Supplementary file 1

Contents

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Table S1 – Treatment of depression guidelines

Guideline	Section/Page	Dose specific text
Guidelines highlighting dose-response effects		
British Association of Psychopharmacology (2015)[1]	Section 3.2 Next-step drug treatment options	*Summary: There is a lack of direct evidence for the efficacy of increasing the dose after initial treatment non-response. Indirect evidence suggests there is a dose response for TCAs, venlafaxine and escitalopram (II) but not for other SSRIs.*
	Section 3.2.1 Dose Increase (C)	*The evidence supporting the efficacy of dose increase is limited, but it could be considered in individual patients especially if:* • *there are minimal side-effects (D) and/or,* • *there has been some improvement on the antidepressant (D) and/or, the current antidepressant has a possible dose response (there is modest evidence for venlafaxine, escitalopram and TCAs) (C).*
Royal Australian and New Zealand College of Psychiatrists (2015)[2]	Page 1108-1109	***An adequate trial of an antidepressant should be a minimum of three weeks at the recommended therapeutic dose.*** *Note, some antidepressants require titration to the maximum recommended dose, whereas others, in particular SSRIs, generally have a flat dose-response curve and high doses do not necessarily improve efficacy.*
Guidelines lacking clarity regarding dose-response effects		
National Institute for Health and Care Excellence CG90 (Sept 2019 Update)[3]	Section 10.15.4.4	*If response is absent or minimal after 3 to 4 weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support (for example, by weekly face-to-face or telephone contact) and consider:* • *increasing the dose in line with the Summary of Product Characteristics if there are no significant side effects or if the person prefers.*
	Section 12.3.1	*When depression does not respond adequately, a common treatment strategy is to increase the dose of the antidepressant within the licensed dosage range. There is little objective evidence to support higher response rates with increasing dose (within the licensed dosage range) for the majority of antidepressants, but this does not preclude the possibility of a beneficial effect being seen in individual patients. Any beneficial effect is likely to be at least partially determined by individual differences in hepatic metabolising enzymes.*
	Section 12.3.2	*Approximately 20 to 30% of patients with depression do not respond to the first antidepressant prescribed (assuming an adequate dose, duration of treatment and compliance with medication; Cowen, 1998). It is normal clinical practice at this point to increase the dose to the maximum tolerated (within licensed limits; see section 12.3.1) and, if there is still no or minimal response, to switch to an alternative antidepressant.*
	Section 12.3.13	*The evidence for effective strategies in people whose depression has not responded adequately to treatment is not strong. A common first-line strategy, increasing the dose, is also not supported by convincing evidence of effectiveness, although this strategy may well be effective in some people, particularly if they have been able to tolerate the drug at the initial dose.*

Guidelines lacking clarity regarding dose-response effects (Continued)		
National Institute for Health and Care Excellence NG 222 (June 2022)[4]	Section 1.9.5	*If a person's depression has had no or a limited response to treatment with antidepressant medication alone, and no obvious cause can be found and resolved, discuss further treatment options with the person and make a shared decision on how to proceed based on their clinical need and preferences. Options include* [a range of options are listed]: • *continuing antidepressant therapy by either increasing the dose or changing the drug. For example, by:* ○ *increasing the dose of the current medication (within the licensed dose range) if the medication is well tolerated; be aware that higher doses of antidepressants may not be more effective and can increase the frequency and severity of side effects; ensure follow-up and frequent monitoring of symptoms and side effects after dose increases.*
	Section 1.9.6	*If a person's depression has had no or a limited response to treatment with a combination of antidepressant medication and psychological therapy, discuss further treatment options with the person and make a shared decision on how to proceed based on their clinical need and preferences. Options include* [a range of options are listed]: *increasing the dose or switching to another antidepressant (see recommendation 1.9.5)*
American Psychiatric Association (2010)[5]	Quick reference guide page 18	*The initial dose should be raised incrementally as tolerated until a therapeutic dose is reached or the patient achieves remission. Titration generally can be accomplished over initial weeks, but more time may be needed depending on development of side effects, the patient's age, and the presence of co-occurring medical and psychiatric conditions.*
	Quick reference guide page 21	***Address inadequate response. Maximizing the Initial Treatment*** *Patients Treated With an Antidepressant:* • *Optimizing (i.e., raising) the dose is a reasonable first step if side-effect burden is tolerable, especially if the upper dosage limit has not yet been reached.* *Some patients may require doses higher than those approved by the Food and Drug Administration.*
Canadian Network for Mood and Anxiety Treatments (CANMAT) (2016)[6]	Section 3.14	***How Long Do You Wait for a Response from an Antidepressant?*** *CANMAT recommends increasing the antidepressant dose for nonimprovers at 2 to 4 weeks if the medication is tolerated and switching to another antidepressant if tolerability is a problem.*
	Section 3.16	***How Do You Manage Inadequate Response to an Antidepressant?*** *If a patient has partial (e.g., 25%-49% reduction in symptom scores) or no response (e.g., <25% reduction) to the initial treatment, clinicians should ensure the treatment is optimized. There is substantial evidence that many patients receive subtherapeutic doses and/or inadequate duration of treatment, and up to 20% may have poor adherence.*

1. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology 2015;29(5):459-525. doi: 10.1177/0269881115581093

2. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand Journal of Psychiatry 2015;49(12):1087-206.

