

THE LANCET Psychiatry

Supplementary appendix

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Optimal dose of selective serotonin reuptake inhibitors, venlafaxine and mirtazapine in major depression: Systematic review and dose-response meta-analysis

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1 Reference list of included studies

1. Alvarez 2012 (11492A, NCT00839423)

- Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol.* 2012;15(5):589-600.
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7. CL3-20098-023

- http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000915/WC500046226.pdf

8. CL3-20098-024

- http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000916/WC500038315.pdf

9. CN104-054 (FDA)

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- Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol* 2004; 14: 457–70.
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- Dunner DL, Dunbar GC. Optimal dose regimen for paroxetine. *J Clin Psychiatry*. 1992;53 Suppl:21-6.
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- Edwards JG, Goldie A. Placebo-controlled trial of paroxetine in depressive illness. *Human Psychopharmacology* 1993;8:203-209
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- <https://clinicaltrials.gov/ct2/show/NCT01441440>

25. Hirayasu 2011a

- Hirayasu Y. A dose-response study of escitalopram in patients with major depressive disorder: a placebo-controlled, double-blind study. *Jpn J Clin Psychopharmacol* 2011;14:871-882.

26. Hirayasu 2011b

- Hirayasu Y. A dose-response and non-inferiority study evaluating the efficacy and safety of escitalopram in patients with major depressive disorder. *Jpn J Clin Psychopharmacol* 2011;14:883-899.

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- Hunter AM, Muthén BO, Cook IA, Leuchter AF. Antidepressant response trajectories and quantitative electroencephalography (QEEG) biomarkers in major depressive disorder. *J Psychiatr Res.* 2010 Jan;44(2):90-8.

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- Hunter AM, Muthén BO, Cook IA, Leuchter AF. Antidepressant response trajectories and quantitative electroencephalography (QEEG) biomarkers in major depressive disorder. *J Psychiatr Res.* 2010 Jan;44(2):90-8.

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32. Kasper 2012 (NCT00807248)

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- 45. Montgomery 1992 (Study 89303 FDA)**
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- 47. MY-1008/BRL-029060/2/CPMS-076**
- <https://www.gsk-clinicalstudyregister.com/study/29060/076#rs>
- 48. NCT00822744 (EudraCT Number2008-001718-26)**
- <https://clinicaltrials.gov/ct2/show/NCT00822744>
 - <https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-001718-26/SK>
- 49. NCT01020799**
- <https://clinicaltrials.gov/ct2/show/NCT01020799>
- 50. NCT01808612**
- <https://clinicaltrials.gov/ct2/show/NCT01808612>
- 51. Nierenberg 2007 (F1J-MC-HMCR, NCT00073411, Pigott 2007)**
- Nierenberg AA, Greist JH, Mallinckrodt CH, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin* 2007; 23: 401–16.
 - <http://www.lillytrials.com/results/Cymbalta.pdf>
 - <https://clinicaltrials.gov/ct2/show/NCT00073411>
- 52. NKD20006 (NCT00048204)**
- <http://www.gsk-clinicalstudyregister.com/study/NKD20006#ps>
 - <https://clinicaltrials.gov/ct2/show/NCT00048204>
- 53. PAR 279 MDUK**
- http://www.gsk-clinicalstudyregister.com/study/29060/012_3?search=compound&compound=paroxetine#rs
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58. SCT-MD-35 (NCT00109044)

- <https://clinicaltrials.gov/ct2/show/NCT00668525>

59. SCT-MD-49 (NCT00668525)

- <https://clinicaltrials.gov/ct2/show/NCT00668525>

60. SER 101 (FDA)

- <https://digitalcollections.ohsu.edu/concern/etds/nk322d61z>

61. SER 310 (FDA)

- <https://digitalcollections.ohsu.edu/concern/etds/nk322d61z>

62. Sramek 1995

- Sramek JJ, Kashkin K, Jasinsky O, Kardatzke D, Kennedy S, Cutler NR. Placebo-controlled study of ABT-200 versus fluoxetine in the treatment of major depressive disorder. *Depression* 1995;3:199-203.

63. Study 62a (FDA) - MILD depression (Dunlop 1990)

- Dunlop SR, Dornseif BE, Wernicke JR, Potvin JH. Pattern analysis shows beneficial effect of fluoxetine treatment in mild depression. *Psychopharmacology bulletin*. 1990;26(2):173-80.
- <https://digitalcollections.ohsu.edu/concern/etds/5h73pw36j>

64. Study 62b (FDA) - MODERATE depression (Wernicke1987)

- Wernicke JF, Dunlop SR, Dornseif BE, Zerbe RL. Fixed-dose fluoxetine therapy for depression. *Psychopharmacology Bulletin*. 1987;23(1):164-68.
- <https://digitalcollections.ohsu.edu/concern/etds/5h73pw36j>

65. Study 89306 (FDA)

- http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020822a_medr_P2.pdf

66. Study F1J-MC-HMAQ - Study Group B (starting page in the pdf document: 147)

- <http://www.lillytrials.com/results/Cymbalta.pdf>

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68. VEN 600A-313 (FDA)

- <https://digitalcollections.ohsu.edu/concern/etds/pk02c992m>

69. VEN XR 367 (FDA)

- <https://digitalcollections.ohsu.edu/concern/etds/z029p503q>

70. Wade 2002 (ESC Study 99001 - FDA)

- Wade A, Michael Lemming O, Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol*. 2002;17(3):95-102.
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73. 003-008 (FDA)

- <https://digitalcollections.ohsu.edu/concern/etds/p8418n49j>

74. 003-042

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75. 003-048

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76. 245 (EMD 68 843-010)

- http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf

77. 246 (SB 659746-003)

- http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000MedR.pdf

2 Characteristics of included studies

Study Name	Year	No. of arms included in MA	No of total study arms	Drug	Sponsored	No. randomized	Mean age (SD)	% Female	Dosing Schedule	Mean Dose Delivered	Baseline Severity Scale	Mean Baseline Severity	Total length of trial (weeks)	Timing of outcome assessment (weeks)	Diagnostic Criteria	Recruitment	Multi/Single Centre	Treatment Setting	Patient Status	Placebo Run in	Rescue Medication			
Alvarez 2012 (11492A, NCT00839423)	2012	4	4	placebo	No	105	42 (10.9)	0.66	Fixed	0	HAMD 24	29.70	6	6	DSM-IV	Cross-Continental	Multi-center	Secondary/Tertiary care	Outpatients only	Unclear	Yes			
				venlafaxine	No	114	45 (10.3)	0.54	Fixed	225	HAMD24	29.40												
Binnemann 2008 (NCT00143091)	2008	2	3	sertraline	Yes	43	49	*	Fixed	100	HAMD 17	23.30	6	6	DSM-IV	Cross-Continental	Multi-center	Unclear	Outpatients only	Yes	Unclear			
				placebo	No	39	49	*	Fixed	0	HAMD 17	23.55												
Bjerkenstedt 2005	2005	2	3	fluoxetine	No	57	50.4 (11.6)	*	Fixed	20	HAMD 21	23.80	6	6	DSM-IV	Europe	Multi-center	Primary care	Outpatients only	Yes	Unclear			
				placebo	No	58	51.4 (11.8)	*	Fixed	0	HAMD 21	25.20												
Brunoni 2012	2012	2	4	sertraline	No	30	41 (12)	*	Fixed	50	MADRS	30.5	6	6	DSM-IV	South America	Single center	Secondary/Tertiary care	Outpatients only	No	Yes			
				placebo	No	30	46.4 (14)	*	Fixed	0	MADRS	30.76												
Burke 2002 (SCT-MD-01)	2002	4	4	escitalopram	Yes	124	40.6 (12.3)	*	Fixed	10	HAMD unspecified	24.30	8	8	DSM-IV	North America	Multi-center	Unclear	Outpatients only	Yes	Unclear			
				escitalopram	Yes	128	39.6 (12.1)	*	Fixed	20	HAMD unspecified	25.80												
				citalopram	Yes	127	40 (11.5)	*	Fixed	40	HAMD unspecified	25.90												
				placebo	No	127	40.3 (10.6)	*	Fixed	0	HAMD unspecified	25.80												
CL3-20098-022	2001	2	3	fluoxetine	no	137	42.9 (11.3)	0.67	Fixed	20	HAMD 17	27.50	24	6	DSM-IV	Europe	Multi-center	Secondary/Tertiary care	Both	Yes	No			
				placebo	No	149	43 (9.5)	0.67	Fixed	0	HAMD 17	28.00												
CL3-20098-023	2001	2	3	paroxetine	No	138	40.9 (11)	0.75	Fixed	20	HAMD 17	26.10	24	6	DSM-IV	Cross-Continental	Multi-center	Secondary/Tertiary care	Both	No	No			
				placebo	No	137	41.2 (10.1)	0.75	Fixed	0	HAMD 17	26.00												
CL3-20098-024	2002	2	4	fluoxetine	No	148	41.3 (10)	0.73	Fixed	20	HAMD 17	26.50	24	6	DSM-IV	Cross-Continental	Multi-center	Secondary/Tertiary care	Both	No	Unclear			
				placebo	No	158	41.6 (11.2)	0.73	Fixed	0	HAMD 17	26.90												
CN104-054 (FDA)	unpublished	2	3	fluoxetine	No	*	*	0.68	Fixed	20	*	*	8	8	Unclear	North America	Multi-center	Unclear	Outpatients	Unclear	Unclear			
				placebo	No	*	*	0.68	Fixed	0	*	*												
Corrigan 2000	2000	2	5	fluoxetine	No	35	42	*	Fixed	20	HAMD 17	22.00	8	8	DSM-III-R	North America	Multi-center	Secondary/Tertiary care	Unclear	Yes	Unclear			
				placebo	No	35	42	*	Fixed	0	HAMD 17	20.80												
	2004	2	4	paroxetine	No	86	42 (10.6)	*	Fixed	20	HAMD 17	20.26	8	8	DSM-IV	Unspecified	Multi-center	Unclear	Outpatients only	Yes	Unclear			

