Online supplement

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Appendix DS1

Search strategy

Literatures searches were performed in the following databases and article indexes:

MEDLINE

CINAHL

EMBASE

PsycInfo

Cochrane Controlled Trials Register

Controlled vocabulary was utilised where appropriate terms were available, supplemented with keyword searches to ensure accurate and exhaustive results. Search results were limited to randomised controlled trials or clinical trials (phase III). Language or publication year limits were not applied to any search.

To illustrate, the following MEDLINE search is indicative of searches performed in the other databases. It should be noted that although searches across the databases were similar, there are database-specific tools and terms that were utilised to ensure effective retrieval.

#1 Depression/Drug therapy [MeSH] OR Depressive Disorder [MeSH]/exp

#2 subthreshold depression OR minor depression OR mild depression OR subsyndromal depression OR non-major depression

#3 Benzodiazepines [MeSH]/exp

#4 Antidepressants [MeSH]/exp OR Antidepressant Agents [MeSH]/exp

#5 #1 OR #2

#6 #5 AND #3

#7 #5 AND #4

#8 #5 AND #3 AND #4

#9 #6 OR #7 OR #8 AND Limits: Randomized Controlled Trial, Clinical Trial, Phase III

An initial weeding process of all retrieved records based on titles and abstracts yielded a result set of 700 articles. The initial weeding eliminated articles in which major depression was the studied indication or

those that compared antidepressant or benzodiazepine therapy with alternative medicines, psychotherapy, or other therapies excluded from this study. Further analysis and review of the remaining 700 articles will determine the final number of articles to be included in this systematic review.

To supplement the searches of published research, the internet was also utilised to locate additional clinical trials, unpublished research and/or grey literature. Websites of pharmaceutical companies, clinical trials, and medical control agencies were searched with a specific focus on clinical trial registries.

Searched websites include:

Clinical Trials.gov: http://clinicaltrials.gov/ct/gui
Eli Lilly: www.lilly.com
Lundbeck: www.lundbeck.com
Organon: www.organon.com
Solvay: www.solvay.com
Pfizer: www.pfizer.com
GlaxoSmithKline: www.gsk.com
Bristol Myers Squibb: www.bms.com
Pierre Fabre : www.pierre-fabre.com
Wyeth: www.wyeth.com
Food and Drug Administration (USA): www.fda.gov
European Medicines Agency (EU): www.emea.europa.eu
Pharmaceuticals and Medical Devices Agency (Japan): www.pmda.go.jp
Therapeutic Goods Administration (Australia): www.tga.gov.au

Appendix DS2

Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	Item no.	Checklist item	Reported on page no.
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	1
Method			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	n/a
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	1–2
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	2 and Appendix DS1
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2 and Fig. 1
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes	2

		for obtaining and confirming data from investigators	
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	2 and Appendix DS2
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I2) for each meta-analysis	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Appendix DS2
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	n/a
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	3, Fig. 1 and Appendix DS3
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	3 and Table DS1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Fig. 2 and Appendix DS4
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Figs 3–5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	3–5 and Figs 3–5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Fig. 2 and Appendix DS4
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression [see item 16])	n/a
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups	5

		(such as health care providers, users, and policy makers)	
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	5
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	5

Appendix DS3

References to excluded studies

Aden GC. Alprazolam in clinically anxious patients with depressed mood. *J Clin Psychiatry* 1983 **44**: 22–4.

Benkert O, Szegedi A, Wetzel H, Staab HJ, Meister W, Philipp M. Dose escalation vs. continued doses of paroxetine and maprotiline: a prospective study in depressed out-patients with inadequate treatment response. *Acta Psychiatr Scand* 1997; **95**: 288–96.

Bosmans JE, Hermens ML, de Bruijne MC, van Hout HP, Terluin B, Bouter LM, et al. Cost-effectiveness of usual general practitioner care with or without antidepressant medication for patients with minor or mild-major depression. *J Affect Disord* 2008; **111**: 106–12.

Brenes GA, Williamson JD, Messier SP, Rejeski WJ, Pahor M, Ip E, et al. Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. *Aging Ment Health* 2007; **11**: 61–8.

Covi L, Lipman RS, Derogatis LR, Smith JE, Pattison JH. Drugs and group psychotherapy in neurotic depression. *Am J Psychiatry* 1974; **131**: 191–8.

Hermens ML, van Hout HP, Terluin B, Ader HJ, Penninx BW, Van Marwijk HW, et al. Clinical effectiveness of usual care with or without antidepressant medication for primary care patients with minor or mild-major depression: a randomized equivalence trial. *BMC Med* 2007; **5**: 36.