3. National Institute for Health and Care Excellence. Clinical Guideline 90: The treatment and management of depression in adults (Updated edition 2019), 2019.

4. National Institute for Health and Care Excellence. National Guideline 222: Depression in adults: treatment and management (June 2022), 2022.

5. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder. Washington DC: American Psychiatric Association 2010.

6. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments. Canadian Journal of Psychiatry 2016;61(9):540-60.

Search strategies

Embase 1975 to 2021

	Searches	Results
1	systematic review$.mp. or exp "systematic review"/	422957
2	meta analysis/	233016
3	dose-response.mp. or exp dose response/	459419
4	1 or 2 or 3	965431
5	antidepressants$.mp. or exp antidepressant agent/	522746
6	ssri.mp. or exp serotonin uptake inhibitor/	291876
7	exp serotonin uptake inhibitor/ or selective serotonin inhibitor$.mp.	291324
8	citalopram.mp. or exp citalopram/	24483
9	escitalopram.mp. or exp escitalopram/	13786
10	fluoxetine.mp. or exp fluoxetine/	50458
11	fluxetine.mp.	33
12	fluvoxamine.mp. or exp fluvoxamine maleate/ or exp fluvoxamine/	14665
13	paroxetine.mp. or exp paroxetine/	29256
14	sertraline.mp. or exp sertraline/	28225
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	524221
16	4 and 15	41674
17	depression.mp. or exp depression/ or exp major depression/	789628
18	major depressive disorder.mp. or exp major depression/	79382
19	unipolar depression.mp.	4133
20	17 or 18 or 19	790950
21	16 and 20	12630
22	limit 21 to human	10975
23	limit 22 to english language	10408
24	limit 23 to yr="1975 - 2021"	10375

Ovid Medline (R) All 1975 to 2021

	Searches	Results
1	systematic review$.mp.	257991
2	meta-analysis.mp. or exp Meta-Analysis/	232434
3	exp Dose-Response Relationship, Drug/ or dose response.mp.	527175
4	1 or 2 or 3	893529
5	Antidepressant$.mp. or exp Antidepressive Agents/	181670
6	exp Serotonin Uptake Inhibitors/ or ssri.mp.	46233
7	selective serotonin inhibitor$.mp.	31
8	citalopram.mp. or exp Citalopram/	7401
9	escitalopram.mp.	2836
10	fluoxetine.mp. or exp Fluoxetine/	14859
11	fluxetine.mp.	7
12	fluvoxamine.mp. or exp Fluvoxamine/	3104
13	paroxetine.mp. or exp Paroxetine/	6572
14	sertraline.mp. or exp Sertraline/	5592
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	197756
16	4 and 15	18050
17	depression.mp. or exp Depression/	445870
18	exp Depressive Disorder/ or exp Depressive Disorder, Major/ or mdd.mp.	120528
19	unipolar depression.mp.	2915
20	17 or 18 or 19	479550
21	16 and 20	6916
22	limit 21 to humans	5337
23	limit 22 to english language	4997
24	limit 23 to yr="1975 - 2021"	4973

Embase, Ovid Medline (R) All, and PsychInfo 1975 to 2021

	Searches	Results
1	Systematic review.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	688896
2	meta-analysis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	611577
3	dose-response.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	977707
4	1 or 2 or 3	1951504
5	citalopram.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	35516
6	escitalopram.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	18398
7	fluxetine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	45
8	fluoxetine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	72941
9	fluvoxamine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	19567
10	paroxetine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	39506
11	sertraline.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	37117
12	ssri.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	23575
13	serotonin uptake inhibitor$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	78664
14	selective serotonin re-uptake inhibitor$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	2129
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	185018
16	depression.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	1549267

17	major depressive disorder.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	88507
18	major depression.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	252537
19	unipolar depression.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy, tc, id, tm]	10391
20	16 or 17 or 18 or 19	1561530
21	4 and 15 and 20	10272
22	limit 21 to humans	9167
23	limit 22 to english language	8732
24	limit 23 to yr="1975 - 2021"	8728