Detke 2004 (HMAY Study Group A)				placebo	No	93	43.67 (12.2)	*	Fixed	0	HAMD 17	19.86												
Dunner 1992 (PAR 29060.09)	1992	5	5	paroxetine	Yes	105	40.6	*	Fixed	10	HAMD 21	25.21	6	6	DSM-III	North America	Multi- center	Other/Uncle ar	Outpatients only	Unclear	Unclear			
				paroxetine	Yes	106	41.6	*	Fixed	20	HAMD 21	25.19												
				paroxetine	Yes	104	41.6	*	Fixed	30	HAMD 21	25.18												
				paroxetine	Yes	106	41.4	*	Fixed	40	HAMD 21	25.03												
				placebo	No	53	40.9	*	Fixed	0	HAMD 21	24.50												
Edwards 1989 (MD/PAR/009 PAR-276)	1989	2	2	paroxetine	Yes	21	45.1	0.55	Fixed	30	HAMD 17	26.80	6	6	DSM-III	Europe	Single center	Secondary/T ertiary care	Outpatients only	Unclear	Yes			
				placebo	No	21	43.3	0.57	Fixed	0	HAMD 17	25.50												
Faber 1995 (SER 103 FDA)	1995	4	4	sertraline	Yes	95	37	0.51	Fixed	50	HAMD17	24.80	6	6	DSM-III	North America	Multi- center	Other/Uncle ar	Outpatients only	Yes	Yes			
				sertraline	Yes	92	37	0.57	Fixed	100	HAMD 17	24.90												
				sertraline	Yes	91	38	0.63	Fixed	200	HAMD 17	25.70												
				placebo	No	91	37	0.44	Fixed	0	HAMD 17	25.30												
Fava 2005	2005	2	3	placebo	No	43	37.8 (12)	*	Fixed	0	HAMD 17	19.90	12	8	DSM-IV	North America	Multi- center	Secondary/T ertiary care	Outpatients only	Yes	Unclear			
				fluoxetine	No	47	36.7 (9.6)	*	Fixed	20	HAMD 17	19.60												
Feighner 1999 (Study 91206 FDA)	1999	4	5	citalopram	Yes	131	38	0.63	Fixed	10	HAMD21	25.1	6	6	DSM-III-R	North America	Multi- center	Unclear	Outpatients only	Yes	Yes			
				citalopram	Yes	130	39	0.66	Fixed	20	HAMD 21	24.2												
				citalopram	Yes	131	39	0.60	Fixed	40	HAMD 21	24.4												
				citalopram	Yes	129	38	0.53	Fixed	60	HAMD 21	24.5												
				placebo	No	129	38	0.55	Fixed	0	HAMD 21	24.6												
Frank 2004	2004	2	2	citalopram	Yes	8	39.12 (6.7)	0.25	Fixed	20	*	*	4	4	DSM-IV	North America	Single center	Secondary/T ertiary care	Outpatients only	No	Unclear			
				placebo	No	8	41.5 (7.1)	0.75	Fixed	0	*	*												
Gastpar 2006	2006	2	3	citalopram	No	127	49.3 (10.7)	0.65	Fixed	20	HAMD unspecified	21.80	6	6	DSM-IV	Europe	Multi- center	Primary care	Outpatients only	Unclear	Unclear			
				placebo	No	130	49.4 (12.7)	0.73	Fixed	0	HAMD unspecified	22.00												
Goldstein 2004a (HMAT - Study Group A, ID#4091)	2004	2	4	placebo	No	90	43.18 (14.5)	*	Fixed	0	HAMD 17	17.79	8	8	DSM-IV	North America	Multi- center	Unclear	Outpatients only	Yes	Unclear			
				paroxetine	Yes	89	44.43 (14.7)	*	Fixed	20	HAMD 17	17.97												
Goldstein 2004b (HMAT - Study Group B, ID#4091)	2004	2	4	placebo	No	89	40.14 (12.9)	*	Fixed	0	HAMD 17	17.19	8	8	DSM-IV	North America	Multi- center	Unclear	Outpatients only	Yes	Unclear			
				paroxetine	No	87	40.25 (11.0)	*	Fixed	20	HAMD 17	17.65												

Griebel 2012 (Study DF15878) (NCT00358631)	2012	2	4	escitalopram	No	84	40.8 (10.7)	0.62	Fixed	10	HAMD 17	23.40	8	8	DSM-IV	North America	Multi- center	Unclear	Outpatients only	Yes	Unclear			
				placebo	No	76	41.2 (12.4)	0.63	Fixed	0	HAMD 17	23.00												
Griebel 2012b (Study DF15879) (NCT00361491)	2012	2	4	paroxetine	No	80	40 (13.2)	0.70	Fixed	20	HAMD 17	24.90	8	8	DSM-IV	Cross- Continental	Multi- center	Unclear	Outpatients only	Yes	Unclear			
				placebo	No	79	40.1 (10.6)	0.73	Fixed	0	HAMD 17	24.80												
Heiligenstein 1994	1994	2	2	fluoxetine	Yes	46	41.6 (10.9)	*	Fixed	20	HAMD 17	21.10	8	8	DSM-III-R	North America	Multi- center	Secondary/T ertiary care	Outpatients only	Yes	Yes			
				placebo	No	43	39.2 (9.8)	*	Fixed	0	HAMD 17	21.60												
Higuchi 2014 (NCT01441440)	2016	3	3	venlafaxine	Yes	174	38.4 (11.9)	0.52	Fixed	75	HAMD 17	*	8	8	DSM-IV	Asia	Multi- center	Unclear	Outpatients only	Unclear	Unclear			
				placebo	No	184	38.6 (11.1)	0.51	Fixed	0	HAMD 17	*												
Hirayasu 2011a	2011	3	3	escitalopram	Yes	105	35.9 (11.2)	*	Fixed	20	HAMD 17	22.20	8	8	DSM-IV	Asia	Multi- center	Both	Outpatients only	No	Yes			
				escitalopram	Yes	100	33.1 (9)	*	Fixed	10	HAMD 17	22.30												
				placebo	No	105	34.7 (8.6)	*	Fixed	0	HAMD 17	22.50												
Hirayasu 2011b	2011	4	4	placebo	No	124	36.4 (10.8)	*	Fixed	0	MADRS	29.00	8	8	DSM-IV	Asia	Multi- center	Both	Outpatients only	Yes	Yes			
				escitalopram	Yes	121	36.3 (9.7)	*	Fixed	10	MADRS	29.40												
				escitalopram	Yes	119	35.7 (9.8)	*	Fixed	20	MADRS	29.80												
Hunter 2010 (Study 1)	2010	2	2	fluoxetine	Yes	14	42.4 (12.6)	0.68	Fixed	20	HAMD 17	22.10	8	8	DSM-IV	North America	Multi- center	Unclear	Outpatients only	Yes	No			
				placebo	No	14	42.4 (12.6)	0.68	Fixed	0	HAMD 17	22.10												
Hunter 2010 (Study 2)	2010	2	2	venlafaxine	Yes	17	44.7 (14)	0.64	Fixed	150	HAMD 17	22.30	8	8	DSM-IV	North America	Multi- center	Unclear	Outpatients only	Yes	No			
				placebo	No	16	44.7 (14)	0.64	Fixed	0	HAMD 17	22.30												
Hunter 2010 (Study 3)	2010	2	2	venlafaxine	Yes	18	38.1 (12.5)	0.55	Fixed	150	HAMD 17	21.50	8	8	DSM-IV	North America	Multi- center	Unclear	Outpatients only	Yes	No			
				placebo	No	15	38.1 (12.5)	0.55	Fixed	0	HAMD 17	21.50												
Jefferson 2000 (29060/785)	2000	5	5	placebo	No	105	40.2 (11.5)	*	Fixed	0	MADRS	31.7	6	6	DSM-IV	North America	Multi- center	Unclear	Outpatients only	No	Unclear			
				paroxetine	Yes	96	41.2 (12.3)	*	Fixed	12.5	MADRS	31.7												
				paroxetine	Yes	103	41.5 (12.1)	*	Fixed	25	MADRS	31.4												
				citalopram	Yes	107	38.4 (11.3)	*	Fixed	20	MADRS	31.4												
				citalopram	Yes	100	39.6 (11.1)	*	Fixed	40	MADRS	31.0												
Kasper 2005a (Study 99024)	2005	3	3	escitalopram	Yes	174	75 (7)	*	Fixed	10	MADRS	28.20	8	8	DSM-IV	Europe	Multi- center	Both	Both	Yes	Unclear			
				fluoxetine	No	164	75 (7)	*	Fixed	20	MADRS	28.50												

