.	<b>Versiani 2005</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
179.	<b>Wade 2003</b>	Unclear risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias
180.	<b>Wade 2007</b>	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
181.	<b>Wang 2015</b>	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
182.	<b>Weisler 1994</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
183.	<b>WELL AK140016</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
184.	<b>Wheatley 1998</b>	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Unclear risk of bias
185.	<b>Winokur 2003</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	Low risk of bias
186.	<b>Yang 2003</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
187.	<b>Yevtushenko 2007</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias
188.	<b>Young 1987</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
189.	<b>Zivkov 1995</b>	Low risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
190.	<b>0600A-654</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Unclear risk of bias	High risk of bias
191.	<b>29060/356</b>	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias



## 6 Results of network meta-analysis

### 6.1 Network diagrams for acceptability

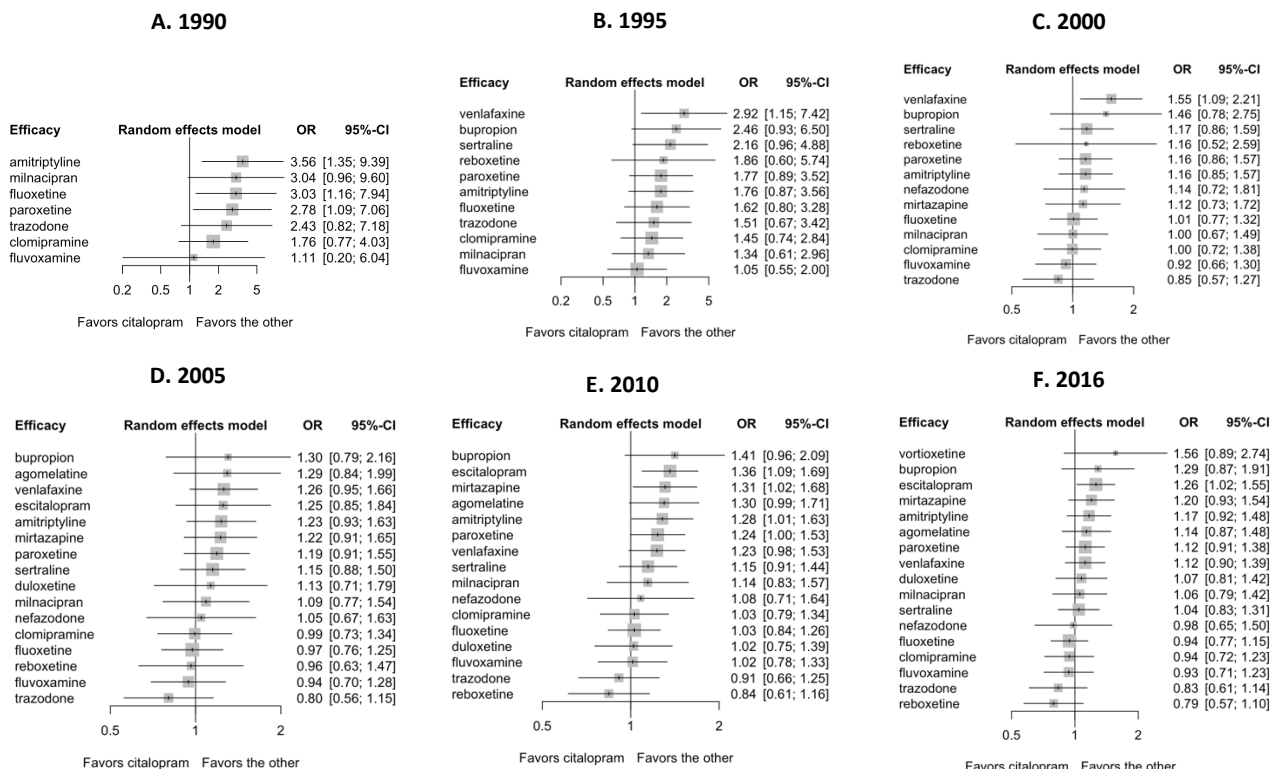


**Figure 2. Network diagrams for acceptability from 1990 to 2016.** Width of the lines is proportionate to the number of studies including that comparison. Size of nodes is proportionate to the number of randomized patients for that arm.



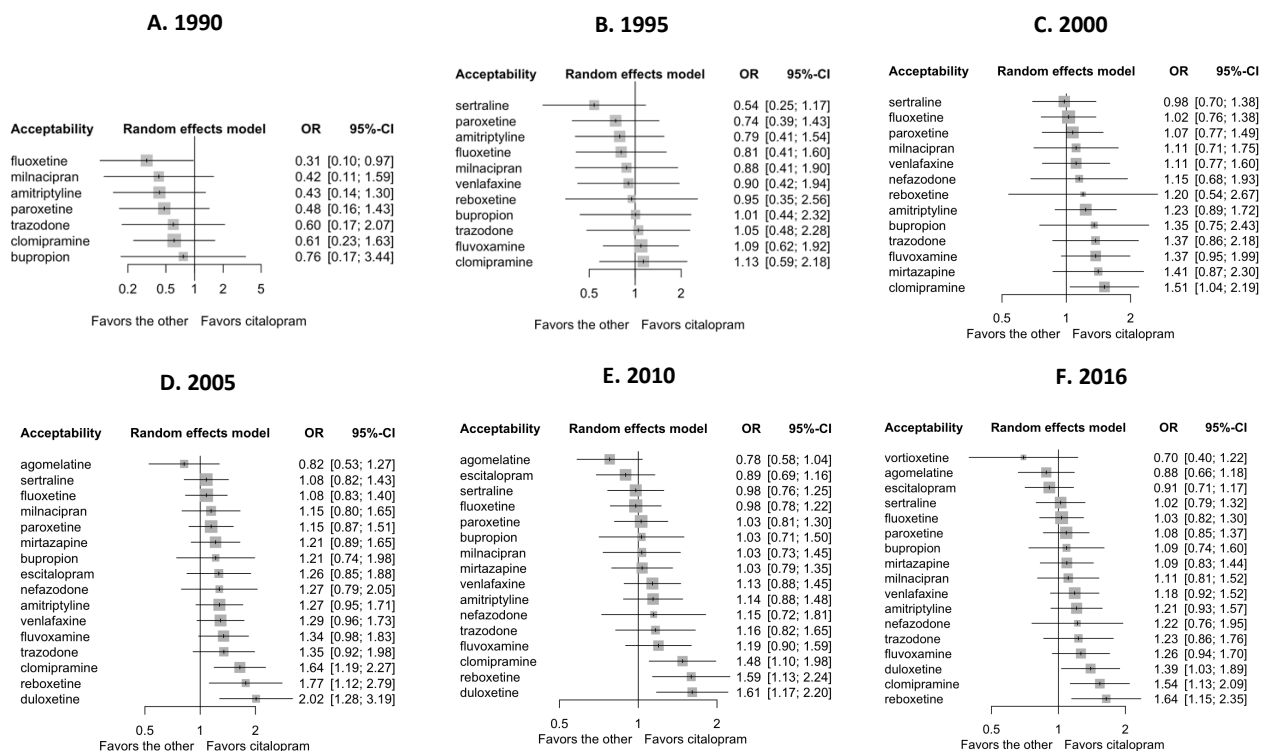
## 6.2 Forest plots

### 6.2.1 Efficacy



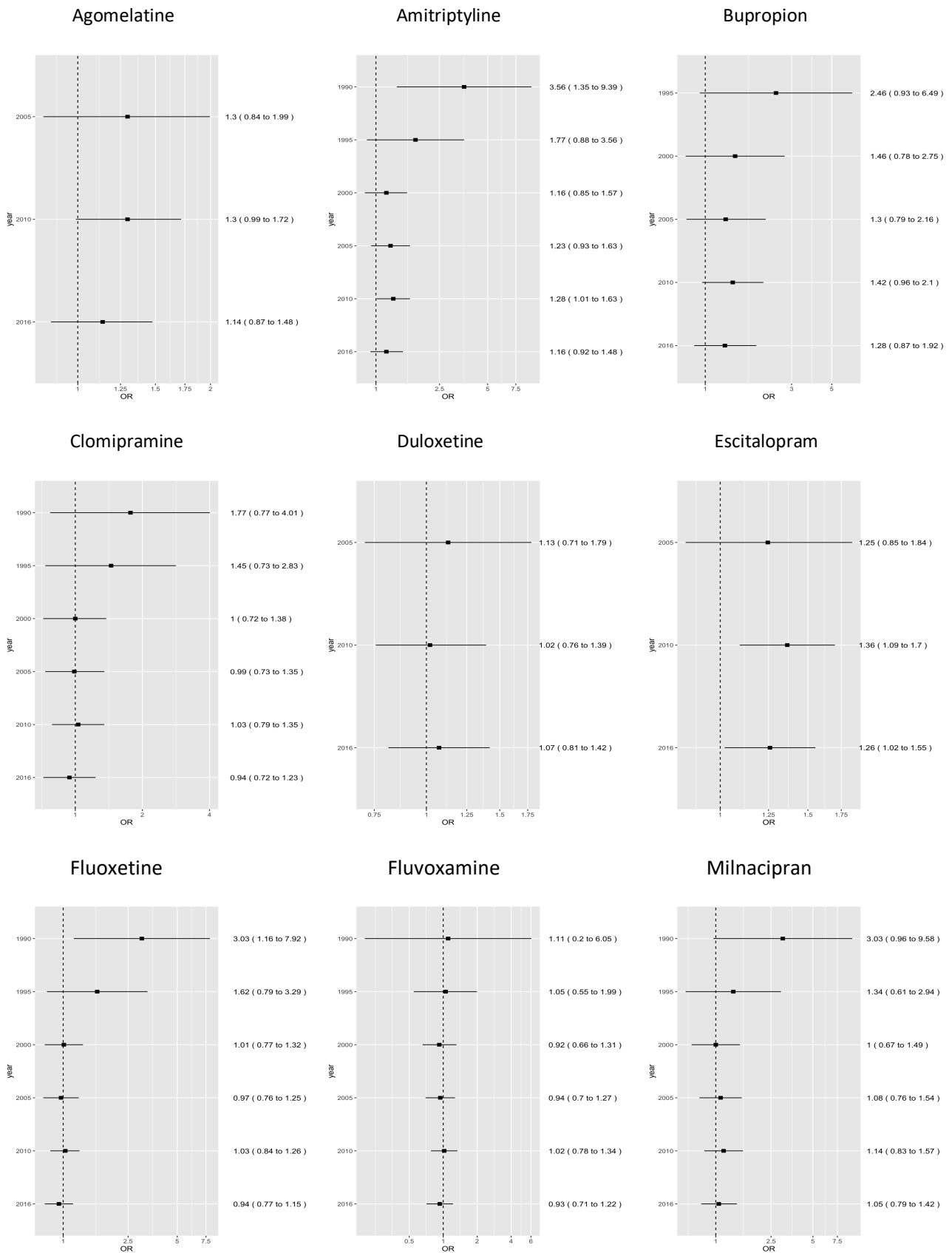
**eFigure 3. Forest plots for efficacy from 1990 to 2016**