Table S2 – Characteristics of reviews meeting inclusion criteria

Study	Indication	Number of primary studies included	Review design	Efficacy & Dose	ADEs & dropouts	Protocol	Placebo included	Patient -level	Flexible dose studies included	Does Standardisation	Study duration	Primary or secondary care
Adli 2005 [1]	Major depression	12	Syst. Narr.	↑ fluv. ↔ cit, fluox, par, sert	↑	Unclear	Yes	No	Reported separately	Study doses used	4-8 wks	Unclear
Altamura 1988 [2]	Depression	2	Narr.	↔ fluox	↑	No	Yes	No	No	Fluox dose	6 wks	Outpatients
Baker 2003 [3]	Major depression	4	Syst. M-A.	? fluox, par, sert	↑	No	No	No	Reported separately	Yes: Low, Medium, High. No clear definition	≤8 wks	Unclear
Barbui 2002 [4]	Depression	103	Syst. M-A.	↑ fluox	↑	No	No	No	Yes	Yes: 20-30mg/d, >30mg/d. Dose range 20-40mg/d & >40mg/d	≤9 wks	Both
Beasley 1990 [5]	MDD	Pooled (n=669)	Pooled. Not Syst.	↔ fluox	↑	No	Yes	No	Yes	Fluox dose	≤8 wks	Outpatients
Beasley 1993 [6]	MDD	3	Narr.	n-a	fluox: ↑ anxiety, agitation, insomnia., drowsiness, asthenia.	No	Yes	Yes	Yes	None	6 wks	Primary care
Benkert 1996 [7]	MDD	7 (+7 Rev)	Narr.	↔ cit, fluox, fluv, par, sert	n-a	No	Yes	No	Yes	Actual doses from other reviews	Not defined	Not defined
Berney 2005 [8]	Depression	14 (+4 Revs)	Narr.	↔ cit, escit, fluox, par, sert. ? fluv	↑ fluox, dropout[a]	No	Yes	No	No	Study doses used	6-8 wks	Both
Bollini 1999 [9]	Depression	33	Syst. M-A.	∩ curvy linear SSRI & non-SSRI grouped	↑	Unclear	Yes	No	Yes	Imip Equiv	6 wks (4-24 wks)	Unclear
Braun 2020 [10]	Depressive disorder	33	Syst. M-A. Net-M-A	↔ SSRI grouped ↔ cit, escit, fluox, fluvox par, sert	↑ SSRI grouped	Yes	Yes	No	Yes	Low, Med, High.	6 wks (2-12 wks)	Unclear
Caley 2002 [11]	Depression	5 (+7 Revs)	Narr.	↑ cit, ∩ fluv, ↔ fluox, sert, ?par	↑	No	Yes	No	Yes	Study doses used	4-6 wks	Both
Cheng [12]	Major depression	115	Model-Bases M-A	↔ cit, escit, fluox, fluvox par, sert	n-a	No	Yes	No	No	Fluox Equiv	4-12wks	Both
Corruble 2000 [13]	Depression	10 (+6 Revs)	Syst. Narr.	SSRI grouped	n-a	No	No	No	No	SSRI study doses used	4-8 wks	Unclear
Dold 2017 [14]	Unipolar depression	5	Syst. M-A. M-R	↔ fluox, par, sert	↑fluox,	No	No	No	Rand. fixed v increased dose	Standard dose: fluox, par 20mg/d, sert 50mg/d, versus higher doses	5 wks (3-8 wks)	Unclear
Dunner 1992 [15]	Depression	Pooled (n=460)	Pooled SKB data only	↔ Par	n-a	No	Yes	Yes	Yes	Par. dose	Acute ≤6 wks Long-term 52 wks	Unclear
Furukawa 2019 [16]	Major depression	66	Syst. M-A	↑ SSRI grouped (to 40mg/d) ↑ cit (to 30mg/d), ↔ escit, fluox, par, ∩ sert.	↑	Yes	Yes	No	No	Fluox Equiv	8 wks (4-12wks)	Both
Furukawa 2020 [17]	Major depression	108	Syst. M-A	↔ SSRI grouped ↔ cit, escit, fluox, par, sert	↑ flexible dose	Yes	Yes	No	Fixed v flex dosing	Fluox Equiv	7 wks (4-12 wks)	Both
Gutsmiedl 2020 [18]	MDD	44	Syst. M-A. M-R	↔ SSRIs & non-SSRI grouped	n-a	Yes	Yes	Yes	Yes	Fluox Equiv	9 wks (4-26 wks)	Both
Hansen 2009 [19]	Depression	74	Syst. M-A. M-R	↑ SSRIs & non-SSRI grouped	n-a	No	Yes	No	Yes	Yes: licensed dose range e.g. fluox <45mg/d low >45mg/d high	7 wks (6-24 wks)	Outpatients
Hamza 2021 [20]	MDD	60	M-A	SSRI grouped (↑ to 40mg/d) ↑ cit (to 30mg/d), par, sert (to 75mg/d), ↔ escit, fluox,,	n-a	No	Yes	No	No	Fluox Equiv. Individual drug effects as fluox equiv not actual drug dose.	8 wks (4-12wks)	Both