				placebo	No	180	75 (7)	*	Fixed	0	MADRS	28.60											
Kasper 2012 (NCT00807248)	2012	2	4	escitalopram	Yes	140	41.6 (12.6)	0.69	Fixed	20	MADRS	35.40	8	8	DSM-IV	Europe	Multi-center	Secondary/Tertiary care	Both	Unclear	No		
				placebo	No	71	42.6 (11.6)	0.75	Fixed	0	MADRS	34.70											
Keller 2006a (Study 059, NCT00035009)	2006	2	3	paroxetine	No	154	39	0.68	Fixed	20	HAMD 17	27.50	8	8	DSM-IV	North America	Multi-center	Unclear	Outpatients only	Unclear	Unclear		
				placebo	No	155	41.4	0.61	Fixed	0	HAMD 17	27.70											
Keller 2006b (Study 061) (NCT00035295)	2006	2	4	paroxetine	No	143	42.2	0.75	Fixed	20	HAMD 17	27.60	8	8	DSM-IV	North America	Multi-center	Unclear	Outpatients only	Unclear	Unclear		
				placebo	No	145	41.1	0.74	Fixed	0	HAMD 17	27.30											
Keller 2006c (Study 062) (NCT00048607)	2006	2	4	paroxetine	No	164	40.6	0.64	Fixed	20	HAMD 17	28.30	8	8	DSM-IV	Cross-Continental	Multi-center	Unclear	Outpatients only	Unclear	Unclear		
				placebo	No	161	41.3	0.71	Fixed	0	HAMD 17	28.30											
Khan 1998	1998	4	4	venlafaxine	Yes	85	43.3	0.68	Fixed	75	HAMD 21	24.30	12	8	DSM-III-R	North America	Multi-center	Unclear	Outpatients only	yes	unclear		
				venlafaxine	Yes	90	40	0.64	Fixed	150	HAMD 21	24.50											
				venlafaxine	Yes	83	43.6	0.60	Fixed	200	HAMD 21	24.80											
				placebo	No	95	40.2	0.61	Fixed	0	HAMD 21	25.10											
Kinoshita 2009	2009	4	4	mirtazapine	Yes	70	39.4 (10.9)	*	Fixed	15	HAMD 17	23.20	6	6	DSM-IV	Asia	Multi-center	Both	Both	No	No		
				mirtazapine	Yes	70	37.7 (10.8)	*	Fixed	30	HAMD 17	22.50											
				mirtazapine	Yes	71	41.6 (12.5)	*	Fixed	45	HAMD 17	22.10											
				placebo	No	70	39.9 (12.8)	*	Fixed	0	HAMD 17	22.50											
Kramer 1998	1998	2	3	paroxetine	Unclear	72	*	*	Fixed	20	HAMD 21	*	6	6	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear		
				placebo	No	70	*	*	Fixed	0	HAMD 24	*											
Lam 1995	1995	2	2	fluoxetine	Yes	36	40.9 (8.6)	*	Fixed	20	HAMD 21	18.70	5	5	DSM-III-R	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	No		
				placebo	No	32	38.1 (9.7)	*	Fixed	0	HAMD 21	18.30											
Learned 2012b Study2 (NCT00420641)	2012	2	3	paroxetine	Yes	166	44.4 (10.9)	0.33	Fixed	30	MADRS	30.30	10	8	DSM-IV	Cross-Continental	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear		
				placebo	No	156	41.8 (10.9)	0.25	Fixed	0	MADRS	31.80											
Loo 2002 (CL2-014)	2002	2	5	placebo	No	139	42.3	0.67	Fixed	0	HAMD 17	27.4	8	8	DSM-IV	Europe	Multi-center	Both	Other/Unclear	Yes	Yes		
				paroxetine	No	147	42.3	0.67	Fixed	20	HAMD 17	27.3											
LopezRodriguez 2004	2004	2	4	fluoxetine	Unclear	10	31.9	*	Fixed	20	HAMD 21	17.27	20	9	DSM-IV	South America	Single center	Primary care	Outpatients only	No	Unclear		
				placebo	No	10	31.9	*	Fixed	0	HAMD 21	17.27											
Mathews 2015 (NCT01473381)	2015	2	4	placebo	No	290	42 (13)	0.56	Fixed	0	MADRS	31.30	10	8	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Unclear	Yes		

				citalopram	No	289	42.6 (12.6)	0.59	Fixed	40	MADRS	31.10										
Miller 1989 (MDUK/29060/II/82/006 (PAR-274) PAR UK 06 - FDA)	1989	2	2	paroxetine	Yes	22	41.6 (13.2)	*	Fixed	30	HAMD 21	23.70	4	4	Feighner	Europe	Single center	Other/Unclear	Outpatients only	Unclear	Unclear	
				placebo	No	25	43.3 (11.8)	*	Fixed	0	HAMD 21	24.20										
Montgomery 1992 (Study 89303 FDA)	unpublished	3	3	citalopram	Yes	70	*	*	Fixed	20	HAMD 17	24.29	6	6	DSM-III-R	*	Multi-center	Other/Unclear	Both	Yes	Yes	
				citalopram	Yes	64	*	*	Fixed	40	HAMD 17	22.98										
				placebo	No	66	*	*	Fixed	0	HAMD 17	23.72										
Moreno 2005	2005	2	3	fluoxetine	No	20	37.7 (9.9)	0.83	Fixed	20	HAMD 21	15.41	8	8	DSM-IV	South America	Single center	Secondary/Tertiary care	Outpatients only	Yes	Yes	
				placebo	No	26	45.9 (10.8)	0.83	Fixed	0	HAMD 21	16.49										
MY-1008/BRL-029060/2/CPMS-076	unpublished	2	3	paroxetine	Yes	4	49.3	1.00	Fixed	30	HAMD 21	*	4	4	DSM-IV	Europe	Multi-center	Other/Unclear	Other/Unclear	Unclear	Unclear	
				placebo	No	4	46.5	0.50	Fixed	0	HAMD 21	*										
NCT00822744 (EudraCT Number2008-001718-26)	unpublished	2	5	escitalopram	Unclear	103	*	*	Fixed	10	HAMD 17	*	8	8	DSM-IV	Cross-Continental	Multi-center	Other/Unclear	Other/Unclear	Unclear	Unclear	
				placebo	No	106	*	*	Fixed	0	HAMD 17	*										
NCT01020799	unpublished	2	3	escitalopram	No	50	36.22 (11.3)	0.44	Fixed	20	HAMD unspecified	24.40	4	4	DSM-IV	North America	Multi-center	Other/Unclear	Other/Unclear	Unclear	Unclear	
				placebo	No	99	41.77 (10.0)	0.49	Fixed	0	HAMD unspecified	24.60										
NCT01808612	unpublished	3	3	fluoxetine	Yes	169	40.5 (11.2)	0.49	Fixed	20	HAMD 21	*	6	6	*	Asia	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear	
				fluoxetine	Yes	84	39.58 (10.6)	0.40	Fixed	40	HAMD 21	*										
				placebo	No	260	38.54 (11.6)	0.50	Fixed	0	HAMD 21	*										
Nierenberg 2007 (F1J-MC-HMCR, NCT00073411, Pigott 2007)	2007	2	3	escitalopram	No	274	43.3 (13)	*	Fixed	10	HAMD 17	17.80	8	8	DSM-IV	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Unclear	
				placebo	No	137	42.5 (12.3)	*	Fixed	0	HAMD 17	17.70										
NKD20006 (NCT00048204)	unpublished	2	3	paroxetine	Yes	125	37.9 (11.9)	0.63	Fixed	20	HAMD 17	24.70	8	8	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Yes	No	
				placebo	No	125	38 (11.3)	0.56	Fixed	0	HAMD 17	24.50										
PAR 279 MDUK	unpublished	2	3	paroxetine	Yes	19	39.7 (18.2)	0.68	Fixed	30	HAMD unspecified	22.80	6	6	*	Europe	Multi-center	Other/Unclear	Other/Unclear	Yes	Unclear	
				placebo	No	10	51.6 (17.3)	0.70	Fixed	0	HAMD unspecified	22.30										
Perahia 2006 (HMAY - Study Group B)	2006	2	4	paroxetine	No	97	45.81 (10.6)	*	Fixed	20	HAMD 17	21.03	8	8	DSM-IV	Unspecified	Multi-center	Other/Unclear	Outpatients only	Yes	Unclear	
				placebo	No	99	44.67 (10.1)	*	Fixed	0	HAMD 17	20.58										
	2008	2	3	venlafaxine	No	169	42.46 (12.4)	0.68	Fixed	75	HAMD 17	22.51	6	6	DSM-IV	Cross-Continental	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear	