### 6.2.2 Acceptability

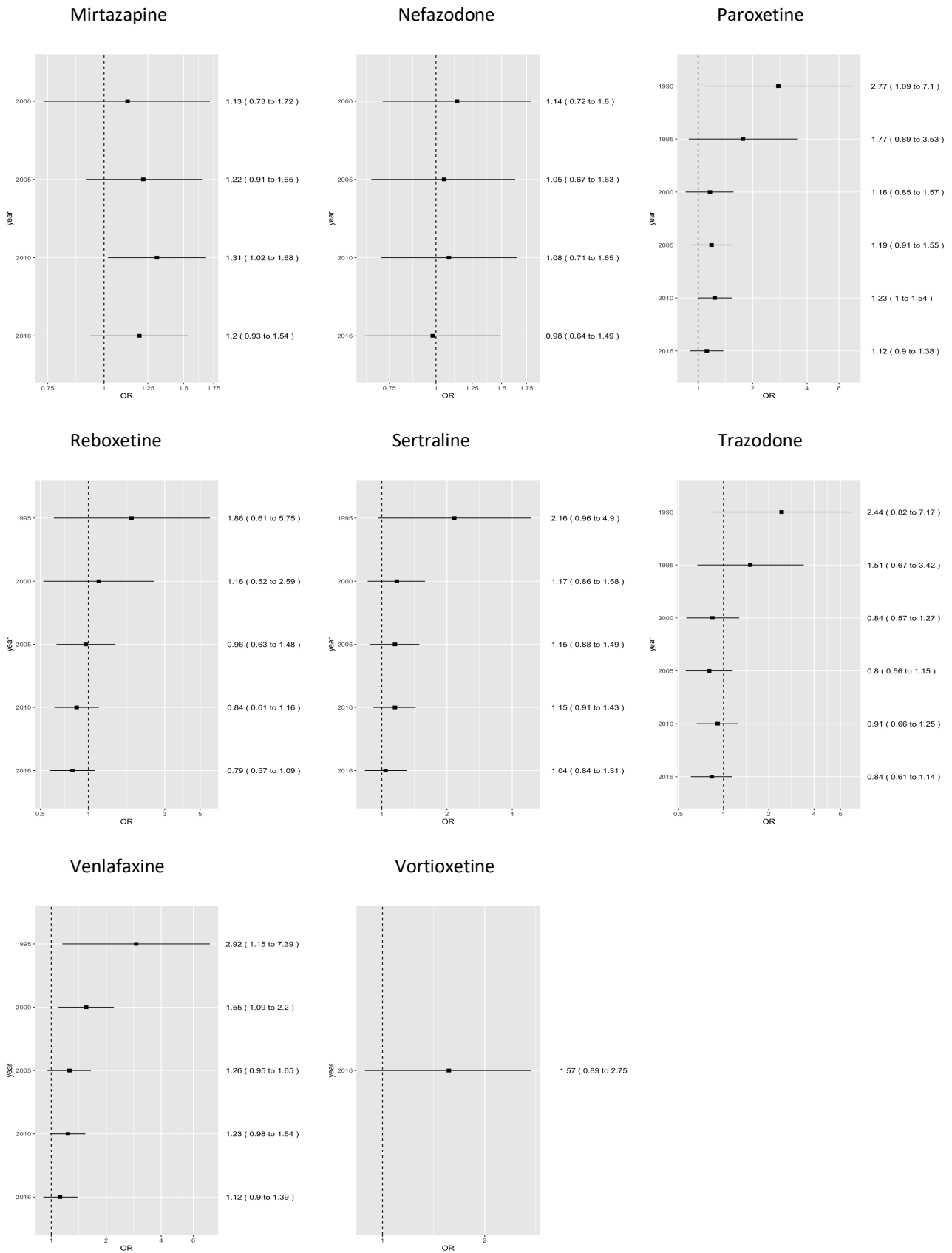


**eFigure 4. Forest plots for acceptability from 1990 to 2016**

### 6.3 Cumulative forest plots over the years for each drug in efficacy



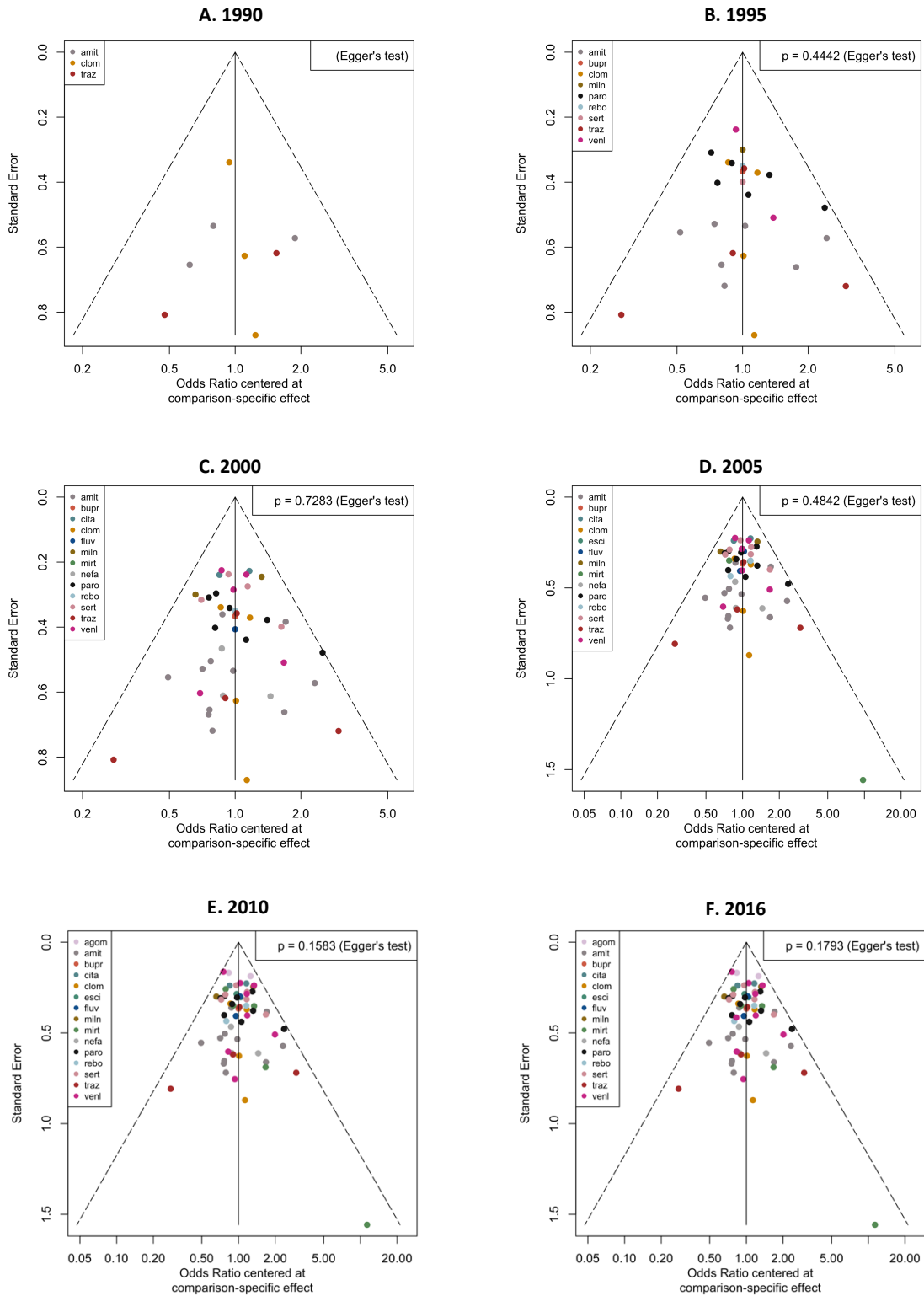
**eFigure 5. Cumulative forest plots for each drug in efficacy over the years (compared with citalopram) (to be cont'd).**