Review characteristics – continued

Study	Indication	Number of primary studies included	Review design	Efficacy & Dose	ADEs & dropouts	Protocol	Placebo included	Patient-level	Flexible dose studies included	Does Standardisation	Study duration (range)	Primary or secondary care
Hieronymus 2016 [21]	Depression	11	M-A. Ind. Data.	↑ cit, par, sert	n-a	Yes	Yes	Yes	Yes	Patient-level doses	≤6 wks	Unclear
Holper 2020 [22]	MDD	153	Net-M-A	↑ escital, fluox, ↔ cit, par	↑ (≤70y) ↑↑ (>70y)	Yes	Yes	No	Yes	Fluox Euqiv	4-12 wks	Both
Jakubovski 2016 [23]	MDD	40	Syst. M-A.	↑ SSRIs grouped	↑	Unclear	Yes	No	Yes	Imip Equiv	6 wks (4-24 wks)	Unclear
Jenner 1992 [24]	Depression	Pooled (n=4668)	Pooled. SKB data only	↔ par	↑	No	Yes	Yes	Reported separately	Par. dose	Mostly 6 wks (≤2 yr)	Both
Khan 2003 [25]	MDD	36	FDA submissions M-A	↔ SSRIs & non-SSRI grouped	↑	No	Yes	No	Reported separately	SSRI study doses used	6-8wks	Unclear
Klemp 2011 [26]	Depression	26	Syst. M-R.	↔ par	n-a	No	Yes	No	Yes	Par dose	8 wks (6-56 wks)	Outpatients
Lam 2006 [27]	MDD	3	M-A. Lundbeck data only	↔ escital	n-a	No	Yes	No	Yes	Escit dose	8 wks	Both
Lane 1995 [28]	Depression	5 (+2 Revs)	Narr.	↔ cit, fluox, par, sert	↑	No	Yes	Not defined	Yes	Not defined	Not defined	Not defined
Montgomery 1994 [29]	Depression	9	M-A. Not Syst.	↔ cit	n-a	No	Yes	No	Yes	Cit dose	4-6 wks	Unclear
Montgomery 1995 [30]	Depression	1	Narr.	↔ sert	↑	No	Yes	No	No	Sert dose	Acute 6-8 wks Long-term 44 wks	Not defined
Montgomery 1995 [31]	Depression	2 (+2 Revs)	Narr.	↔ cit	n-a	No	Yes	No	Yes	Cit dose	≤24 wks	Both
Murdoch 2005 [32]	MDD	Pooled (n=1307)	Pooled Lundbeck Forrest	n-a	↑ escital	No	Yes	No	Yes	Escit dose	Not defined	Not defined
Oliva 2021 [33]	MDD	Not defined	Syst. M-A.	n-a	↑ N&V cit, esciatl	Yes	Yes	No	Unclear	Low v high dose	6-12 wks	Not defined
Papakostas 2010 [34]	MDD	9	Syst. M-A.	↑ SSRIs grouped	↑	No	Yes	No	Yes	Usual dose (10mg/d escit, 20mg/d cit, fluox, par, 50mg/d sert, fluv), intermediate, double (double usual) & higher.	6 wks	Not defined
Parker 2000 [35]	Depression	1 (+1 Rev)	Narr.	↑ cit	↑	No	Yes	No	Yes	Cit dose	4-6 wks	Not defined
Purgato 2015 [36]	Unipolar major depression	173	Syst. M-R.	↔ fluox	n-a	No	Yes	No	Yes	Yes: Mean doses poorly reported: min and max doses to DDDs then PDD/DDD. Grouped: ≤20mg/d or 20-80mg/d	Majority ≤6 wks	Both
Preskorn 1995 [37]	Depression	3	Narr.	↔ sert	↑	No	Yes	No	No	Sert dose	≤8 wks	Outpatients
Rifkin 1997 [38]	Depression	4	Narr.	↔ fluox, par, sert	n-a	No	Yes	No	No	SSRI study doses used	Not defined	Not defined
Ruhe 2006 [39]	Depression	8	Syst. Narr.	↔ cit, fluox, par, sert ∩ fluv,	n-a	Unclear	No	No	Yes	SSRI study doses used	8 wks (3-12 wks)	Unclear
Safer 2016 [40]	MDD & other MH conditions	33	Narr.	↔ SSRI & non-SSRI grouped ↔ cit, escit, fluox, fluv, par, sert	↑	No	Yes	No	No	SSRI study doses used	8-28 wks	Not defined

Review characteristics – continued

Study	Indication	Number of primary studies included	Review design	Efficacy & Dose	ADEs & dropouts	Protocol	Placebo included	Patient-level	Flexible dose studies included	Does Standardisation	Study duration (range)	Primary or secondary care
Tan 1999 [41]	MDD & other MH conditions	2 (+1 Rev)	Narr.	?cit	↑	No	Yes	No	Yes	Cit dose	6 wks (3-24 wks)	Not defined
Vaswani 2003 [42]	MDD & other MH conditions	3 (+5 Revs)	Narr.	↑ cit (to 40mg/d), ↔ fluox, fluv, par, sert	↑	No	Yes	Not defined	Yes	Not defined	Not defined	Not defined

