Antidepressants for treatment of depression in primary care: a systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Evidence for the effectiveness of drug treatment for depression in primary care settings remains limited, with little information on newer antidepressant classes.

AIM: To update an earlier Cochrane review on the effectiveness of antidepressants in primary care to include newer antidepressant classes, and to examine the efficacy of individual agents.

METHODS: Selection criteria included antidepressant studies with a randomly assigned placebo group where half or more subjects were recruited from primary care. The Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) group searched multiple databases to identify eligible studies. Data extraction was performed independently by two reviewers. Data were analysed using Revman version 5.3.5.

RESULTS: In total, 17 papers and 22 comparisons were included for analysis. Significant benefits in terms of response were found for tricyclic antidepressants (TCA) with a relative risk (RR) = 1.23 (95% CI, 1.01–1.48), and serotonin selective reuptake inhibitors (SSRI) with a RR = 1.33 (95% CI, 1.20–1.48). Mianserin was effective for continuous outcomes. Numbers needed to treat (NNT) for TCA = 8.5; SSRI = 6.5; and venlafaxine = 6. Most studies were industry-funded and of a brief duration (≤ 8 weeks). There was evidence of publication bias. There were no studies comparing newer antidepressants against placebo.

CONCLUSION: Antidepressants such as TCA, SSRI, SNRI (serotonin–norepinephrine reuptake inhibitor) and NaSSA (noradrenergic and specific serotonergic antidepressant) classes appear to be effective in primary care when compared with placebo. However, in view of the potential for publication bias and that only four studies were not funded by industry, caution is needed when considering their use in primary care.

KEYWORDS: Antidepressant agents; primary health care; placebos; clinical trial; meta-analysis; general practice

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Introduction

Depression is a leading cause for global disease burden. In many places around the world, depression is mainly managed in primary care settings where the prevalence of depressive disorders has been estimated to range from 10 to 20%.[1,2] Despite this, much of the evidence for the effectiveness of drug treatments used for depression have been based on studies conducted on patients treated in secondary and tertiary settings. Observational studies have found the naturalistic course of depressive disorders encountered in primary care tends to be less severe

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WHAT GAP THIS FILLS

What is already known: Much of the evidence on drug treatment of depression has been based on studies conducted in secondary and tertiary settings where the spectrum and course of illness tends to be more severe and complicated than depression encountered in primary care, raising questions about the effectiveness of antidepressants in patients being treated for depression in primary care settings. An earlier Cochrane review examined the effectiveness of TCA and SSRI in primary care settings and found both to be effective.

What this study adds: This study updates the Cochrane review by including newer antidepressant classes and calculating NNTs for individual drugs where data were available. There was evidence to support the effectiveness of TCAs and SSRIs when compared to placebo, and evidence of efficacy for SNRIs and NaSSA. NNT for TCA and SSRI classes and for specific agents (venlafaxine, amitriptyline, sertraline, escitalopram) were calculated. Publication bias and high levels of industry funding has also been reported and it is suggested that clinicians take this in to account when considering using antidepressant medication for depression in primary care.

and less complicated than those seen in specialist settings, with many primary care patients going into remission without treatment.[3] As a result, there is ongoing debate about the effectiveness of antidepressant therapy for the management of primary care depression amid concerns that previous evidence may have been based on biased reporting or false-positive results.[4,5] In summary, the evidence for benefit with antidepressants is mainly in cases of severe depression, and yet most depression in general practice is mild to moderate.

This current review was conducted primarily to update and extend an earlier Cochrane review on antidepressants use in primary care, which was limited to the evidence for the effectiveness of tricyclic (TCA) and selective serotonin reuptake inhibitors (SSRI) against placebo.[6] As newer antidepressant drug classes have become available in recent years, this review update was conducted to allow a more complete review of current papers and to examine the effectiveness of specific agents within each drug class. Recent reviews have suggested that some drugs may be more effective than others, raising the possibility that the benefits of antidepressants may not necessarily be a class effect.[7] Knowledge of the NNT for individual agents would be helpful in informing clinicians on antidepressant choice when managing depression in primary care settings. The aim of this study was to assess the effectiveness of all classes of antidepressants versus placebo in primary care patients.

Methods

Using a population, intervention, control and outcome (PICO) format, inclusion criteria for study selection were:

- **Population**. Primary care studies that examined the outcomes of antidepressant treatment of patients with depression where there was a placebo comparison group. 'Primary care studies' were defined as ≥ 50% of the study sample being subjects who have been recruited from primary care settings. 'Patients with depression' were defined as subjects diagnosed with depression by a primary care clinician or by diagnostic inventory or criteria.
- **Intervention**. Any class of antidepressant medication. The treating clinician could be from primary or secondary care, as we were interested in the drug/placebo difference and any non-drug skill would apply equally to all arms of the trials.
- **Comparison**. Placebo.
- **Outcomes**. Response or remission to treatment for dichotomous outcomes, and the Hamilton Depression Rating Scale (HAM-D) or the Montgomery Asberg Rating Scale (MADRS) for continuous outcomes.