***eFigure 5 (cont'd). Cumulative forest plots for each drug in efficacy over the years (compared with citalopram).***

## 6.4 Comparison-adjusted funnel plots

### 6.4.1 Efficacy

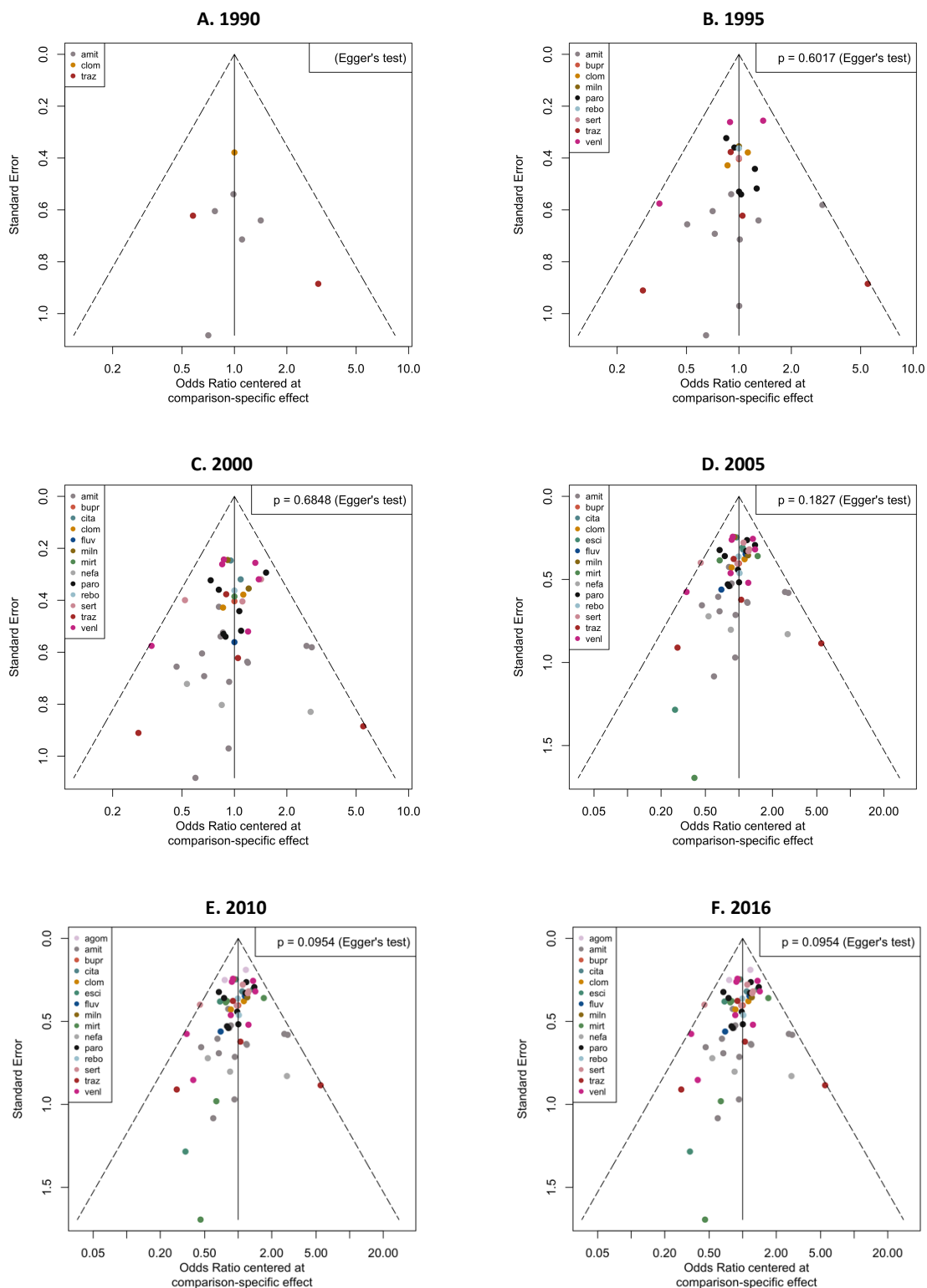


Egger's test for asymmetry:  $p=0.15$

Egger's test for asymmetry:  $p=0.18$

**eFigure 6. Funnel plots for efficacy from 1990 to 2016 (all the comparisons with fluoxetine).**

### 6.4.2 Acceptability



**Figure 7. Funnel plots for acceptability from 1990 to 2016 (all the comparisons with fluoxetine).**

## 7 Quality of evidence (GRADE) tables based on CINeMA

### 7.1 Efficacy

(1) 1990.

*eTable 3. CINeMA assessment for efficacy in 1990.*

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amitriptyline: fluoxetine	4	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: paroxetine	6	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: trazodone	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: fluoxetine	3	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Clomipramine: fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: paroxetine	4	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Fluoxetine: trazodone	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: citalopram	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: fluoxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram: fluvoxamine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: milnacipran	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: paroxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: paroxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(2) 1995

*eTable 4. CINeMA assessment for efficacy in 1995.*

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amitriptyline: fluoxetine	8	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: fluvoxamine	2	Some concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Very low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: paroxetine	11	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: sertraline	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: trazodone	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: fluoxetine	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	Very low
Clomipramine: fluvoxamine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: sertraline	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: milnacipran	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	6	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: reboxetine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: sertraline	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluvoxamine: milnacipran	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: paroxetine	1	Some concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Very low
Amitriptyline: bupropion	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: citalopram	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Bupropion: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: fluoxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: sertraline	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: venlafaxine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: venlafaxine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Fluoxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: sertraline	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: venlafaxine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Milnacipran: paroxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: sertraline	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Reboxetine: sertraline	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Sertraline: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Sertraline: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Trazodone: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low



(3) 2000

eTable 5. CINeMA assessment for efficacy in 2000.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amitriptyline: fluoxetine	12	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: paroxetine	12	Some concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Very low
Amitriptyline: sertraline	3	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: trazodone	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram: sertraline	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Clomipramine: fluoxetine	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Major concerns	Very low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: milnacipran	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: sertraline	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: venlafaxine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Fluoxetine: fluvoxamine	1	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: mirtazapine	1	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Moderate
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	7	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: reboxetine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: sertraline	4	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Low
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: venlafaxine	5	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine: milnacipran	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: sertraline	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Mirtazapine: paroxetine	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate

Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Nefazodone: paroxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: venlafaxine	1	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Trazodone: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: bupropion	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: venlafaxine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: venlafaxine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

Milnacipran: paroxetine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: sertraline	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Mirtazapine: sertraline	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Mirtazapine: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Nefazodone: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Reboxetine: sertraline	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Sertraline: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Sertraline: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate

(4) 2005

eTable 6. CINeMA assessment for efficacy in 2005.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Agomelatine: paroxetine	1	No concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
Agomelatine: venlafaxine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Very low
Amitriptyline: fluoxetine	12	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: paroxetine	13	No concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Low
Amitriptyline: sertraline	4	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: trazodone	2	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: venlafaxine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: paroxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: escitalopram	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: venlafaxine	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Clomipramine: fluoxetine	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Major concerns	Very low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: milnacipran	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: sertraline	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: venlafaxine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram: fluoxetine	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram: sertraline	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram: venlafaxine	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: mirtazapine	3	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate

Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	9	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluoxetine: reboxetine	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: sertraline	6	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: venlafaxine	6	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: mirtazapine	2	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: sertraline	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Milnacipran: paroxetine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: sertraline	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Mirtazapine: paroxetine	5	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: sertraline	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Mirtazapine: venlafaxine	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Nefazodone: paroxetine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Paroxetine: sertraline	2	Some concerns	Undetected	No concerns	No concerns	Major concerns	No concerns	Low
Paroxetine: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Paroxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Low
Reboxetine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Sertraline: venlafaxine	3	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Trazodone: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Agomelatine: amitriptyline	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: bupropion	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: citalopram	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Agomelatine: duloxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: escitalopram	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: fluoxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
Agomelatine: fluvoxamine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Agomelatine: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: mirtazapine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Agomelatine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Agomelatine: sertraline	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: trazodone	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: bupropion	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: duloxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: escitalopram	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Amitriptyline: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: duloxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: escitalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: duloxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: duloxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: escitalopram	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Duloxetine: escitalopram	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Duloxetine: fluoxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Duloxetine: milnacipran	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Duloxetine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Duloxetine: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram: fluvoxamine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram: mirtazapine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram: paroxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram: trazodone	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Nefazodone: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Reboxetine: sertraline	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Sertraline: trazodone	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low

(5) 2010

eTable 7. CINeMA assessment for efficacy in 2010.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Agomelatine: escitalopram	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: fluoxetine	2	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Agomelatine: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Amitriptyline: fluoxetine	12	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: paroxetine	13	No concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Low
Amitriptyline: sertraline	4	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: trazodone	2	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: venlafaxine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: paroxetine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: sertraline	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: venlafaxine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: escitalopram	7	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Citalopram: reboxetine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Low
Citalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: venlafaxine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Clomipramine: fluoxetine	4	Some concerns	Suspected	No concerns	No concerns	Major concerns	Major concerns	Very low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: milnacipran	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: sertraline	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine:trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: venlafaxine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: escitalopram	2	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Duloxetine: paroxetine	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate



Escitalopram: fluoxetine	2	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Escitalopram: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: mirtazapine	5	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	9	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine: reboxetine	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: sertraline	6	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Low
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: venlafaxine	8	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: mirtazapine	2	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: sertraline	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	Major concerns	Very low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Milnacipran: paroxetine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: sertraline	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: paroxetine	5	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: sertraline	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Mirtazapine: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Nefazodone: paroxetine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	1	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Paroxetine: sertraline	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine: trazodone	2	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Paroxetine: venlafaxine	2	Some concerns	Undetected	No concerns	No concerns	Major concerns	Major concerns	Very low
Reboxetine: venlafaxine	1	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Sertraline: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Sertraline: venlafaxine	3	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
Trazodone: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Agomelatine: amitriptyline	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: bupropion	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: citalopram	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High

Agomelatine:clomipramine	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: duloxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: fluvoxamine	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Agomelatine: mirtazapine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: nefazodone	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: reboxetine	0	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Agomelatine: sertraline	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: trazodone	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Amitriptyline: bupropion	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: duloxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: escitalopram	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: mirtazapine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: duloxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: escitalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Citalopram: duloxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: trazodone	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: duloxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: escitalopram	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine: fluoxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Duloxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Duloxetine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Duloxetine: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Duloxetine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine: sertraline	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Escitalopram: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: nefazodone	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Escitalopram: trazodone	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Nefazodone: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Reboxetine: sertraline	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(6) 2016

eTable 8. CINeMA assessment for efficacy in 2016.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Agomelatine: duloxetine	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: escitalopram	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Amitriptyline: fluoxetine	12	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: paroxetine	13	No concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Low
Amitriptyline: sertraline	4	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: trazodone	2	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: venlafaxine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: paroxetine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: sertraline	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: venlafaxine	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: escitalopram	10	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: reboxetine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: sertraline	3	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	Major concerns	Low
Clomipramine: fluoxetine	4	Some concerns	Suspected	No concerns	No concerns	Major concerns	Major concerns	Very low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: milnacipran	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: sertraline	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: venlafaxine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine: escitalopram	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine: paroxetine	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate

Duloxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: fluoxetine	2	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Escitalopram: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: mirtazapine	5	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	9	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine: reboxetine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: sertraline	6	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Major concerns	Low
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: venlafaxine	9	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Fluvoxamine: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: mirtazapine	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: sertraline	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	Major concerns	Very low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: paroxetine	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: sertraline	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: paroxetine	5	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: sertraline	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Mirtazapine: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Nefazodone: paroxetine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Paroxetine: sertraline	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine: trazodone	2	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Paroxetine: venlafaxine	2	Some concerns	Undetected	No concerns	No concerns	Major concerns	Major concerns	Very low
Reboxetine: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Sertraline: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	Very low
Sertraline: venlafaxine	3	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Trazodone: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Venlafaxine: vortioxetine	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: amitriptyline	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low

Agomelatine: bupropion	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: citalopram	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: clomipramine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Agomelatine: fluvoxamine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Agomelatine: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Agomelatine: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: nefazodone	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: reboxetine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Agomelatine: sertraline	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Agomelatine: trazodone	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: vortioxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Amitriptyline: bupropion	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: duloxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: escitalopram	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: mirtazapine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Amitriptyline: vortioxetine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: duloxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: escitalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: vortioxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: duloxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Citalopram: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Clomipramine: duloxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low

Clomipramine: escitalopram	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: vortioxetine	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine: fluoxetine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Duloxetine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Duloxetine: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Escitalopram: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Escitalopram: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Escitalopram: trazodone	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram: vortioxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: vortioxetine	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: trazodone	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: venlafaxine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: vortioxetine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Mirtazapine: vortioxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Nefazodone: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low



Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Reboxetine: sertraline	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: vortioxetine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Sertraline: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Trazodone: vortioxetine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate

## 7.2 Acceptability

(1) 1990

*eTable 9. CINeMA assessment for acceptability in 1990.*

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amitriptyline: bupropion	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: fluoxetine	5	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: paroxetine	9	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: trazodone	3	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: fluoxetine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: paroxetine	4	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: trazodone	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: citalopram	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: fluoxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low



Citalopram: fluoxetine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Citalopram: fluvoxamine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: paroxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: paroxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: paroxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(2) 1995

*eTable 10. CINeMA assessment for acceptability in 1995.*

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amitriptyline:bupropion	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline:fluoxetine	9	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	Very low
Amitriptyline:fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline:milnacipran	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline:paroxetine	14	Some concerns	Suspected	No concerns	Some concerns	No concerns	Major concerns	Very low
Amitriptyline:sertraline	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Amitriptyline:trazodone	3	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion:fluoxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion:trazodone	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram:clomipramine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:fluvoxamine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine:fluoxetine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine:fluvoxamine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine:paroxetine	6	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine:sertraline	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low

Fluoxetine:milnacipran	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine:paroxetine	6	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:reboxetine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine:sertraline	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine:trazodone	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine:venlafaxine	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine:milnacipran	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine:paroxetine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline:citalopram	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline:clomipramine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline:venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion:citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion:clomipramine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion:fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion:milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion:paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion:sertraline	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion:venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:fluoxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram:milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram:sertraline	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram:trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram:venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine:milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine:trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine:venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine:fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine:sertraline	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Fluvoxamine:trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine:venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran:paroxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

Milnacipran:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran:sertraline	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Milnacipran:trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran:venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine:reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine:sertraline	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine:trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Paroxetine:venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Reboxetine:sertraline	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine:trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine:venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Sertraline:trazodone	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Sertraline:venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Trazodone:venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(3) 2000

*eTable 11. CINeMA assessment for acceptability in 2000.*

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amitriptyline: bupropion	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: fluoxetine	13	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Major concerns	Very low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: mirtazapine	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Amitriptyline: paroxetine	16	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Amitriptyline: sertraline	3	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: trazodone	3	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: clomipramine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Low
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: sertraline	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Clomipramine: fluoxetine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: sertraline	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: fluvoxamine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: mirtazapine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	7	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Fluoxetine: reboxetine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluoxetine: sertraline	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: venlafaxine	6	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: milnacipran	1	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: sertraline	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Mirtazapine: paroxetine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: paroxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: venlafaxine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low

Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Citalopram: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Citalopram: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: paroxetine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: sertraline	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Mirtazapine: sertraline	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Mirtazapine: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Paroxetine: sertraline	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Reboxetine: sertraline	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Reboxetine: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Sertraline: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Sertraline: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Trazodone: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(4) 2005

eTable 12. CINeMA assessment for acceptability in 2005.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Agomelatine: paroxetine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Agomelatine: venlafaxine	2	No concerns	Undetected	No concerns	No concerns	No concerns	Major concerns	Moderate
Amitriptyline: bupropion	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: fluoxetine	13	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	No concerns	Suspected	No concerns	Some concerns	No concerns	Major concerns	Low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: mirtazapine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: paroxetine	17	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: sertraline	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: trazodone	3	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: venlafaxine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: paroxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Citalopram: clomipramine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	Major concerns	Very low
Citalopram: escitalopram	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: fluoxetine	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Clomipramine: fluoxetine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: sertraline	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: venlafaxine	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Escitalopram: fluoxetine	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: venlafaxine	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Fluoxetine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine: mirtazapine	3	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	9	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate

Fluoxetine: reboxetine	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluoxetine: sertraline	5	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: venlafaxine	7	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluvoxamine: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: mirtazapine	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: sertraline	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: paroxetine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: sertraline	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Mirtazapine: paroxetine	5	No concerns	Undetected	No concerns	Some concerns	No concerns	Major concerns	Moderate
Mirtazapine: sertraline	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Mirtazapine: venlafaxine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Nefazodone: paroxetine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine: sertraline	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Paroxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline: venlafaxine	3	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: amitriptyline	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: bupropion	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: citalopram	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: clomipramine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Agomelatine: duloxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: escitalopram	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: fluoxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: sertraline	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: trazodone	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate



Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: duloxetine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: escitalopram	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: duloxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: escitalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: duloxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Citalopram: venlafaxine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Clomipramine: duloxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: escitalopram	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: escitalopram	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Duloxetine: fluoxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: milnacipran	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Duloxetine: mirtazapine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine: paroxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate



Duloxetine: reboxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Duloxetine: sertraline	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Escitalopram: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Escitalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram: mirtazapine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Escitalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram: paroxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Escitalopram: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Nefazodone: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Reboxetine: sertraline	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Reboxetine: venlafaxine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Trazodone: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(5) 2010

eTable 13. CINeMA assessment for acceptability in 2010.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Agomelatine: escitalopram	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: fluoxetine	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Agomelatine: paroxetine	2	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	High
Agomelatine: venlafaxine	2	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	High
Amitriptyline: bupropion	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: fluoxetine	13	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	No concerns	Suspected	No concerns	Some concerns	No concerns	Major concerns	Low
Amitriptyline: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: mirtazapine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: paroxetine	17	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: sertraline	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: trazodone	3	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: venlafaxine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: paroxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: venlafaxine	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram: clomipramine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Low
Citalopram: escitalopram	5	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Moderate
Citalopram: reboxetine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Citalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	Major concerns	Low
Clomipramine: fluoxetine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: sertraline	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Duloxetine: escitalopram	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Duloxetine: paroxetine	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Duloxetine: venlafaxine	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Escitalopram: fluoxetine	3	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High

Escitalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: venlafaxine	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Fluoxetine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluoxetine: mirtazapine	5	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	9	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluoxetine: reboxetine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Fluoxetine: sertraline	5	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: venlafaxine	8	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: mirtazapine	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: sertraline	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Milnacipran: paroxetine	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: sertraline	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Mirtazapine: paroxetine	5	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Mirtazapine: sertraline	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Mirtazapine: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Nefazodone: paroxetine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Paroxetine: sertraline	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine: trazodone	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Sertraline: venlafaxine	3	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: amitriptyline	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: bupropion	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Agomelatine: citalopram	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: clomipramine	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: duloxetine	0	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Agomelatine: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate

Agomelatine: mirtazapine	0	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Agomelatine: nefazodone	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: reboxetine	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Agomelatine: sertraline	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: trazodone	0	No concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Moderate
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: duloxetine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Amitriptyline: escitalopram	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Bupropion: duloxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Bupropion: escitalopram	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Bupropion: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: duloxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Citalopram: venlafaxine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Clomipramine: duloxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: escitalopram	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: fluoxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Duloxetine: milnacipran	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low

Duloxetine: mirtazapine	0	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Duloxetine: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Duloxetine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Duloxetine: sertraline	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Duloxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Escitalopram: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Moderate
Escitalopram: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Escitalopram: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Escitalopram: trazodone	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Milnacipran: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Milnacipran: venlafaxine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Mirtazapine: reboxetine	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Nefazodone: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Reboxetine: sertraline	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Reboxetine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Reboxetine: venlafaxine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Trazodone: venlafaxine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low

(6) 2016

eTable 14. CINeMA assessment for acceptability in 2016.

Comparison	No. of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Agomelatine: duloxetine	1	No concerns	Undetected	No concerns	No concerns	No concerns	Major concerns	Moderate
Agomelatine: escitalopram	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Moderate
Agomelatine: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Agomelatine: venlafaxine	2	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
Amitriptyline: bupropion	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: fluoxetine	13	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: fluvoxamine	3	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Amitriptyline: mirtazapine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Amitriptyline: paroxetine	17	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: sertraline	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Amitriptyline: trazodone	3	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Amitriptyline: venlafaxine	2	Some concerns	Suspected	No concerns	No concerns	Major concerns	No concerns	Very low
Bupropion: fluoxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: paroxetine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Bupropion: trazodone	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
Bupropion: venlafaxine	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Citalopram: clomipramine	1	Some concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Low
Citalopram: escitalopram	7	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: fluoxetine	2	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Citalopram: fluvoxamine	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Citalopram: mirtazapine	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Citalopram: reboxetine	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Citalopram: sertraline	2	No concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	Low
Citalopram: venlafaxine	1	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Clomipramine: fluoxetine	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Clomipramine: paroxetine	6	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: sertraline	2	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
Clomipramine: venlafaxine	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Low
Duloxetine: escitalopram	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Duloxetine: paroxetine	2	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
Duloxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate

Escitalopram: fluoxetine	3	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: paroxetine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: sertraline	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Escitalopram: venlafaxine	2	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine: fluvoxamine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: milnacipran	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluoxetine: mirtazapine	5	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Fluoxetine: nefazodone	3	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Fluoxetine: paroxetine	9	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Fluoxetine: reboxetine	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Fluoxetine: sertraline	5	Some concerns	Undetected	No concerns	No concerns	Major concerns	No concerns	Low
Fluoxetine: trazodone	4	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluoxetine: venlafaxine	8	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: milnacipran	2	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Fluvoxamine: mirtazapine	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Moderate
Fluvoxamine: paroxetine	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: sertraline	2	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Fluvoxamine: venlafaxine	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: paroxetine	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Milnacipran: sertraline	1	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Mirtazapine: paroxetine	5	No concerns	Undetected	No concerns	No concerns	Major concerns	No concerns	Moderate
Mirtazapine: sertraline	1	No concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Mirtazapine: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Low
Mirtazapine: venlafaxine	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Nefazodone: paroxetine	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Nefazodone: sertraline	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Paroxetine: reboxetine	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Paroxetine: sertraline	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Paroxetine: trazodone	2	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	Moderate
Paroxetine: venlafaxine	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Sertraline: trazodone	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
Sertraline: venlafaxine	3	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
Venlafaxine: vortioxetine	1	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
Agomelatine: amitriptyline	0	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Agomelatine: bupropion	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Agomelatine: citalopram	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Agomelatine: clomipramine	0	No concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Moderate

Agomelatine: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Agomelatine: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Agomelatine: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Agomelatine: nefazodone	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Agomelatine: reboxetine	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	High
Agomelatine: sertraline	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Agomelatine: trazodone	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Agomelatine: vortioxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Moderate
Amitriptyline: citalopram	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Amitriptyline: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Amitriptyline: duloxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Amitriptyline: escitalopram	0	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Amitriptyline: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Amitriptyline: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Amitriptyline: vortioxetine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Bupropion: citalopram	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Bupropion: clomipramine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Bupropion: duloxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Bupropion: escitalopram	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Low
Bupropion: fluvoxamine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Bupropion: milnacipran	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Bupropion: mirtazapine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Bupropion: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Bupropion: reboxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Bupropion: sertraline	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Bupropion: vortioxetine	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Citalopram: duloxetine	0	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
Citalopram: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	Low
Citalopram: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Citalopram: paroxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Citalopram: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Citalopram: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Moderate
Clomipramine: duloxetine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	Very low
Clomipramine: escitalopram	0	Some concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Low
Clomipramine: milnacipran	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Clomipramine: mirtazapine	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Clomipramine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low



Clomipramine: reboxetine	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Clomipramine: trazodone	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Clomipramine: vortioxetine	0	No concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Moderate
Duloxetine: fluoxetine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
Duloxetine: fluvoxamine	0	Some concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	Very low
Duloxetine: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Duloxetine: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Duloxetine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Duloxetine: reboxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Duloxetine: sertraline	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
Duloxetine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Duloxetine: vortioxetine	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	High
Escitalopram: fluvoxamine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Escitalopram: milnacipran	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Escitalopram: mirtazapine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Escitalopram: nefazodone	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Escitalopram: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
Escitalopram: trazodone	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Escitalopram: vortioxetine	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Moderate
Fluoxetine: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Fluvoxamine: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Fluvoxamine: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Fluvoxamine: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Fluvoxamine: vortioxetine	0	No concerns	Suspected	No concerns	No concerns	Some concerns	Some concerns	Low
Milnacipran: mirtazapine	0	No concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Low
Milnacipran: nefazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Milnacipran: reboxetine	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Milnacipran: trazodone	0	No concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Low
Milnacipran: venlafaxine	0	No concerns	Suspected	No concerns	Some concerns	Some concerns	Some concerns	Low
Milnacipran: vortioxetine	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
Mirtazapine: nefazodone	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Mirtazapine: reboxetine	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
Mirtazapine: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
Nefazodone: reboxetine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Nefazodone: trazodone	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
Nefazodone: venlafaxine	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
Nefazodone: vortioxetine	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate

<b>Paroxetine: vortioxetine</b>	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
<b>Reboxetine: sertraline</b>	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
<b>Reboxetine: trazodone</b>	0	Some concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low
<b>Reboxetine: venlafaxine</b>	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
<b>Reboxetine: vortioxetine</b>	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	High
<b>Sertraline: vortioxetine</b>	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
<b>Trazodone: venlafaxine</b>	0	Some concerns	Suspected	No concerns	Major concerns	No concerns	Some concerns	Very low
<b>Trazodone: vortioxetine</b>	0	No concerns	Suspected	No concerns	Some concerns	No concerns	Some concerns	Low

# 8 Exemplar screen shots of the Shiny application

## (1) Home page

### Introduction

#### Interactive Plots to Demonstrate the Evolution of Evidence for Antidepressants in the Acute Treatment of Major Depression



The data used in this study comes from GRISelda (Group of Researchers Investigating Specific Efficacy of Individual Drugs for Acute depression) [1]. Double-blind RCTs of the acute phase treatment with 21 antidepressants for adult patients ( $\geq 18$  years old) with a primary diagnosis of major depression were systematically searched and included. About one in four trials included in the dataset comes from unpublished data, and two come from both published and unpublished sources.

In the network meta-analysis, we use two primary outcomes: efficacy and acceptability. Efficacy was measured by the response rate of the intervention, defined as the proportion of patients who showed 50% or greater reduction on a validated depression severity scales from baseline. Acceptability was measured by the all-cause discontinuation rate, defined as the proportion of patients who withdrew early due to any reasons.

[1] Cipriani A, Furukawa TA, Salanti G, et al, 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391, 1357-1366.