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Table S3 – Risk of bias

	Review		Phase 2				Phase 3
	Author	**Year**	**1. Study eligibility criteria**	**2. Identification and selection of studies**	**3. Data collection and study appraisal**	**4. Synthesis and findings**	**RISK OF BIAS IN THE REVIEW**
1	Adli	2005	Low	High	High	Low	High
2	Altamura	1988	High	High	High	High	High
3	Baker	2003	Low	High	High	High	High
4	Barburi	2002	Low	Low	High	Unclear	High
5	Beasley	1990	Low	High	High	Low	High
6	Beasley	1993	Unclear	High	High	High	High
7	Benkert	1996	Unclear	Unclear	High	Unclear	Unclear
8	Berney	2005	Unclear	High	High	Low	High
9	Bollini	1999	Low	Low	Unclear	High	High
10	Braun	2020	Low	Low	Low	Low	Low
11	Cheng	2020	Low	Unclear	Low	Low	Low
12	Caley	2002	Unclear	Unclear	High	Unclear	High
13	Corruble	2000	Low	Unclear	Unclear	Unclear	High
14	Dold	2017	Low	Low	Low	Low	Low
15	Dunner	1992	Unclear	Unclear	High	Low	Unclear
16	Furukawa	2019	Unclear	Low	Low	Low	Low
17	Furukawa	2020	Low	Low	Low	Low	Low
18	Gutsmiedl	2020	Low	Unclear	Low	Unclear	Unclear
19	Hamza	2021	Low	Unclear	Unclear	Low	Unclear
20	Hansen	2009	Low	Unclear	High	High	High
21	Hieronymus	2016	Low	High	Unclear	High	High
22	Holper	2019	Low	Low	Low	High	High
23	Jakubovski	2016	High	High	High	High	High
24	Jenner	1992	Unclear	High	High	Low	High
25	Khan	2003	Low	Unclear	High	Low	Unclear
26	Klemp	2011	Low	Low	Unclear	Unclear	Unclear
27	Lam	2006	Low	High	High	High	High
28	Lane	1995	Unclear	Unclear	High	High	High
29	Mongomery	1995	High	High	High	High	High
30	Montgomery	1995	Unclear	Unclear	Unclear	Low	Unclear
31	Montgomery	1994	Unclear	Unclear	High	High	High
32	Murdoch	2005	Low	Unclear	Unclear	Unclear	Unclear
33	Oliva	2021	Low	Low	High	High	High
34	Papakostas	2010	Low	High	High	Unclear	High
35	Parker	2000	Low	High	Unclear	Low	High
36	Preskorn	1995	Unclear	Unclear	Unclear	Low	Unclear
37	Purgato	2015	Unclear	Low	Unclear	Low	Unclear
38	Rifkin	1997	Unclear	Unclear	Unclear	Unclear	High
39	Ruhe	2006	Unclear	High	Low	Low	High
40	Safer	2016	Unclear	Unclear	Unclear	Unclear	Unclear
41	Tan	1999	Unclear	Unclear	Unclear	Low	Unclear
42	Vaswani	2003	Unclear	Unclear	Unclear	Unclear	Unclear

Table S4 – Primary studies quality rating

160 primary studies included in the reviews (N=5) assessed as being at low risk of bias. Of the 160 primary studies overall risk of bias was rated as low 34 (21%), moderate 120 (75%) and high 6 (4%).

Study ID	Dep. severity	Braun 2020	Cheng 2020	Dold 2017	Furukawa 2019	Furukawa 2020	Overall risk of bias
1. Alexopoulos 2004 (Poster SCT-MD-27)		n/a	Mod.	n/a	n/a	Mod.	Mod.
2. Amin 1984		n/a	Mod.	n/a	n/a	n/a	Mod.
3. Barber 2011		n/a	n/a	n/a	n/a	Mod.	Mod.
4. Benkert 1997		n/a	n/a	Mod.	n/a	n/a	Mod.
5. Binnemann2008 (NCT00143091)		n/a	Mod.	n/a	Mod.	n/a	Mod.
6. Bjerkenstedt 1985		Mod.	n/a	n/a	n/a	n/a	Mod.
7. Bjerkenstedt2005		n/a	Low	n/a	Low	Low	Low
8. Bosc 1997a (Study 014 - Andreoli2002)		n/a	Mod.	n/a	n/a	Mod.	Mod.
9. Bose 2008 (SCT-MD-13)		n/a	n/a	n/a	n/a	Mod.	Mod.
10. Brunoni 2012		n/a	Low	n/a	Low	Low	Low
11. Buchsbaum 1997		n/a	Mod.	n/a	n/a	n/a	Mod.
12. Burke2002 (SCT-MD-01)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
13. Byerley1988		n/a	Low	n/a	n/a	n/a	Low
14. CAGO178A2303 (NCT00463242)		n/a	Mod.	n/a	n/a	Mod.	Mod.
15. Cassano 2002 (29060/421)		n/a	Mod.	n/a	n/a	n/a	Mod.
16. CL3-20098-022		n/a	n/a	n/a	Mod.	Mod.	Mod.
17. CL3-20098-023		n/a	n/a	n/a	Low	Low	Low
18. CL3-20098-024		n/a	n/a	n/a	Low	Low	Low
19. Claghorn 1996		n/a	Mod.	n/a	n/a	n/a	Mod.
20. Clayton 2003 (Study 050)		n/a	Mod.	n/a	n/a	Mod.	Mod.
21. Clayton 2006a (WELL AK130926)		n/a	n/a	n/a	n/a	Mod.	Mod.
22. Clayton 2006b (WELL AK130927)		n/a	Mod.	n/a	n/a	Mod.	Mod.
23. CN104-054 (FDA)		n/a	n/a	n/a	Mod.	Mod.	Mod.
24. Cohn 1985a		n/a	Mod.	n/a	n/a	Mod.	Mod.
25. Coleman 1999 (AK1A4002)		n/a	Mod.	n/a	n/a	Mod.	Mod.
26. Coleman 2001 (AK1A4007)		n/a	Mod.	n/a	n/a	Mod.	Mod.
27. Corrigan 2000		n/a	Mod.	n/a	Mod.	Mod.	Mod.
28. Croft 1999 (AK1A4001)		n/a	Low	n/a	n/a	Mod.	Mod.
29. Davidson 2002 (HDTSG) (NCT00005013)		n/a	Low	n/a	n/a	Low	Low
30. Detke 2004 (HMAY Study Group A)	Mild	n/a	Low	n/a	Low	Low	Low
31. Doogan 1994		n/a	Low	n/a	n/a	Low	Low
32. Dornseif 1998		n/a	n/a	High	n/a	n/a	High
33. Dube 2010 (NCT00420004)		n/a	n/a	n/a	n/a	Mod.	Mod.