Johnston EC, Cunningham Owens DG, Frith CD, McPherson K, Riley CDG, Gold A. Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychol Med* 1980; **10**: 321–8.

Katon W, Robinson P, Von KM, Lin E, Bush T, Ludman E, et al. A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry* 1996; **53**: 924–32.

Katon W, Von KM, Lin E, Walker E, Simon GE, Bush T, et al. Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *JAMA* 1995; **273**: 1026–31.

Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, et al. Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. *Health Technol Assess* 2009; **13**: iii–xi, 1.

Kimura M, Robinson RG, Kosier JT. Treatment of cognitive impairment after poststroke depression : a double-blind treatment trial. *Stroke* 2000; **31**: 1482–6.

Lecrubier Y, Bourin M, Moon CA, Schifano F, Blanchard C, Danjou P, et al. Efficacy of venlafaxine in depressive illness in general practice. *Acta Psychiatr Scand* 1997; **95**: 485–93.

Lipman RS, Covi L, Rickels K, McNair DM, Downing R, Kahn RJ, et al. Imipramine and chlordiazepoxide in depressive and anxiety disorders. *Arch Gen Psychiatry* 1986; **43**: 68–77.

Lynch DJ, Tamburrino MB, Nagel R. Telephone counseling for patients with minor depression: preliminary findings in a family practice setting. J Fam Pract 1997; **44**: 293–8.

Miranda J, Munoz R. Intervention for minor depression in primary care patients. *Psychosom Med* 1994; **56**: 136–41.

Mossey JM, Knott KA, Higgins M, Talerico K. Effectiveness of a psychosocial intervention, interpersonal counseling, for subdysthymic depression in medically ill elderly. *J Gerontol A Biol Sci Med Sci* 1996; **51**: M172–8.

Murray V, von Arbin M, Bartfai A, Berggren AL, Landtblom AM, Lundmark J, et al. Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. *J Clin Psychiatry* 2005; **66**: 708–16.

Parnett L, Sommacal S, Morselli Labate AM, Senin U. Multicentre controlled randomised double-blind placebo study of minaprine in elderly patients suffering from prolonged depressive reactions. *Clin Drug Investig* 1993; **6**: 181–8.

Pecknold JC, Van Den Steen N. Trimipramine in the treatment of anxious-depressed out-patients. *Current Ther Res* 1978; **22**: 94–100.

Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. *Am J Psychiatry* 2000; **157**: 351–9.

Rocca P, Calvarese P, Faggiano F, Marchiaro L, Mathis F, Rivoira E, et al. Citalopram versus sertraline in late-life nonmajor clinically significant depression: a 1-year follow-up clinical trial. *J Clin Psychiatry* 2005; **66**: 360–9.

Rouillon F, Markabi S, Febvre N, Phillips R, Vaillant J. [Controlled study of treatment of residual depression by clomipramine versus placebo]. *Encephale* 1994; **20**: 139–45.

Singh NA, Clements KM, Fiatarone MA. A randomized controlled trial of progressive resistance training in depressed elders. *J Gerontol A Biol Sci Med Sci* 1997; **52**: M27–35.

Spek V, Cuijpers P, Nyklicek I, Smits N, Riper H, Keyzer J, et al. One-year follow-up results of a randomized controlled clinical trial on internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years. *Psychol Med* 2008; **38**: 635–9.

Spek V, Nyklicek I, Cuijpers P, Pop V. Alexithymia and cognitive behaviour therapy outcome for subthreshold depression. *Acta Psychiatr Scand* 2008; **118**: 164–7.

Szegedi A, Wetzel H, Angersbach D, Philipp M, Benkert O. Response to treatment in minor and major depression: results of a double-blind comparative study with paroxetine and maprotiline. *J Affect Disord* 1997; **45**: 167–78.

Wells KB, Schoenbaum M, Duan N, Miranda J, Tang L, Sherbourne C. Cost-effectiveness of quality improvement programs for patients with subthreshold depression or depressive disorder. *Psychiatr Serv* 2007; **58**: 1269–78.

Appendix DS4

Risk of bias and GRADE table

Barrett *et al* 2001[35]

Item	Judgement	Description
Allocation concealment?	Unclear	No details are reported.
Blinding?	Yes	Quote: 'Treatment assignments were held by a local pharmacist and were available to study personnel only in the event of medical emergency'
Incomplete outcome data addressed?	No	Subjects failing to complete the study were not included in the analysis.
Free of selective reporting?	Unclear	The study protocol is not available.
Free of other bias?	Yes	

Burrows *et al* 2002[36]

Item	Judgement	Description
Allocation concealment?	Yes	Quote: 'Subjects were randomized by an on-site pharmacist'.
Blinding?	Unclear	Quote: 'double-blind'. It is reported that investigators remained blinded to the treatment assignment.
Incomplete outcome data addressed?	No	Four subjects failed to complete the study and were not included in the analysis.
Free of selective reporting?	Unclear	The study protocol is not available.
Free of other bias?	Unclear	Sponsorship bias cannot be excluded.