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

**Choose the type of RCT**

Including placebo-controlled trials

Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

**Show the pooled evidence since**

1978

**Show the pooled evidence until**

2016

The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

**Check the publication status of RCTs**

Pool data from published RCTs only

### Input

Network Plots and Basic Information   2 Dimensional Plots   Forest Plots   League Tables   Pairwise Comparisons   Funnel Plots

**The efficacy network:**

**Output**

The number of included studies: 179  
The number of included treatments: 18  
The network includes the following treatments:  
agomelatine fluoxetine paroxetine venlafaxine escitalopram duloxetine bupropion trazodone sertraline citalopram clomipramine fluvoxamine amitriptyline milnacipran mirtazapine nefazodone reboxetine vortioxetine

The overall heterogeneity Q-statistic is: 137.685 , and the p value for the test is 0.028  
The overall inconsistency Q-statistic is: 76.618 , and the p value for the test is 0.043  
The I-squared is: 0.23  
The tau (square-root of between-study variance) is: 0.179

**The acceptability network:**

The number of included studies: 174  
The number of included treatments: 18  
The network includes the following treatments:  
agomelatine fluoxetine paroxetine venlafaxine escitalopram duloxetine amitriptyline bupropion trazodone citalopram clomipramine fluvoxamine sertraline milnacipran mirtazapine nefazodone reboxetine vortioxetine

The overall heterogeneity Q-statistic is: 100.227 , and the p value for the test is 0.613  
The overall inconsistency Q-statistic is: 70.478 , and the p value for the test is 0.054  
The I-squared is: 0.074  
The tau (square-root of between-study variance) is: 0.109

**Note:**

- (1) The size of the node is proportionate to the number of randomized patients, and the thickness of the line is proportionate to the number of studies.
- (2) The *netmeta* package in R adopts generalized Cochran's Q statistic to assess the assumption of homogeneity and consistency. It is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. This Q statistic can be decomposed in a sum of within-design Q statistics (used to assess heterogeneity among direct comparisons) and one between-designs Q statistic (used to assess inconsistency between direct and indirect evidence). We provide both Q statistics and their p values for the test.
- (3) The I-squared statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance.
- (4) In random-effects meta-analysis, the extent of variation among the effects observed in different studies (between-study variance) is referred to as tau-squared . tau-squared is the variance of the effect size parameters across the population of studies and it reflects the variance of the true effect sizes. The square root of this number is referred to as tau.

## (2) Two-dimensional plots

### (a) Only head-to-head trials

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

**Choose the type of RCT**

Including placebo-controlled trials

Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

**Show the pooled evidence since**

1978

**Show the pooled evidence until**

2016

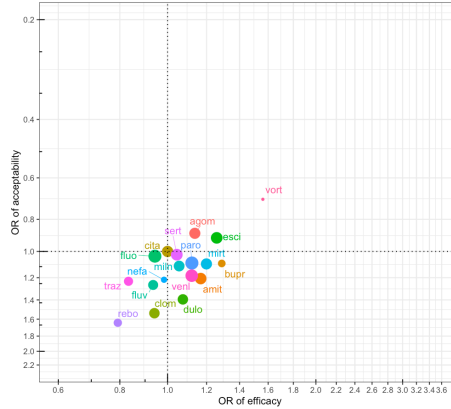
The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

**Check the publication status of RCTs**

Pool data from published RCTs only

[Network Plots and Basic Information](#)
[2 Dimensional Plots](#)
[Forest Plots](#)
[League Tables](#)
[Pairwise Comparisons](#)
[Funnel Plots](#)

The 2 Dimensional Plot for Both Efficacy and Acceptability

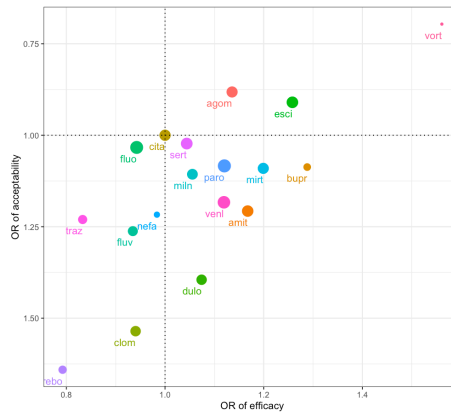


Please click the plot to see a zoomed one with the optimal ranges of x and y axis. (The zoomed plot will be displayed below.)

**Note:**

- (1) Drugs in the upper right area are better balanced in both efficacy and acceptability.
- (2) The size of the node is proportionate to the number of randomized patients.
- (3) If placebo-controlled trials are included, the plot will display 2 sets of result. The solid circles indicate results from full dataset, while the empty circles indicate results from only published data.

**The zoomed figure with optimal x and y axis ranges.**



## (b) Including placebo-controlled trials

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

### Choose the type of RCT

- Including placebo-controlled trials
- Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

### Show the pooled evidence since

1978

### Show the pooled evidence until

2016

The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

### Check the publication status of RCTs

- Pool data from published RCTs only

Network Plots and Basic Information

2 Dimensional Plots

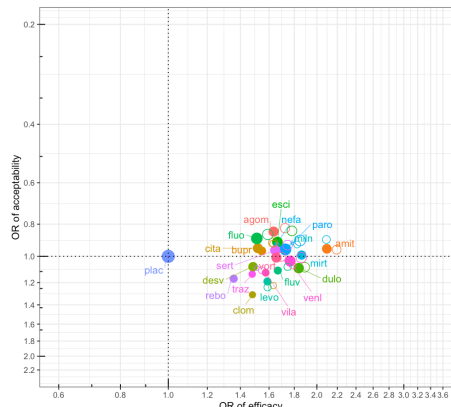
Forest Plots

League Tables

Pairwise Comparisons

Funnel Plots

### The 2 Dimensional Plot for Both Efficacy and Acceptability



Please click the plot to see a zoomed one with the optimal ranges of x and y axis. (The zoomed plot will be displayed below.)

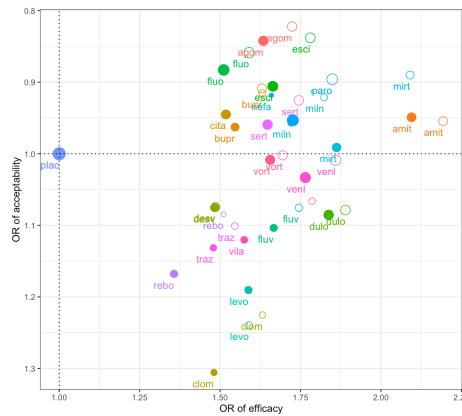
#### Note:

(1) Drugs in the upper right area are better balanced in both efficacy and acceptability.

(2) The size of the node is proportionate to the number of randomized patients.

(3) If placebo-controlled trials are included, the plot will display 2 sets of result. The solid circles indicate results from full dataset, while the empty circles indicate results from only published data.

**Two sets of dots: solid circles – full data; empty circles – published data only (exaggerated effects)**



## (c) Integrating confidence in the evidence

### The 2 Dimensional Plot Showing Efficacy and Acceptability Together with Confidence in the Evidence

We assessed the confidence in the evidence every 5 years since 1990, for head-to-head trials. We believe that it should be as important to see how credible the evidence are, as with the relative effect estimates. We evaluated it at 3 levels: RCT-level, comparison-level and drug-level. At **RCT-level**, we assessed the risk of bias for each RCT based on Cochrane Collaboration risk of bias tool. At **comparison-level**, we evaluated it at each time point using *CINeMA framework* [2] through the dedicated software. Finally, the information was synthesized at **drug-level**. We combined the efficacy, acceptability and confidence in the evidence (at drug-level) in one 2 dimensional plot at each time point.

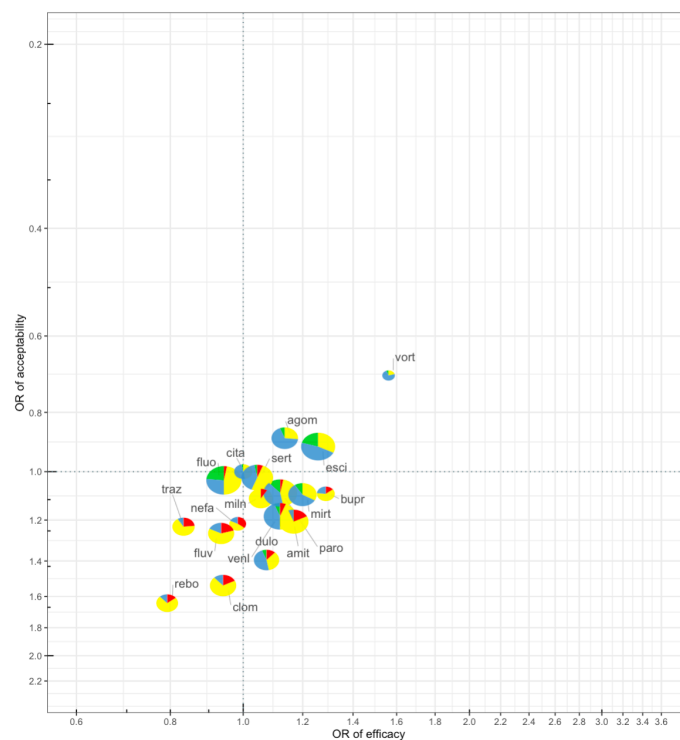
\*\*Since the confidence in the evidence was only assessed for **head-to-head trials** at **5-year interval**, this 2 dimensional plot is not as versatile as other functions. The conditions in the left sidebar are not applicable to it. **ONLY THE YEARS LISTED BELOW CAN BE SELECTED FOR THIS PLOT.**

All the evidence before the chosen year are synthesized. Please choose the ending time point.

Show the pooled evidence until

2016

[2] CINeMA: Confidence in Network Meta-Analysis [Software]. Institute of Social and Preventive Medicine, University of Bern, 2017. Available from cinema.ispm.unibe.ch.



Please click the plot to see a zoomed one with the optimal ranges of x and y axis. (The zoomed plot will be displayed below.)

### 2 Dimensional Plot for Efficacy, Acceptability and Confidence in the Evidence

**Note:** (1) Drugs in the upper right area are better balanced in both efficacy and acceptability.

(2) The size of the node is proportionate to the inverse of the width of 95%CI regarding efficacy. The bigger the node, the more precise the CI is.