34. Dunbar 1993a (Claghorn1992, Rickels1989, Rickels1992, PAR 02-001 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
35. Dunbar 1993b (Claghorn1992, PAR 02-002 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
36. Dunbar 1993c (Smith1992, PAR 02-003 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
37. Dunbar 1993d (Kiev1992, PAR 02-004 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
38. Dunner 1992 (PAR 29060.09)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
39. Edwards1989 (MD/PAR/009 PAR-276)		n/a	Mod.	n/a	Mod.	n/a	Mod.
40. Fabre 1987	Mild	High	n/a	n/a	n/a	n/a	High
41. Fabre 1995 (SER 103 FDA)		Low	Mod.	n/a	Mod.	Mod.	Mod.
42. Fabre 1996		n/a	Low	n/a	n/a	n/a	Low
43. Fava 1998		n/a	Mod.	n/a	n/a	n/a	Mod.
44. Fava 2005	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
45. Feighner 1989a		n/a	Mod.	n/a	n/a	n/a	Mod.
46. Feighner 1989b		n/a	Low	n/a	n/a	n/a	Low
47. Feighner 1993a (Feighner 1989c PAR 03 001 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
48. Feighner 1993b (Cohn1990 Cohn1992 PAR 03 002 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
49. Feighner 1993c (PAR 03 003 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
50. Feighner 1993d (Shrivastava1992 PAR 03 004 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
51. Feighner 1993e (Peselow1989 PAR 03 005 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
52. Feighner 1993f (Fabre1992 PAR 03 006 - FDA)		n/a	Mod.	n/a	n/a	n/a	Mod.
53. Feighner 1999 (Study 91206 FDA)		Low	Mod.	n/a	Mod.	Mod.	Mod.
54. Fieve 1986		High	n/a	n/a	n/a	n/a	High
55. Frank 2004		n/a	n/a	n/a	Mod.	Mod.	Mod.
56. Gastpar 2006		n/a	Low	n/a	Low	Low	Low
57. Ghose 1997		Low	n/a	n/a	n/a	n/a	Low
58. Golden 2002a (29060/448)		n/a	Mod.	n/a	n/a	Mod.	Mod.
59. Golden 2002b (29060/449)		n/a	Mod.	n/a	n/a	Mod.	Mod.
60. Goldstein 2002 (HMAQ - Study Group A)	Mild	n/a	Mod.	n/a	n/a	Mod.	Mod.