Perahia 2008b (HMCQ, NCT00067912)				venlafaxine	No	171	40.64 (11.4)	0.62	Fixed	150	HAMD 17	22.24												
Rapaport 2009 (BRL-29060/874) (NCT00067444)	2009	3	3	paroxetine	Yes	168	67 (6.10)	*	Fixed	12.5	HAMD 17	22.25	10	10	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Yes	Unclear			
				paroxetine	Yes	177	67 (6.56)	*	Fixed	25	HAMD 17	22.74												
				placebo	No	180	68 (6.7)	*	Fixed	0	HAMD 17	22.41												
Rudolph 1998 (VEN 600A-203 (FDA))	1998	4	4	venlafaxine	Yes	89	43.6 (10.9)	0.40	Fixed	75	HAMD 21	26.00	6	6	DSM-III	North America	Multi-center	Secondary/Tertiary care	Outpatients only	Yes	Yes			
				venlafaxine	Yes	89	43.1 (9.61)	0.43	Fixed	225	HAMD 21	26.00												
				venlafaxine	Yes	88	43.8 (10.3)	0.33	Fixed	375	HAMD 21	24.90												
				placebo	No	92	41.5 (11.3)	0.32	Fixed	0	HAMD 21	25.30												
SCT-MD-35 (NCT00109044)	unpublished	2	4	escitalopram	YES	138	39.6 (11.7)	*	Fixed	4	MADRS	29.80	8	8	DSM-IV	North America	Multi-center	Other/Unclear	Outpatients only	Unclear	Unclear			
				placebo	No	135	43.3 (13.5)	*	Fixed	0	MADRS	30.3												
SCT-MD-49 (NCT00668525)	unpublished	3	3	escitalopram	Yes	325	41.4 (12.3)	0.64	Fixed	10	HAMD 24	29.30	8	8	DSM-IV	North America	Multi-center	Other/Unclear	Other/Unclear	Yes	Unclear			
				escitalopram	Yes	332	40.4 (11.9)	0.69	Fixed	28	HAMD 24	29.30												
				placebo	No	220	42.3 (12.7)	0.63	Fixed	*	HAMD 24	28.90												
SER 101 (FDA)	unpublished	4	5	sertraline	Yes	26	*	*	Fixed	50	HAMD 17	*	4	4	DSM-III	North America	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Unclear			
				sertraline	Yes	24	*	*	Fixed	100	HAMD 17	*												
				sertraline	Yes	23	*	*	Fixed	200	HAMD 17	*												
				placebo	No	26	*	*	Fixed	0	HAMD 17	*												
SER 310 (FDA)	unpublished	4	4	sertraline	Yes	33	*	*	Fixed	50	*	*	4	4	DSM-III	Europe	Multi-center	Secondary/Tertiary care	Inpatients only	Yes	Yes			
				sertraline	Yes	35	*	*	Fixed	100	*	*												
				sertraline	Yes	37	*	*	Fixed	200	*	*												
				placebo	No	34	*	*	Fixed	0	*	*												
Sramek 1995	1995	2	3	fluoxetine	No	72	33.9	0.60	Fixed	20	HAMD 24	28.20	9	9	DSM-III-R	North America	Single center	Other/Unclear	Other/Unclear	Yes	Unclear			
				placebo	No	72	33.9	0.60	Fixed	0	HAMD 24	27.50												
Study 62a (FDA) - MILD depression (Dunlop 1990)	1990	4	4	fluoxetine	Yes	104	38.31	0.59	Fixed	60	HAMD 21	17.20	6	6	DSM-III	*	Multi-center	Other/Unclear	Outpatients only	Yes	Unclear			
				fluoxetine	Yes	105	39.8	0.56	Fixed	40	HAMD 21	16.83												
				fluoxetine	Yes	107	39.97	0.62	Fixed	20	HAMD 21	16.99												
				placebo	No	56	38.96	0.50	Fixed	0	HAMD 21	17.41												
Study 62b (FDA) - MODERATE	1987	4	4	fluoxetine	Yes	105	39.93	0.58	Fixed	60	HAMD 21	24.20	6	6	DSM-III	*	Multi-center	Other/Unclear	Outpatients only	Yes	Unclear			

depression (Wernicke 1987)				fluoxetine	Yes	103	41.15	0.56	Fixed	40	HAMD 21	24.19									
				fluoxetine	Yes	100	39.4	0.60	Fixed	20	HAMD 21	24.72									
				placebo	No	48	38.56	0.50	Fixed	0	HAMD 21	24.25									
Study 89306 (FDA)	unpublis hed	3	3	citalopram	Yes	88	*	*	Fixed	20	MADRS	32.70	6	6	DSM-III-R	*	Multi- center	Both	Both	Yes	Yes
				citalopram	Yes	97	*	*	Fixed	40	MADRS	31.30									
				placebo	No	89	*	*	Fixed	0	MADRS	33.14									
Study F1J-MC- HMAQ - Study Group B	unpublis hed	3	3	placebo	No	75	41.39 (11.8)	*	Fixed	0	HAMD 17	18.32	10	8	DSM-IV	North America	Multi- center	Other/Uncle ar	Outpatients only	Yes	Unclear
				fluoxetine	No	37	39.65 (12.7)	*	Fixed	20	HAMD 17	20.03									
Trivedi 2004 (29060/810)	2004	2	3	placebo	No	149	38.4 (12.1)	*	Fixed	0	HAMD 17	23.8	8	8	DSM-IV	North America	Multi- center	Other/Uncle ar	Other/Unclea r	Yes	Unclear
				paroxetine	Yes	156	38.6 (10.8)	*	Fixed	12.5	HAMD 17	23.2									
				paroxetine	Yes	154	39.4 (10.8)	*	Fixed	25	HAMD 17	23.5									
VEN 600A-313 (FDA)	unpublis hed	3	4	venlafaxine	Yes	76	38	0.70	Fixed	75	HAMD 21	25.57	6	6	DSM-III-R	North America	Unclear	Other/Uncle ar	Outpatients only	Yes	Yes
				venlafaxine	Yes	82	39	0.61	Fixed	200	HAMD 21	25.57									
				placebo	No	79	38	0.69	Fixed	0	HAMD 21	25.39									
VEN XR 367 (FDA)	unpublis hed	4	4	venlafaxine	Yes	83	*	0.70	Fixed	75	HAMD 21	26.49	8	8	DSM-III-R	Europe	Multi- center	Other/Uncle ar	Outpatients only	Yes	Yes
				venlafaxine	Yes	82	*	0.61	Fixed	150	HAMD 21	27.11									
				paroxetine	No	81	*	0.54	Fixed	20	HAMD 21	26.13									
				placebo	No	83	*	0.67	Fixed	0	HAMD 21	26.60									
Wade 2002 (ESC Study 99001 - FDA)	2002	2	2	placebo	No	189	40 (12)	0.78	Fixed	0	MADRS	28.70	8	8	DSM-IV	Cross- Continental	Multi- center	Primary care	Outpatients only	Yes	Unclear
				escitalopram	Yes	191	41 (11)	0.74	Fixed	10	MADRS	29.20									
Wernicke 1988	1988	4	4	placebo	No	77	39	0.61	Fixed	0	HAMD unspecified	25.9	6	6	DSM-III	North America	Multi- center	Other/Uncle ar	Other/Unclea r	Yes	Unclear
				fluoxetine	Yes	94	39	0.61	Fixed	5	HAMD unspecified	25.5									
				fluoxetine	Yes	91	39	0.61	Fixed	20	HAMD unspecified	25.0									
				fluoxetine	Yes	92	39	0.61	Fixed	40	HAMD unspecified	25.4									
Yevtushenko 2007	2007	2	3	citalopram	No	111	34.8 (6.4)	0.58	Fixed	10	MADRS	35.40	6	6	DSM-IV	Europe	Multi- center	Secondary/T ertiary care	Outpatients only	Unclear	Yes
				citalopram	No	110	35.1 (6.5)	0.56	Fixed	20	MADRS	35.70									
003-008 (FDA)	unpublis hed	5	5	mirtazapine	Yes	30	41	0.70	Fixed	5	HAMD21	25.3	6	6	DSM-III	North America	Single center	Other/Uncle ar	Outpatients only	Yes	Unclear
				mirtazapine	Yes	30	38	0.63	Fixed	15	HAMD 21	26.00									
				mirtazapine	Yes	30	40	0.71	Fixed	30	HAMD 21	25.50									

				mirtazapine	Yes	30	43	0.62	Fixed	60	HAMD21	25.0									
				placebo	No	30	39	0.61	Fixed	0	HAMD 21	25.80									
003-042	unpublis hed	4	4	mirtazapine	Yes	70	41 (10.8)	0.71	Fixed	15	HAMD 21	25.30	8	8	DSM-IV	North America	Multi- center	Other/Uncle ar	Outpatients only	Yes	Unclear
				mirtazapine	Yes	70	39.8 (10.2)	0.56	Fixed	30	HAMD 21	24.70									
				mirtazapine	Yes	70	42.2 (12.9)	0.60	Fixed	45	HAMD 21	25.00									
				placebo	No	70	40.8 (10.8)	0.66	Fixed	0	HAMD 21	25.90									
003-048	unpublis hed	3	3	mirtazapine	Yes	210	41.4 (12.1)	0.60	Fixed	45	HAMD 17	22.30	8	8	DSM-IV	North America	Multi- center	Other/Uncle ar	Other/Unclea r	Yes	Unclear
				fluoxetine	No	210	40.8 (11.6)	0.58	Fixed	60	HAMD 17	22.80									
				placebo	No	72	40.2 (11.5)	0.61	Fixed	0	HAMD 17	23.00									
245 (EMD 68 843-010)	unpublis hed	3	5	fluoxetine	No	92	*	*	Fixed	20	HAMD 17	23.50	8	8	DSM-IV	North America	Multi- center	Other/Uncle ar	Outpatients only	Yes	Unclear
				placebo	No	99	*	*	Fixed	0	HAMD 17	23.40									
246 (SB 659746- 003)	unpublis hed	2	4	citalopram	No	117	*	*	Fixed	20	HAMD 17	23.10	8	8	DSM-IV	North America	Multi- center	Other/Uncle ar	Outpatients only	Yes	Unclear
				placebo	No	129	*	*	Fixed	0	HAMD 17	23.30									

3 Risk of bias table of included studies

For details about the rating criteria, see published protocol (Furukawa et al., BMJ Open 2016). ‘Stated not tested’ refers to the mention of double-blind procedures used in the methods section of a paper, but maintenance of blinding is not tested.