(3) The colors in each pie chart is proportionate to the numbers of mixed estimates for the drug in question evaluated at four levels of GRADE certainty of evidence. The four levels are: **green-high**, **blue-moderate**, **yellow-low**, **red-very low**.

### (3) Forest plots

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

**Choose the type of RCT**

- Including placebo-controlled trials
- Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

**Show the pooled evidence since**

1978

**Show the pooled evidence until**

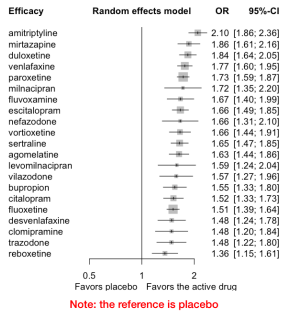
2016

The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

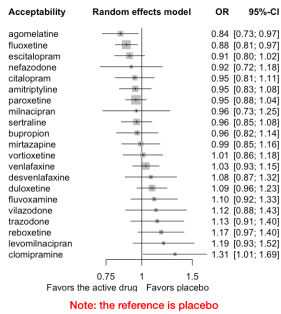
**Check the publication status of RCTs**

- Pool data from published RCTs only

The Forest Plot for Efficacy



The Forest Plot for Acceptability



# (4) League tables

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

**Choose the type of RCT**

- Including placebo-controlled trials
- Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

**Show the pooled evidence since**

1978

**Show the pooled evidence until**

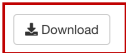
2016

The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

**Check the publication status of RCTs**

- Pool data from published RCTs only

- Network Plots and Basic Information
- 2 Dimensional Plots
- Forest Plots
- League Tables**
- Pairwise Comparisons
- Funnel Plots



You can download league table (in the form of csv file) here.

**Note:** The lower left half shows efficacy, and the upper right half shows acceptability.

**Caution:** The league table cannot be constructed if the drugs in the efficacy network and the acceptability network do not match. So please make sure of it in the 'Basic Information', before you try to download the league table.

## The Colored League Table Showing Efficacy and Acceptability Together with Confidence in the Evidence

We assessed the confidence in the evidence every 5 years since 1990, for head-to-head trials. We believe that it should be as important to see how credible the evidence are, as with the relative effect estimates. We evaluated it at 3 levels: RCT-level, comparison-level and drug-level. At **RCT-level**, we assessed the risk of bias for each RCT based on Cochrane Collaboration risk of bias tool. At **comparison-level**, we evaluated it at each time point using *CiNeMA framework* [2] through the dedicated software. Finally, the information was synthesized at **drug-level**. We combined the efficacy, acceptability and confidence in the evidence (at drug-level) in one 2 dimensional plot at each time point.

This colored league table shows the confidence in the evidence together with efficacy and acceptability at comparison level. We colored each cell of the league table in terms of the overall confidence in evidence between two drugs: **green indicated high, blue indicated moderate, yellow indicated low, and red indicated very low** confidence in evidence.

\*\*Since the confidence in the evidence was only assessed for **head-to-head trials at 5-year interval**, this table is not as versatile as other functions. The conditions in the left sidebar are not applicable to it. **ONLY THE YEARS LISTED BELOW CAN BE SELECTED FOR THIS TABLE.**

All the evidence before the chosen year are synthesized. Please choose the ending time point.

**Show the pooled evidence until**

2016

[2] CiNeMA: Confidence in Network Meta-Analysis [Software]. Institute of Social and Preventive Medicine, University of Bern, 2017. Available from cinema.ispm.unibe.ch.

agomelatine	0.73 (0.57 to 0.94)	0.81 (0.56 to 1.18)	0.88 (0.66 to 1.18)	0.67 (0.43 to 0.77)	0.63 (0.48 to 0.83)	0.97 (0.75 to 1.25)	0.85 (0.69 to 1.05)	0.70 (0.52 to 0.94)	0.80 (0.59 to 1.08)	0.81 (0.62 to 1.05)	0.73 (0.46 to 1.15)	0.81 (0.57 to 1.01)	0.64 (0.37 to 0.92)	0.86 (0.67 to 1.11)	0.72 (0.51 to 1.02)	0.75 (0.69 to 0.93)	1.27 (0.77 to 2.15)
0.97 (0.76 to 1.25)	0.81 (0.78 to 1.17)	0.88 (0.60 to 1.50)	0.67 (0.60 to 1.02)	0.63 (0.56 to 1.12)	0.97 (0.88 to 1.09)	0.85 (0.68 to 1.38)	0.70 (0.74 to 1.23)	0.80 (0.88 to 1.42)	0.81 (0.88 to 1.37)	0.73 (0.64 to 1.54)	0.81 (0.94 to 1.31)	0.64 (0.64 to 1.54)	0.86 (0.96 to 1.44)	0.72 (0.72 to 1.34)	0.75 (0.83 to 1.24)	1.27 (0.61 to 2.96)	
0.88 (0.59 to 1.31)	0.91 (0.64 to 1.32)	0.99 (0.74 to 1.40)	0.71 (0.48 to 1.05)	0.78 (0.58 to 1.14)	1.19 (0.87 to 1.73)	1.05 (0.75 to 1.46)	0.85 (0.58 to 1.27)	0.98 (0.69 to 1.48)	0.99 (0.69 to 1.42)	1.00 (0.53 to 1.53)	0.66 (0.42 to 1.03)	1.06 (0.74 to 1.52)	0.88 (0.59 to 1.31)	1.06 (0.66 to 1.27)	0.88 (0.66 to 1.27)	1.56 (0.88 to 2.83)	
1.14 (0.87 to 1.48)	1.17 (0.92 to 1.48)	1.29 (0.87 to 1.91)	0.65 (0.48 to 0.88)	0.65 (0.53 to 0.97)	1.19 (0.86 to 1.41)	0.97 (0.77 to 1.21)	0.79 (0.66 to 1.07)	0.90 (0.66 to 1.24)	0.82 (0.70 to 1.20)	0.82 (0.51 to 1.31)	0.82 (0.51 to 1.31)	0.82 (0.47 to 1.26)	0.86 (0.57 to 1.16)	0.86 (0.57 to 1.16)	0.86 (0.66 to 1.09)	1.44 (0.82 to 2.51)	
1.21 (0.81 to 1.60)	1.24 (0.87 to 1.59)	1.37 (0.92 to 2.05)	1.06 (0.81 to 1.39)	1.09 (0.85 to 1.50)	1.69 (1.26 to 2.26)	1.49 (1.17 to 1.89)	1.22 (0.89 to 1.67)	1.32 (1.02 to 1.51)	1.40 (0.92 to 1.73)	1.35 (0.97 to 1.68)	1.35 (0.72 to 1.84)	1.42 (0.83 to 1.42)	1.42 (0.57 to 1.29)	1.42 (0.94 to 1.99)	1.31 (0.93 to 1.49)	2.31 (1.13 to 3.48)	
1.06 (0.81 to 1.36)	1.09 (0.83 to 1.42)	1.20 (0.80 to 1.81)	0.93 (0.70 to 1.23)	0.88 (0.65 to 1.18)	1.53 (1.19 to 1.98)	1.35 (1.07 to 1.71)	1.11 (0.81 to 1.51)	1.27 (0.92 to 1.73)	1.15 (0.97 to 1.68)	1.15 (0.72 to 1.84)	1.32 (0.83 to 1.90)	0.85 (0.57 to 1.29)	1.36 (0.94 to 1.99)	1.13 (0.79 to 1.63)	1.18 (0.93 to 1.49)	2.00 (1.13 to 3.48)	
0.90 (0.71 to 1.10)	0.93 (0.74 to 1.17)	1.02 (0.69 to 1.33)	0.78 (0.65 to 0.98)	0.75 (0.57 to 0.97)	0.85 (0.67 to 1.09)	0.85 (0.67 to 1.09)	0.72 (0.64 to 0.87)	0.82 (0.61 to 1.11)	0.81 (0.64 to 1.08)	0.75 (0.47 to 1.18)	0.84 (0.68 to 1.04)	0.84 (0.58 to 1.13)	0.84 (0.52 to 1.14)	0.84 (0.46 to 1.43)	0.77 (0.72 to 1.47)	1.31 (0.82 to 1.98)	
1.21 (0.98 to 1.48)	1.24 (1.05 to 1.47)	1.37 (0.96 to 1.95)	1.06 (0.87 to 1.30)	1.06 (0.80 to 1.40)	1.33 (1.03 to 1.62)	1.14 (0.81 to 1.26)	0.82 (0.64 to 1.04)	0.83 (0.73 to 1.19)	0.84 (0.78 to 1.15)	0.85 (0.55 to 1.30)	0.95 (0.83 to 1.09)	0.83 (0.45 to 1.28)	0.83 (0.85 to 1.21)	0.83 (0.62 to 1.13)	0.87 (0.75 to 1.02)	1.48 (0.88 to 2.50)	
1.22 (0.92 to 1.62)	1.25 (0.98 to 1.59)	1.38 (0.92 to 2.07)	1.07 (0.82 to 1.40)	1.01 (0.76 to 1.34)	1.15 (0.85 to 1.56)	1.35 (1.03 to 1.70)	0.82 (0.81 to 1.26)	1.14 (0.84 to 1.55)	1.35 (0.89 to 1.90)	1.18 (0.65 to 1.67)	1.34 (0.65 to 1.67)	1.18 (0.92 to 1.48)	1.18 (0.94 to 1.61)	0.77 (0.72 to 1.47)	0.89 (0.82 to 1.38)	1.81 (1.03 to 3.18)	
1.08 (0.80 to 1.46)	1.11 (0.85 to 1.43)	1.22 (0.80 to 1.85)	0.95 (0.70 to 1.27)	0.89 (0.67 to 1.19)	1.02 (0.74 to 1.40)	1.19 (0.89 to 1.59)	0.89 (0.70 to 1.14)	0.89 (0.66 to 1.18)	0.91 (0.66 to 1.18)	1.02 (0.66 to 1.18)	1.02 (0.66 to 1.18)	1.02 (0.66 to 1.18)	1.02 (0.66 to 1.18)	0.93 (0.71 to 1.22)	0.93 (0.71 to 1.22)	1.59 (0.90 to 2.86)	
0.95 (0.73 to 1.23)	0.97 (0.78 to 1.22)	1.07 (0.73 to 1.58)	0.83 (0.65 to 1.07)	0.78 (0.60 to 1.02)	0.96 (0.68 to 1.18)	1.05 (0.82 to 1.34)	0.78 (0.65 to 0.95)	0.78 (0.66 to 1.17)	0.88 (0.66 to 1.17)	0.88 (0.66 to 1.17)	0.88 (0.66 to 1.17)	0.88 (0.66 to 1.17)	0.88 (0.66 to 1.17)	0.89 (0.65 to 1.22)	0.89 (0.75 to 1.14)	1.59 (0.91 to 2.70)	
1.15 (0.75 to 1.77)	1.19 (0.79 to 1.78)	1.31 (0.78 to 2.19)	1.02 (0.67 to 1.55)	1.02 (0.62 to 1.46)	1.09 (0.71 to 1.69)	0.96 (0.65 to 1.41)	0.95 (0.62 to 1.41)	1.07 (0.62 to 1.66)	1.07 (0.69 to 1.66)	1.12 (0.60 to 1.85)	1.12 (0.74 to 1.71)	1.12 (0.77 to 1.63)	1.12 (0.66 to 1.64)	0.99 (0.66 to 1.40)	0.99 (0.66 to 1.40)	1.75 (0.90 to 3.40)	
1.01 (0.82 to 1.25)	1.04 (0.89 to 1.22)	1.15 (0.80 to 1.65)	0.84 (0.72 to 1.10)	0.84 (0.68 to 1.03)	0.96 (0.76 to 1.21)	1.12 (0.93 to 1.36)	0.83 (0.67 to 1.05)	0.94 (0.67 to 1.25)	0.94 (0.60 to 1.29)	0.94 (0.60 to 1.29)	0.94 (0.60 to 1.29)	0.94 (0.60 to 1.29)	0.94 (0.60 to 1.29)	0.94 (0.60 to 1.29)	0.94 (0.60 to 1.29)	1.56 (0.92 to 2.63)	
1.63 (1.00 to 2.60)	1.67 (1.05 to 2.60)	1.68 (1.02 to 2.67)	1.26 (0.91 to 1.75)	1.19 (0.83 to 1.70)	1.36 (0.94 to 1.96)	1.59 (1.13 to 2.23)	1.18 (0.82 to 1.62)	1.33 (0.91 to 1.94)	1.33 (1.07 to 1.94)	1.34 (0.97 to 2.01)	1.41 (1.04 to 1.93)	1.41 (0.97 to 1.93)	1.41 (0.97 to 1.93)	1.41 (0.97 to 1.93)	1.41 (0.97 to 1.93)	2.36 (1.22 to 4.36)	
1.09 (0.85 to 1.38)	1.12 (0.92 to 1.35)	1.23 (0.85 to 1.80)	0.96 (0.77 to 1.20)	0.90 (0.71 to 1.14)	1.00 (0.79 to 1.34)	1.21 (0.97 to 1.66)	0.90 (0.77 to 1.06)	1.01 (0.70 to 1.32)	1.01 (0.64 to 1.39)	1.01 (0.64 to 1.39)	1.01 (0.64 to 1.39)	1.01 (0.64 to 1.39)	1.01 (0.64 to 1.39)	1.01 (0.64 to 1.39)	1.01 (0.64 to 1.39)	1.77 (0.86 to 2.52)	
1.36 (0.99 to 1.88)	1.40 (1.06 to 1.88)	1.55 (1.03 to 2.32)	1.20 (0.82 to 1.65)	1.20 (0.82 to 1.65)	1.29 (0.92 to 1.81)	1.13 (0.74 to 1.56)	1.13 (0.87 to 1.48)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.27 (0.81 to 1.56)	1.77 (0.98 to 3.19)	
1.01 (0.81 to 1.27)	1.04 (0.86 to 1.27)	1.15 (0.81 to 1.64)	0.89 (0.72 to 1.11)	0.89 (0.66 to 1.06)	0.89 (0.72 to 1.11)	1.12 (0.92 to 1.37)	0.84 (0.73 to 0.98)	0.84 (0.65 to 1.06)	0.84 (0.73 to 1.23)	0.84 (0.59 to 1.31)	0.84 (0.85 to 1.17)	0.84 (0.51 to 1.17)	0.84 (0.51 to 1.17)	0.84 (0.51 to 1.17)	0.84 (0.51 to 1.17)	1.72 (1.03 to 2.85)	
0.73 (0.41 to 1.26)	0.75 (0.43 to 1.30)	0.83 (0.44 to 1.55)	0.64 (0.36 to 1.13)	0.60 (0.34 to 1.07)	0.60 (0.39 to 1.22)	0.83 (0.46 to 1.41)	0.60 (0.35 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	0.60 (0.38 to 1.04)	1.72 (0.43 to 2.11)	