61. Goldstein 2004a (HMAT - Study Group A, ID#4091)	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
62. Goldstein 2004b (HMAT - Study Group B, ID#4091)	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
63. Gorman 2002 (SCT-MD-02)		n/a	Mod.	n/a	n/a	Mod.	Mod.
64. Griebel 2012 (Study DF15878) (NCT00358631)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
65. Griebel 2012b (Study DF15879) (NCT00361491)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
66. Guy (1986)[27]		Mod.	n/a	n/a	n/a	n/a	Mod.
67. Hebenstreit 1989		Mod.	n/a	n/a	n/a	n/a	Mod.
68. Heiligenstein 1994	Mild	n/a	Low	n/a	Low	Low	Low
69. Higuchi 2009		n/a	Low	n/a	n/a	Low	Low
70. Higuchi 2011 (PCR112810, NCT00866294)		n/a	Low	n/a	n/a	Low	Low
71. Hirayasu 2011a		Low	Low	n/a	Low	Low	Low
72. Hirayasu 2011b		Low	Low	n/a	Low	Low	Low
73. Hunter 2010 (Study 1)		n/a	n/a	n/a	Mod.	Mod.	Mod.
74. Jefferson 2000 (29060/785)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
75. Kasper 2005a (Study 99024)		n/a	n/a	n/a	Mod.	Mod.	Mod.
76. Kasper2012 (NCT00807248)		n/a	Mod.	n/a	Mod.	n/a	Mod.
77. Kato 2018		Mod.	n/a	n/a	n/a	n/a	Mod.
78. Katz 2004		n/a	n/a	n/a	n/a	Low	Low
79. Keller 2006a (Study059) (NCT00035009)		n/a	n/a	n/a	Mod.	Mod.	Mod.
80. Keller 2006b (Study061) (NCT00035295)		n/a	n/a	n/a	Mod.	Mod.	Mod.
81. Keller 2006c (Study062) (NCT00048607)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
82. Kramer 1998		n/a	n/a	n/a	Mod.	Mod.	Mod.
83. Lam 1995		n/a	Mod.	n/a	Mod.	Mod.	Mod.
84. Learned 2012 (NCT00420641)		n/a	Mod.	n/a	Mod.	n/a	Mod.
85. Lepola 2003 (ESC 99003)		n/a	Low	n/a	n/a	Low	Low
86. Loo 2002 (CL2-014)		n/a	Low	n/a	Mod.	Mod.	Mod.
87. Lopez Rodriguez 2004		n/a	Mod.	n/a	Mod.	Mod.	Mod.
88. Lydiard 1997		n/a	Mod.	n/a	n/a	Mod.	Mod.
89. M/2020/0046 (Study 046)		n/a	Mod.	n/a	n/a	Mod.	Mod.
90. M/2020/0047 (Study 047)		n/a	Mod.	n/a	n/a	Mod.	Mod.
91. Mao 2015 (NCT01098318)	Mild	n/a	Mod.	n/a	n/a	Mod.	Mod.
92. Mathews 2015 (NCT01473381)		Low	Low	n/a	Low	n/a	Low
93. McGrath 2000		n/a	n/a	n/a	n/a	Mod.	Mod.
94. Mendels 1999 (Study 85A - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.

95. Miller 1989 (MDUK/29060/III/82/006 (PAR-274) PAR UK 06 - FDA)		n/a	Mod.	n/a	Mod.	n/a	Mod.
96. Mischoulon 2014 (NCT00101452)		n/a	Mod.	n/a	n/a	Mod.	Mod.
97. Montgomery 1992 (Study 89303 FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
98. Moreno 2005		n/a	Mod.	n/a	Mod.	Mod.	Mod.
99. Moscovitch 2004		n/a	Low	n/a	n/a	Low	Low
100. Mundt 2012 (NCT00406952)		n/a	Mod.	n/a	n/a	Mod.	Mod.
101. MY-1008/BRL-029060/2/CPMS-076		n/a	n/a	n/a	Mod.	n/a	Mod.
102. MY-1042/BRL-029060/CPMS-251		n/a	Mod.	n/a	n/a	Mod.	Mod.
103. MY-1043/BRL-029060/115		n/a	n/a	n/a	n/a	Mod.	Mod.
104. MY-1045/BRL-029060/1 (PAR 128)		n/a	Mod.	n/a	n/a	Mod.	Mod.
105. NCT00822744 (EudraCT Number2008-001718-26)		n/a	n/a	n/a	Mod.	Mod.	Mod.
106. NCT01020799		n/a	Low	n/a	Low	n/a	Low
107. NCT01808612		Low	n/a	n/a	Low	Low	Low
108. Nemeroff 2007		n/a	Mod.	n/a	n/a	Mod.	Mod.
109. Nierenberg 2007 (F1J-MC-HMCR, NCT00073411, Pigott2007)		n/a	Low	n/a	Low	Low	Low
110. Ninan 2003 (poster SCT-MD-26)		n/a	Mod.	n/a	n/a	Mod.	Mod.
111. NKD20006 (NCT00048204)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
112. Norton 1984		n/a	Low	n/a	n/a	n/a	Low
113. Olie 1997		n/a	Low	n/a	n/a	Mod.	Mod.
114. PAR 279 MDUK		n/a	Mod.	n/a	Mod.	n/a	Mod.
115. Perahia 2006 (HMAY - Study Group B)	Mild	n/a	Low	n/a	Low	Low	Low
116. PZ/109 (Hieronymus 2016)		n/a	Mod.	n/a	n/a	n/a	Mod.
117. PZ/111 (Hieronymus 2016)		n/a	Mod.	n/a	n/a	n/a	Mod.
118. Rapaport 2009 (BRL-29060/874) (NCT00067444)		Low	n/a	n/a	Mod.	Mod.	Mod.
119. Ravindran 1995		n/a	n/a	n/a	n/a	Mod.	Mod.
120. Reimherr 1990 (SER 104 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
121. Rosenberg 1994		Low	n/a	n/a	n/a	n/a	Low
122. Roth 1990		n/a	Mod.	n/a	n/a	n/a	Mod.
123. Rudolph 1999		n/a	Low	n/a	n/a	Low	Low
124. Ruhe 2009		n/a	n/a	Low	n/a	n/a	Low
125. Schatzberg 2006a		n/a	n/a	n/a	n/a	Mod.	Mod.
126. Schneider 2003		n/a	n/a	n/a	n/a	Low	Low
127. Schweizer 1990		n/a	n/a	High	n/a	n/a	High