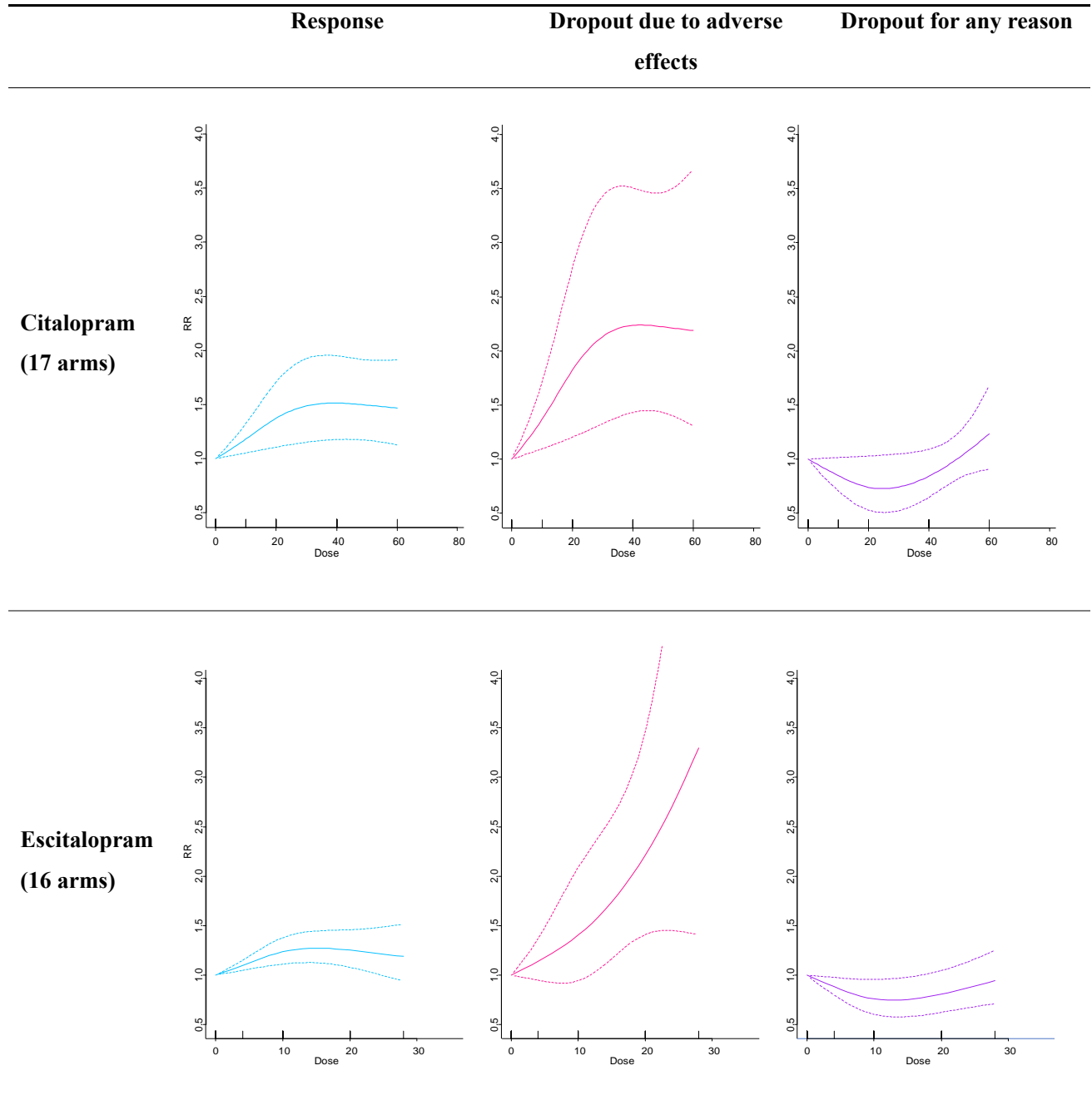
StudyID	Sequence_generation	Allocation_concealment	Blinding_participant	Blinding_therapist	Blinding_assessor	Selective_reporting_bias	Attrition_bias
1. Alvarez 2012	Low risk of bias	Low risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	Low risk of bias	High risk of bias
2. Binnemann 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	Unclear risk of bias
3. Bjerkenstedt 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
4. Brunoni 2012	Low risk of bias	Low risk of bias	Low risk of bias	Stated but not tested	Unclear risk of bias	Unclear risk of bias	Low risk of bias
5. Burke 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
6. CL3-20098-022	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
7. CL3-20098-023	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
8. CL3-20098-024	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
9. CN104-054	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Unclear risk of bias
10. Corrigan 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	High risk of bias
11. Detke 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	Low risk of bias
12. Dunner 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	Unclear risk of bias
13. Edwards 1989	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Stated but not tested	Unclear risk of bias	Low risk of bias	High risk of bias
14. Faber 1995	Low 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
15. Fava 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	Unclear risk of bias
16. Feighner 1999	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
17. Frank 2004	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Unclear risk of bias
18. Gastpar 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
19. Goldstein 2004a	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. Goldstein 2004b	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. Griebel 2012	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
22. Griebel 2012b	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
23. Heiligenstein 1994	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

24.	Higuchi 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	Low risk of bias
25.	Hirayasu 2011a	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
26.	Hirayasu 2011b	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
27.	Hunter 2010 (Study 1)	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Unclear risk of bias
28.	Hunter 2010 (Study 2)	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Unclear risk of bias
29.	Hunter 2010 (Study 3)	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Unclear risk of bias
30.	Jefferson 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	High risk of bias
31.	Kasper 2005a	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
32.	Kasper 2012	Low 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
33.	Keller 2006a	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
34.	Keller 2006b	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
35.	Keller 2006c	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
36.	Khan 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
37.	Kinoshita 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	Unclear risk of bias
38.	Kramer 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
39.	Lam 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
40.	Learned 2012b Study2	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
41.	Loo 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
42.	LopezRodriguez 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
43.	Mathews 2015	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
44.	Miller 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	High risk of bias
45.	Montgomery 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	Unclear risk of bias
46.	Moreno 2005	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
47.	MY-1008/CPMS-076	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
48.	NCT00822744	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.	NCT01020799	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
50.	NCT01808612	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
51.	Nierenberg 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	Unclear risk of bias
52.	NKD20006	Unclear 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
53.	PAR 279 MDUK	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
54.	Perahia 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

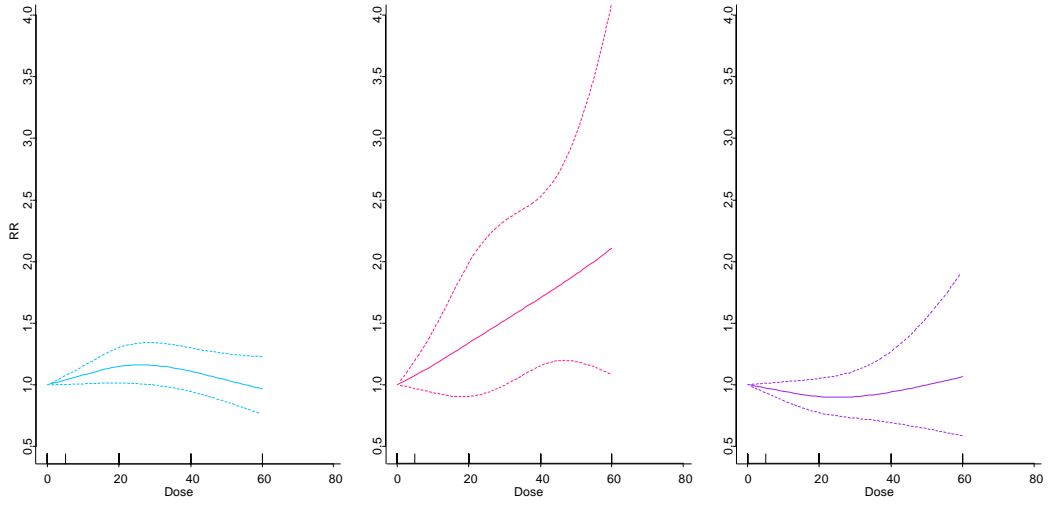
55.	Perahia 2008b	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
56.	Rapaport 2009	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	Low risk of bias	Unclear risk of bias
57.	Rudolph 1998	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
58.	SCT-MD-35	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
59.	SCT-MD-49	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
60.	SER 101	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
61.	SER 310	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Unclear risk of bias	High risk of bias	Unclear risk of bias
62.	Sramek 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
63.	Study 62a	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
64.	Study 62b	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
65.	Study 89306	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
66.	Study F1J-MC-HMAQ- Study Group 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
67.	Trivedi 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
68.	VEN 600A-313	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.	VEN XR 367	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
70.	Wade 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
71.	Wernicke1988	Unclear risk of bias	Unclear risk of bias	Stated but not tested	Stated but not tested	Stated but not tested	High risk of bias	Unclear risk of bias
72.	Yevtushenko 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	Low risk of bias
73.	003-008	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
74.	003-042	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
75.	003-048	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
76.	245 (EMD 68 843-010)	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
77.	246 (SB 659746-003)	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