**Note:** The lower left half shows efficacy, and the upper right half shows acceptability.



## (5) Pairwise comparisons

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

**Choose the type of RCT**

Including placebo-controlled trials

Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

**Show the pooled evidence since**

1978

**Show the pooled evidence until**

2016

The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

**Check the publication status of RCTs**

Pool data from published RCTs only

[Network Plots and Basic Information](#) [2 Dimensional Plots](#) [Forest Plots](#) [League Tables](#) **Pairwise Comparisons** [Funnel Plots](#)

Select the 2 two drugs that you would like to compare the relative effect:

**Drug A**  **VS.** **Drug B (reference drug)**

The OR for efficacy of amitriptyline compared with fluoxetine is: 1.386 ( 1.215 to 1.582 )  
The OR for acceptability of amitriptyline compared with fluoxetine is: 1.075 ( 0.932 to 1.24 )

**Note:** Please wait a moment for the result, since it needs time to process. The OR is with reference to Drug B.

## (6) Comparison-adjusted funnel plots

Choose the type of RCT you would like to synthesize: the reference drug will be placebo if all the trials are included, and the reference will be citalopram if only head-to-head trials are included.

**Choose the type of RCT**

Including placebo-controlled trials

Only head-to-head trials

Choose the period of network meta-analysis: RCTs conducted during this period will be pooled for the analysis.

**Show the pooled evidence since**

1978

**Show the pooled evidence until**

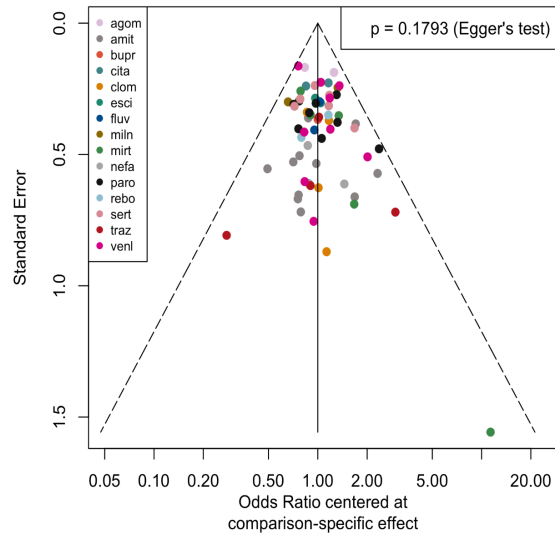
2016

The dataset includes all published and unpublished data. If you would like to see the results from published data only, please check the box below.

**Check the publication status of RCTs**

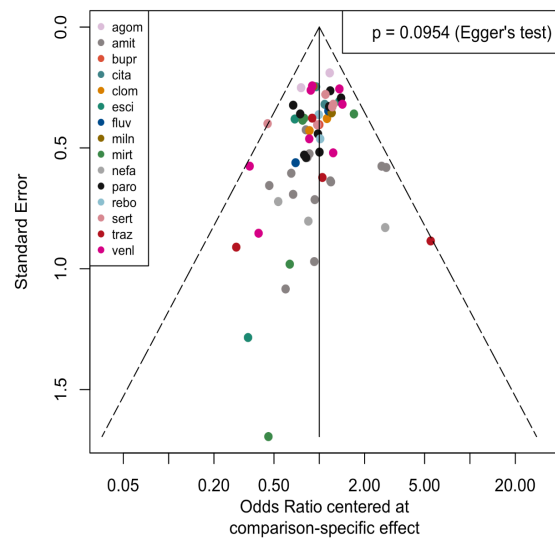
Pool data from published RCTs only

The Comparison-adjusted Funnel Plot for Efficacy



Note: only fluoxetine-controlled studies are included in this plot.

The Comparison-adjusted Funnel Plot for Acceptability



Note: only fluoxetine-controlled studies are included in this plot.