128. Schweizer 2001		n/a	n/a	Mod.	n/a	n/a	Mod.
129. SCT-MD-35 (NCT00109044)		n/a	n/a	n/a	Mod.	n/a	Mod.
130. SCT-MD-49 (NCT00668525)		Mod.	Low	n/a	Low	Mod.	Mod.
131. SER 101 (FDA)		Mod.	n/a	n/a	High	High	High
132. SER 310 (FDA)		Mod.	n/a	n/a	Mod.	Mod.	Mod.
133. SER 315 (FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
134. Sheehan2009a		n/a	Mod.	n/a	n/a	n/a	Mod.
135. Silverstone 1999		n/a	Mod.	n/a	n/a	Mod.	Mod.
136. Sramek 1995		n/a	Low	n/a	Low	Low	Low
137. Stahl 2000		n/a	Mod.	n/a	n/a	Mod.	Mod.
138. Stark 1985 (Study 27 - FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
139. Study 19 (Fabre 1985)		n/a	Mod.	n/a	n/a	n/a	Mod.
140. Study 25 (Rickels 1986)		n/a	Mod.	n/a	n/a	n/a	Mod.
141. Study 62a (FDA) - (Dunlop1990)	Mild	Mod.	Mod.	n/a	Mod.	Mod.	Mod.
142. Study 62b (FDA)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
143. Study 89306 (FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
144. Study F1J-MC-HMAQ - Study Group B	Mild	n/a	Mod.	n/a	Mod.	Mod.	Mod.
145. Suri 2000		Mod.	n/a	n/a	n/a	n/a	Mod.
146. Trivedi 2004 (29060/810)		Low	Mod.	n/a	Mod.	Mod.	Mod.
147. Tural 2003		High	n/a	n/a	n/a	n/a	High
148. VEN XR 367 (FDA)		n/a	Mod.	n/a	Mod.	Mod.	Mod.
149. Wade 2002 (ESC Study 99001 - FDA)		n/a	Low	n/a	Low	Low	Low
150. Walczak 1996		Mod.	n/a	n/a	n/a	n/a	Mod.
151. Wang 2014 (EUCTR2005-005052-40, NCT00351169, D1448C00004)		n/a	Mod.	n/a	n/a	Low	Low
152. WELL AK1A4006		n/a	Mod.	n/a	n/a	Mod.	Mod.
153. Wernicke 1987		Mod.	n/a	n/a	n/a	n/a	Mod.
154. Wernicke 1988		Mod.	n/a	n/a	Mod.	Mod.	Mod.
155. Yevtushenko 2007		Low	n/a	n/a	Low	n/a	Low
156. 003-048		n/a	Mod.	n/a	Low	n/a	Mod.
157. 244 (EMD 68 843-009) (FDA)		n/a	Mod.	n/a	n/a	Mod.	Mod.
158. 245 (EMD 68 843-010) (FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
159. 246 (SB 659746-003) (FDA)		Mod.	Mod.	n/a	Mod.	Mod.	Mod.
160. 29060/07/01		n/a	Mod.	n/a	n/a	n/a	Mod.

Primary studies references

160 primary studies from the 5 reviews assessed as being at low risk of bias

1. Alexopoulos 2004 (poster SCT-MD-27)
    - 1. Alexopoulos GSG, J.; Zhang, D. A placebo-controlled trial of escitalopram and sertraline in the treatment of major depressive disorder. Neuropsychopharmacology 2004;29
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2. Amin 1984
    - Amin MM, Ananth JV, Coleman BS, Darcourt G, Farkas T, Goldstein B, Lapierre YD, Paykel E, Wakelin JS. Fluvoxamine: antidepressant effects confirmed in a placebo-controlled international study. Clinical Neuropharmacology 1984;7(suppl 1):580-581.
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    - Barber JP, Barrett MS, Gallop R, Rynn MA, Rickels K. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012 Jan;73(1):66-73.
4. Benkert 1997
    - Benkert O, Szegedi A, Wetzel H, et al. Dose escalation vs. continued doses of paroxetine and maprotiline: A prospective study in depressed out-patients with inadequate treatment response. Acta Psychiatrica Scandinavica 1997;95(4):288-96.
5. Binnemann 2008 (NCT00143091)
    - Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. Am J Psychiatry. 2008;165(5):617-20.
6. Bjerkenstedt 1985
    - Bjerkenstedt L, Edman G, Flyckt L. Clinical and biochemical effects of citalopram, a selective 5-HT reuptake inhibitor - A dose-response study in depressed patients. *Psychopharmacology* 1985;87(3):253-59.
7. Bjerkenstedt 2005
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