4 Dose-outcome curves

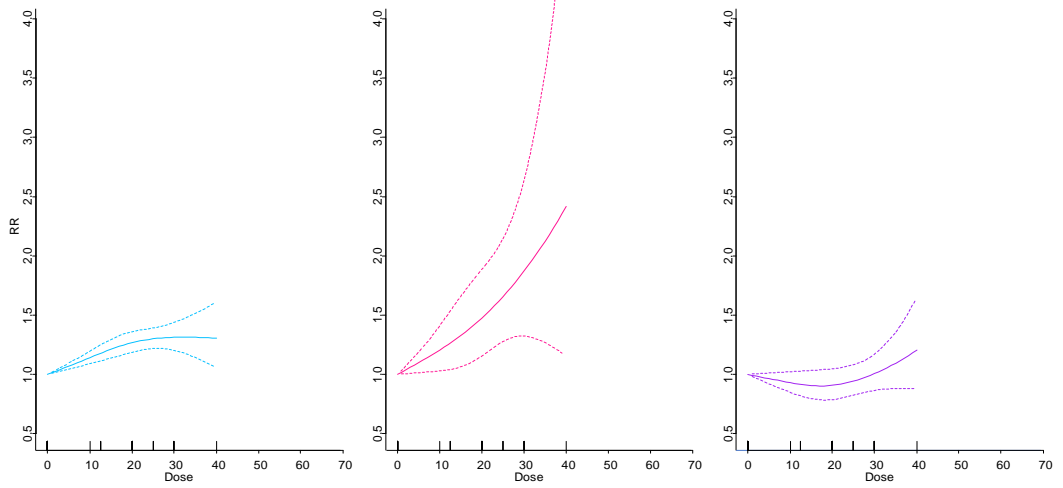
eFigure 1. Dose-outcome relationships for individual SSRI



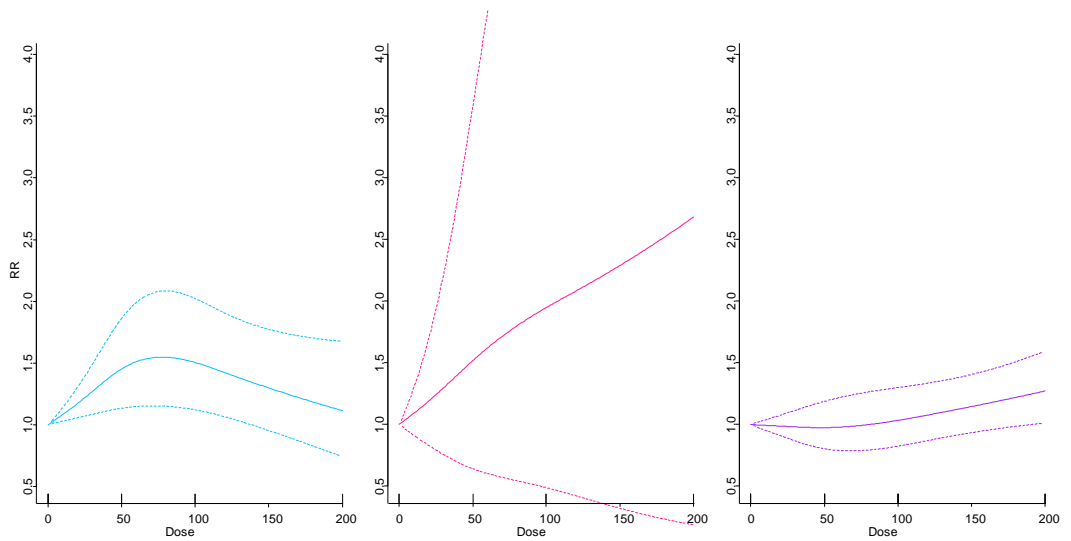
**Fluoxetine
(27 arms)**



**Paroxetine
(28 arms)**



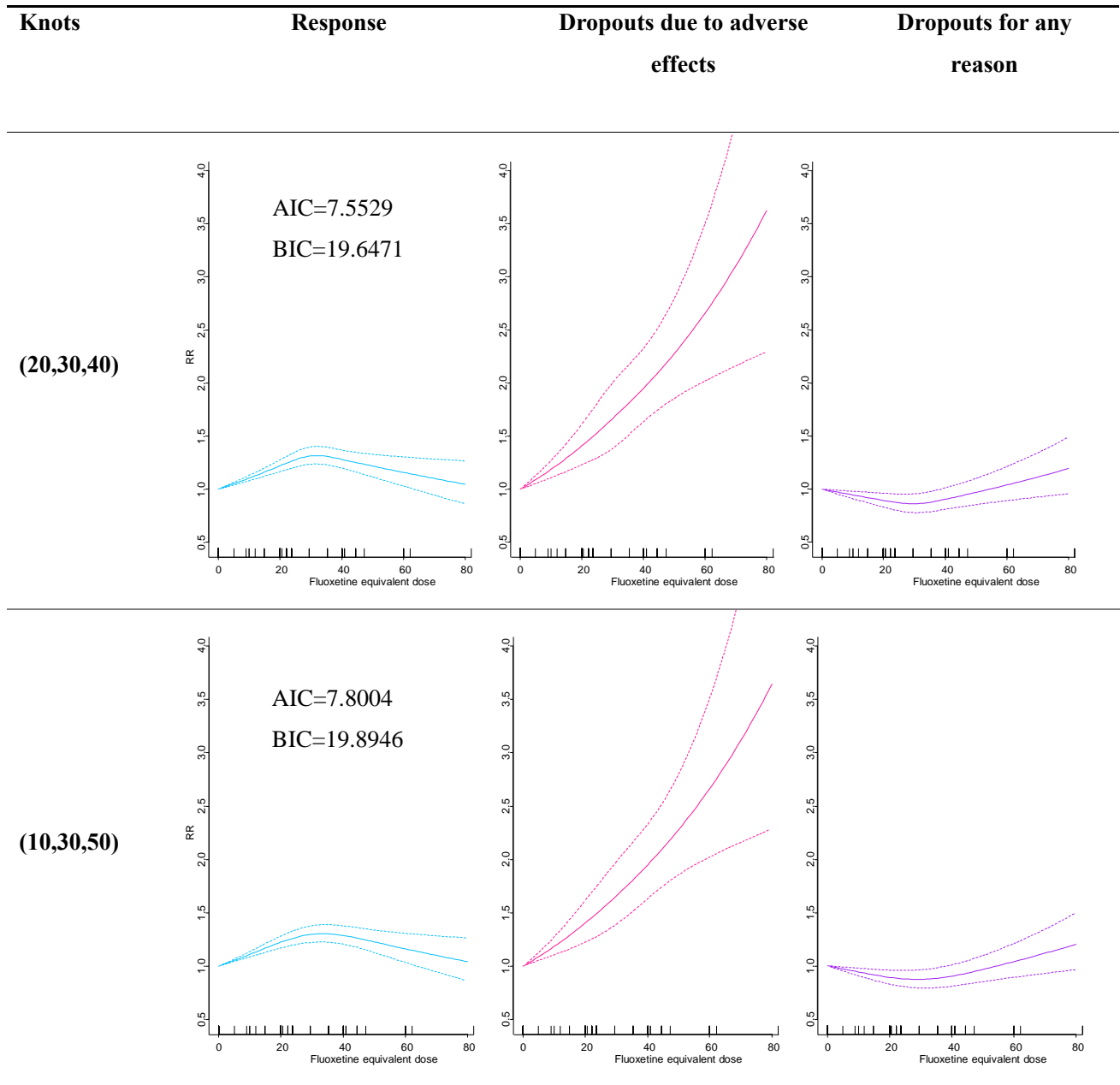
**Sertraline
(11 arms)**



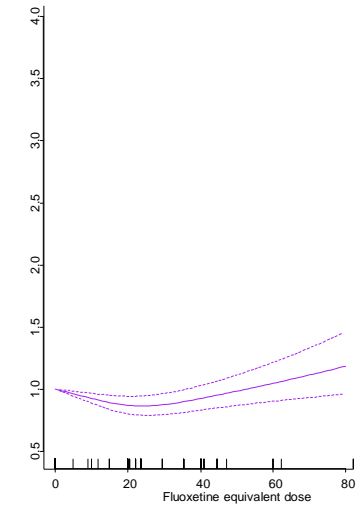
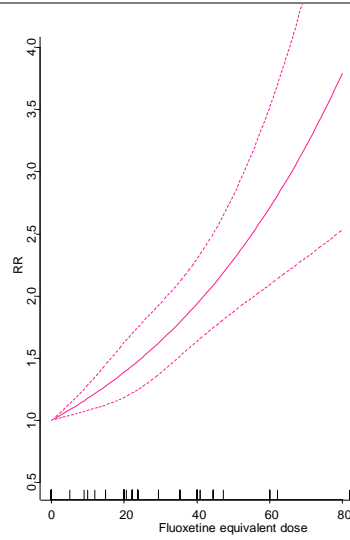
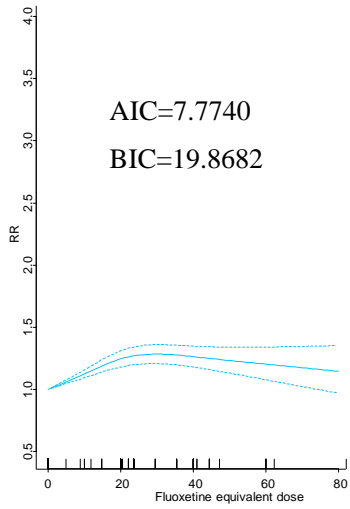
Each tick on the horizontal axis represents the dosage examined in a study arm.

The dotted lines represent 95% confidence intervals.