Davidson *et al* 1988[37]

Item	Judgement	Description
Allocation concealment?	Unclear	No details are reported.
Blinding?	Unclear	Quote: 'double-blind'.
Incomplete outcome data addressed?	No	All efficacy comparisons were limited to the group of patients that completed at least three weeks' treatment.
Free of selective reporting?	Unclear	The study protocol is not available.
Free of other bias?	Unclear	Sponsorship bias cannot be excluded.

Judd *et al* 2004[38]

Item	Judgement	Description
Allocation concealment?	Unclear	No details are reported.
Blinding?	Unclear	Quote: 'double-blind'.
Incomplete outcome data addressed?	Unclear	The majority of dropout patients were included in the analysis. However, it is not clear the statistical technique used to inpute incomplete outcome data.
Free of selective reporting?	Unclear	The study protocol is not available.
Free of other bias?	Unclear	Sponsorship bias cannot be excluded.

Paykel *et al* 1988[39]

Item	Judgement	Description
Allocation concealment?	Unclear	No details are reported.
Blinding?	Unclear	Quote: 'double-blind'.
Incomplete outcome data addressed?	Unclear	No details are reported.
Free of selective reporting?	Unclear	The study protocol is not available.
Free of other bias?	Yes	

Williams *et al* 2000[42]

Item	Judgement	Description
Allocation concealment?	Yes	Quote: 'The coordinating centre created consecutively numbered envelopes containing concealed assignment codes that were assigned sequentially to eligible patients by a research associate'.
Blinding?	Yes	Quote: 'Treatment assignments were held by the study statistician'.
Incomplete outcome data addressed?	No	Subjects failing to complete the study were not included in the analysis.
Free of selective reporting?	Unclear	The study protocol is not available.
Free of other bias?	Yes	

Evidence profile: GRADE table

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressants	placebo	Relative (95% CI)	Absolute	Quality	Importance
symptom reduction (follow-up mean 8.6 weeks; measured with: Hamilton Depression Rating Scale (17 items); Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106	108	-	MD 0.93 lower (2.27 lower to 0.41 higher)	⨁◯◯◯ LOW	CRITICAL
failure to respond (follow-up mean 8.3 weeks)												
4	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/137 (56.9%)	77/137 (56.2%)	RR 1.01 (0.83 to 1.25)	6 more per 1000 (from 96 fewer to 141 more)	⨁◯◯◯ LOW	CRITICAL
failure to respond - with imputation												
6	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	138/234 (59%)	146/234 (62.4%)	RR 0.94 (0.81 to 1.08)	37 fewer per 1000 (from 119 fewer to 50 more)	⨁◯◯◯ LOW	CRITICAL
functioning (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		CRITICAL
development of depressive episode												
0	no evidence					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per		CRITICAL

	availabl e									1000 (from 0 fewer to 0 fewer)		
treatment acceptability (follow-up mean 10 weeks)												
2	random ised trials	no serious limitati ons	serious[4]	no serious indirect ness	serious	none	25/93 (26.9%)	23/93 (24.7 %)	RR 1.06 (0.65 to 1.73)	15 more per 1000 (from 87 fewer to 181 more)	⨁⨁◯◯ LOW	IMPORT ANT

1. All three included studies were described as randomized, double blind and placebo controlled. However, in one study dropout rates were not reported, and in two studies standard deviations were lacking. One study recruited individuals with both major and minor depression, and reported results separately.
2. All four included studies were described as randomized, double blind and placebo controlled. However, in three studies dropout rates were not reported, and in all four studies it is not clear how incomplete outcome data were managed. One study recruited individuals with both major and minor depression, and reported results separately. Two studies recruited individuals with both minor depression and dysthymia, and reported results separately.
3. All six included studies were described as randomized, double blind and placebo controlled. However, in four studies dropout rates were not reported. Four studies recruited individuals with both minor depression and major depression or dysthymia, and reported results separately. In this analysis we included two studies (Judd 2004 and Paykel 1988) with dichotomous data imputed from continuous scores.
4. Although the I-squared revealed no heterogeneity, visual inspection of the forest plot suggested some inconsistency