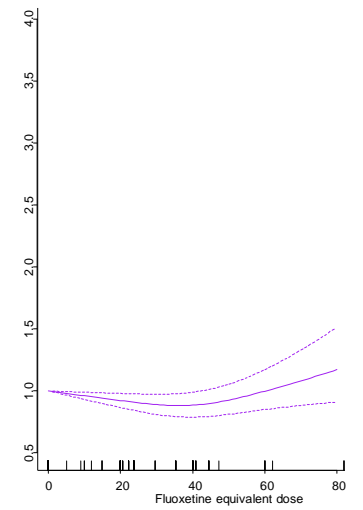
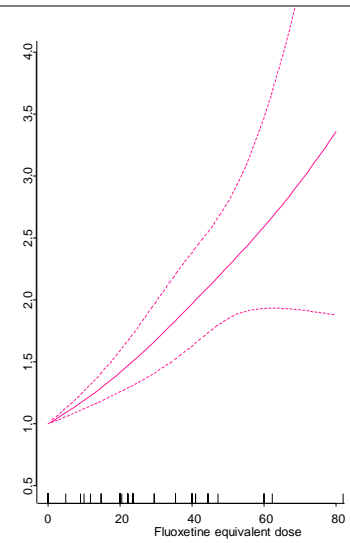
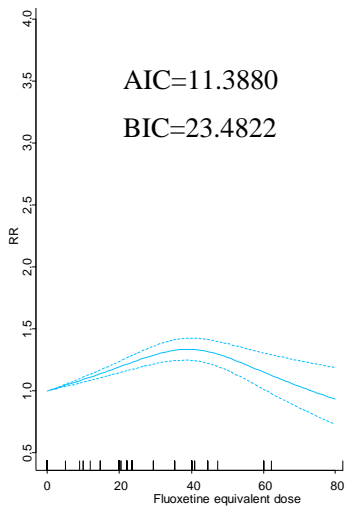
eFigure 2. Spline curves using various knots and their goodness-of-fit



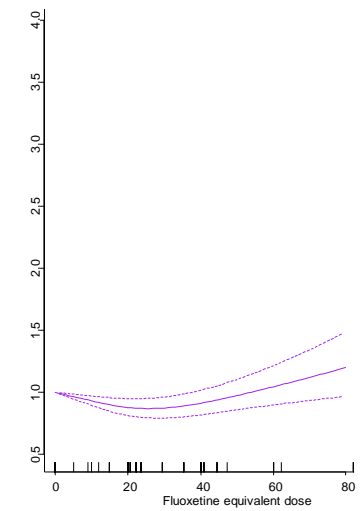
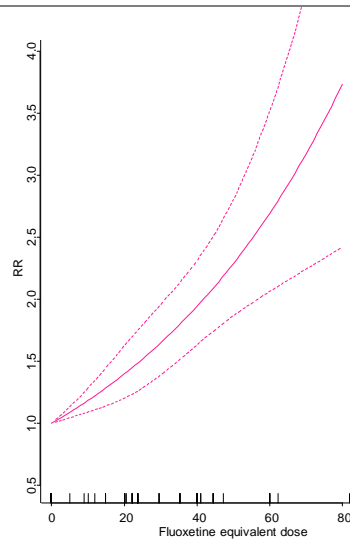
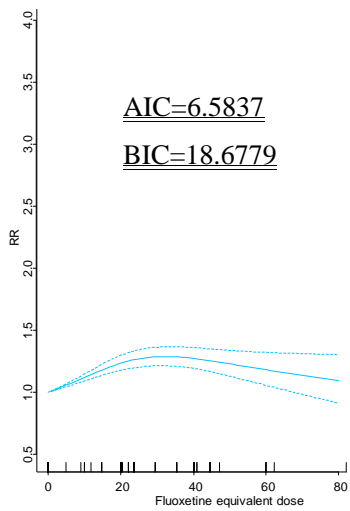
(10,20,40)



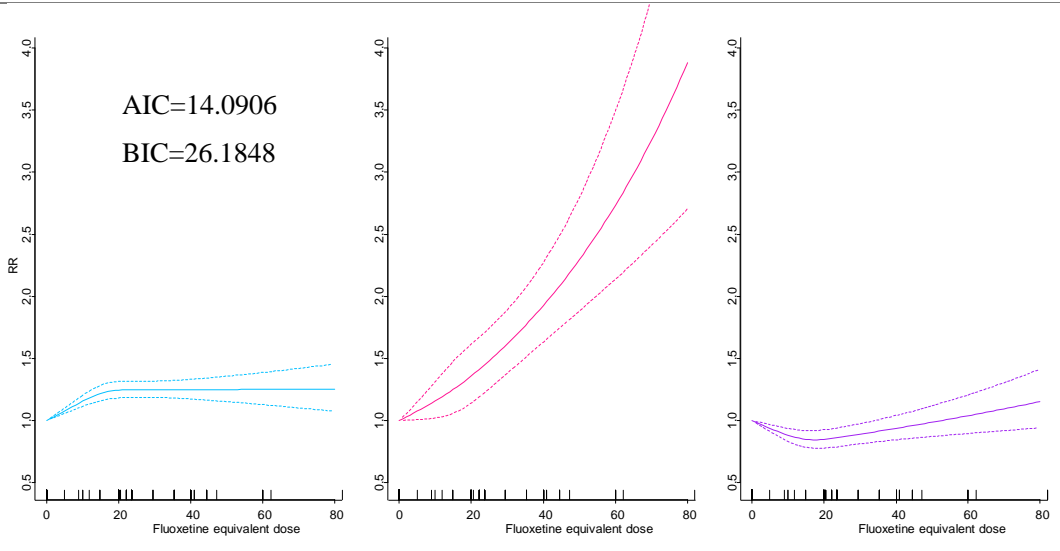
(20,40,60)



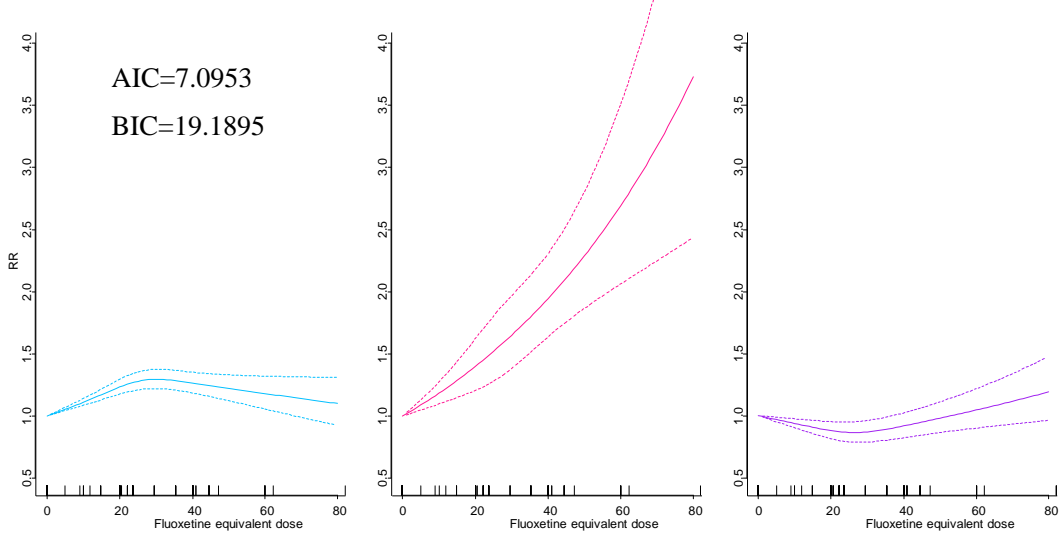
(10,20,50)



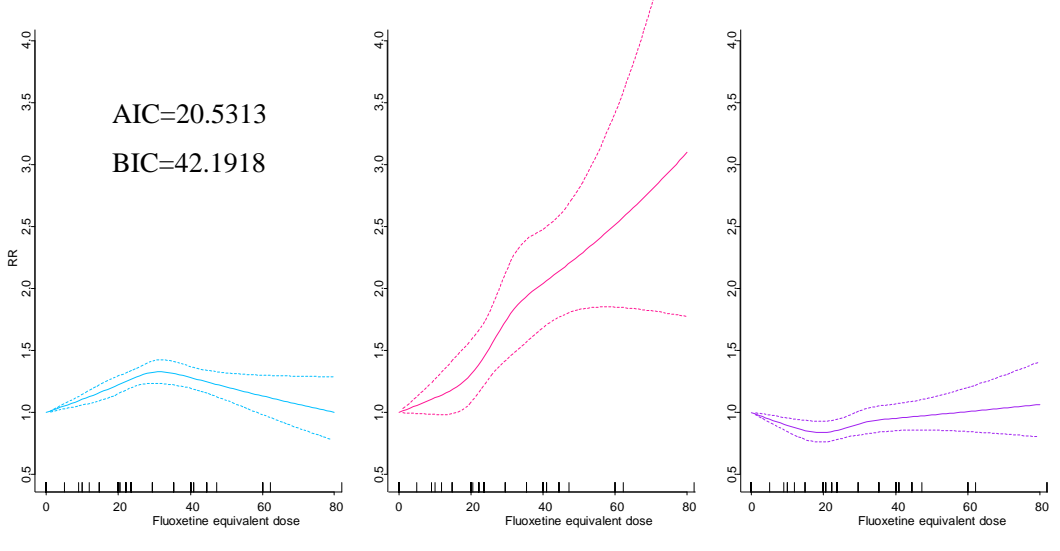
(5,15,25)



(15,25,40)



(10,20,30,40)



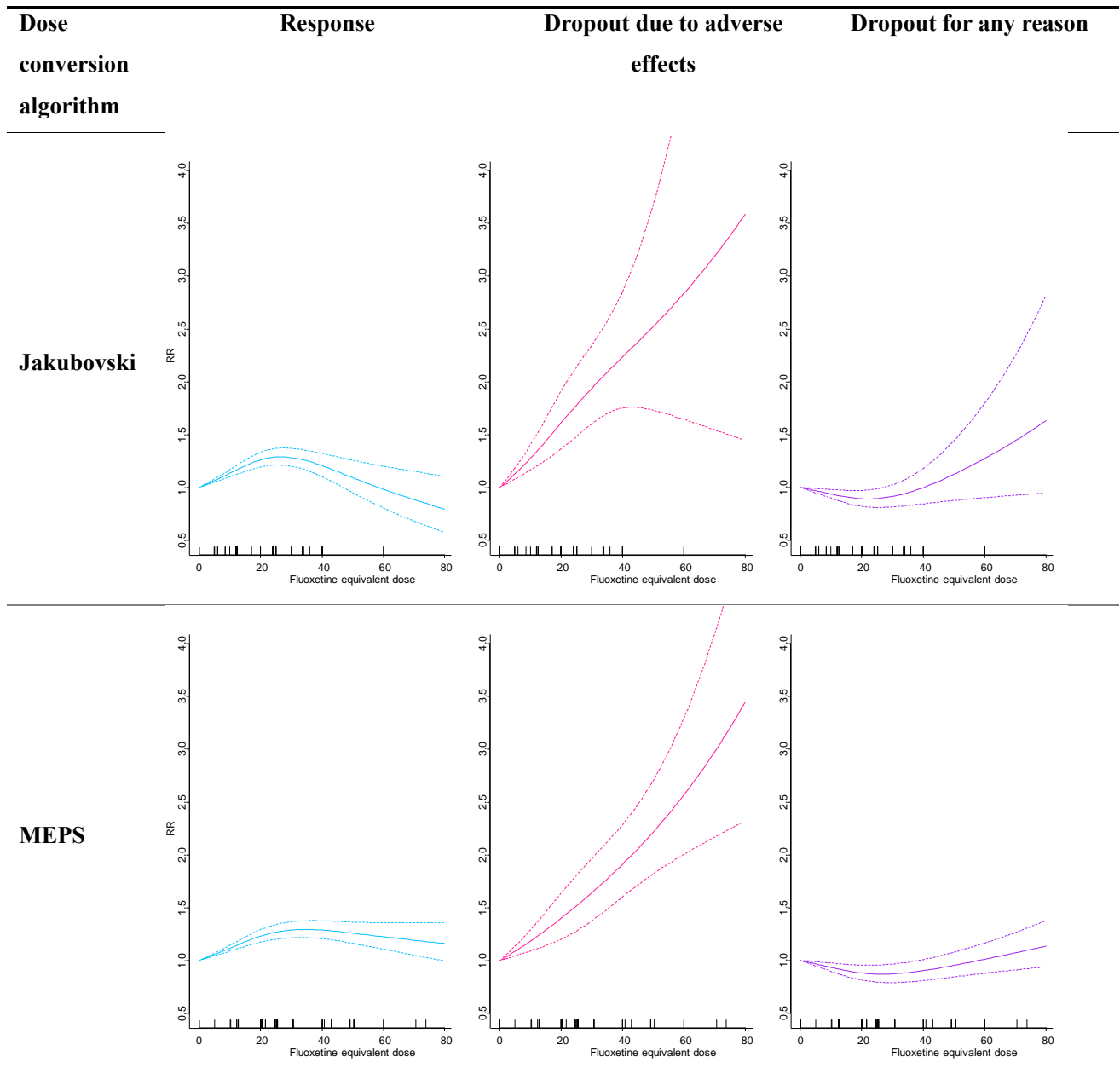
Each tick on the horizontal axis represents the dosage examined in a study arm.

The dotted lines represent 95% confidence intervals.

AIC: Akaike Information Criterion, BIC: Baeyesian Information Criterion

The double underline shows the model with the best fit.

eFigure 3. Dose-outcome relationships using different dose conversion algorithms

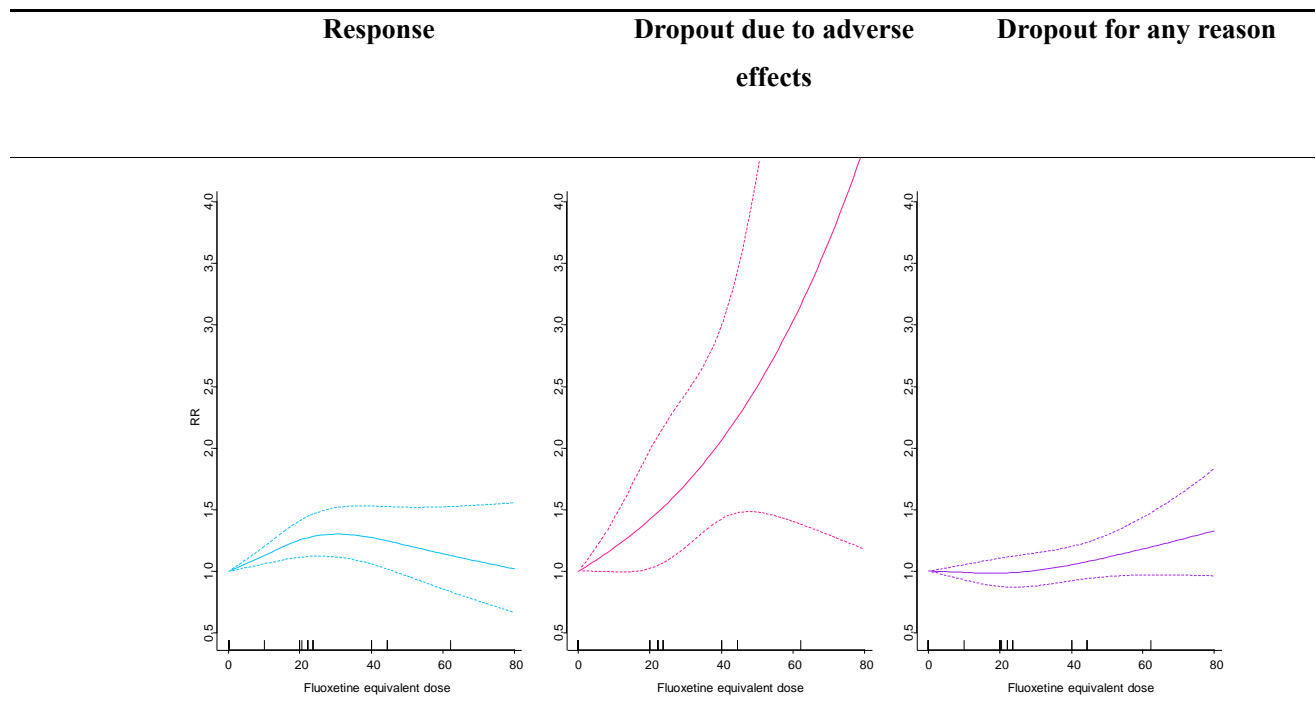


Each tick on the horizontal axis represents the dosage examined in a study arm.

The dotted lines represent 95% confidence intervals.

MEPS: Medical Expenditure Panel Survey

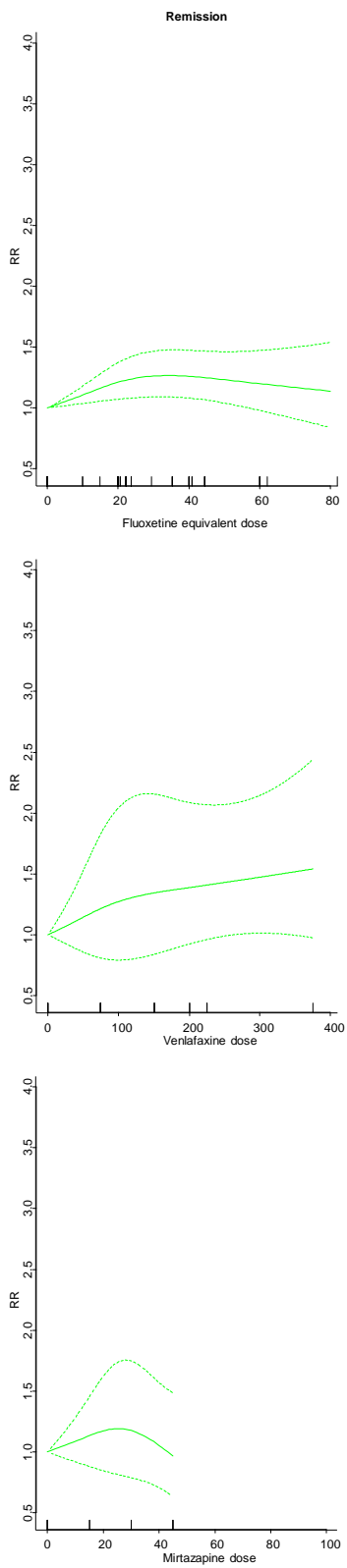
eFigure 4. Dose-outcome relationships among studies at low risk of bias only



Each tick on the horizontal axis represents the dosage examined in a study arm.

The dotted lines represent 95% confidence intervals.

eFigure 5. Dose-remission relationship for SSRIs, venlafaxine and mirtazapine



Each tick on the horizontal axis represents the dosage examined in a study arm.

The dotted lines represent 95% confidence intervals.