The search was conducted by the Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) Group and included studies from the earlier Cochrane review and a CCDAN-Clinical Trials Registry update search (to examine records added to the registry from January 2007 to October 2015). The CCDAN search includes the databases of MEDLINE (1950–), EMBASE (1974–) and PsycINFO (1967–), and the Cochrane Central Register of Controlled Trials (CENTRAL) to include review-specific searches of additional databases. Reports of trials were also sourced from international trial registers via the World

Health Organization's trials portal (ICTRP), ClinicalTrials.gov, and drug companies. Finally, hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses were performed. This search was updated in October 2015. Search terms used were for antidepressants versus placebo in primary care. The search is one page long, but in summary includes multiple terms for mood conditions (eg depression, dysthymia), generic names of all antidepressant medication, placebo, drug classes (eg SSRI, TCA, etc.) and primary care settings including general practice and ambulatory care. The search included all languages and references lists of papers were searched. We also wrote to authors of papers to see if they knew of any relevant papers we did not have. The final search was done in October 2015 and the full search results are available from the authors. Three authors (BA, WM and SH) selected the studies from the abstracts. Full papers were obtained where there was disagreement or uncertainty. Data were extracted from the selected papers in duplicate by two authors and recorded on a standardised data extraction form (Appendix 1). Data recorded included the PICO, funding sources, adverse events and those leading to withdrawal and the reviewer's judgement on risk of bias. The principal summary measure used was relative risk (RR) and effect sizes were translated into NNTs to enable easier interpretation by clinicians. We measured standard mean differences for continuous outcomes and RRs, and NNTs for dichotomous outcomes to ensure a significant finding on a continuous outcome was also significant on a dichotomous outcome. Where standard deviations (s.d.) were not reported, we used the highest value of s.d. from other studies in that class, including the highest s.d. for the active drug and the highest s.d. for the placebo. We also measured withdrawal for any reason (WFAR) to quantify the dropout rates. The Cochrane RevMan software (version 5.3.5) was used to perform statistical analyses using a random effects model as the most conservative option. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (see Supplementary Material available at journal's website) was followed.[8]

Results

The previous Cochrane review reported on 15 papers.[6] The literature search identified 151 papers from 01 January 2007 to 31 December 2013 (Figure 1). In addition, a search before 2007 excluding known studies found five potential studies, none of which met the inclusion criteria. Two papers were removed because one was an abstract[9] and the other was an early publication of the same study[10] that was superseded by the full paper for the study.[11] A paper from the earlier review was removed because the authors decided it did not meet the participant entry criteria.[12]

Two new papers came from the Linde (2015)[13] review.[14,15] An additional search from 01 January 2014 to 23 October 2015 found two additional studies.[18,19] In summary, four new papers were found; one was excluded from our earlier review and a duplicate was removed. The final review included 17 papers with 10 TCA, nine SSRI, one venlafaxine and two mianserin comparisons with placebo.

Figure 1. Number of randomized trials (RCTs) found from the search strategy

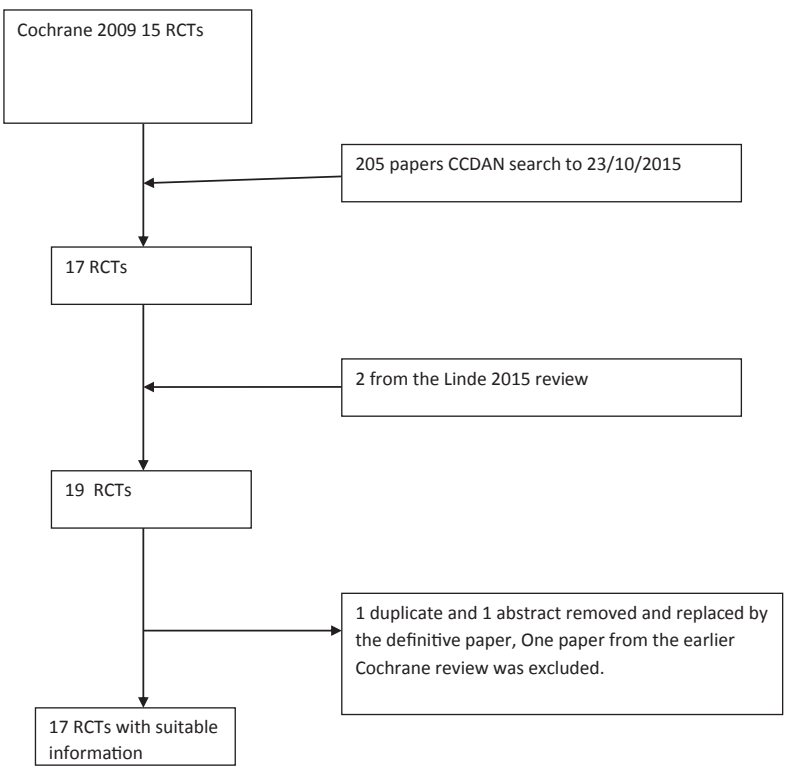


Table 1. Characteristics of randomised trials of antidepressants versus placebo by antidepressant class

Study year	Diagnosis	Age (years)	Dose of drug	Size of study	Responsible for treatment	Duration (weeks)	Outcome	Funder bias
Tricyclic								
Barge-Schaapveld *et al.*[25]	MDD & HAM-D 17 ≥ 18	16–65	50 mg/day increasing to 200 mg/day	63	GP	6	HAM-D 17	Yes
Blashki *et al.*[26]	Heterogeneous and women only	> 15	75 or 150 mg	82	GP and psychiatrist	4	HAM-D 17	Yes
Doogan and Langdon[27]	MDD	> 18	75 up to 150 mg*	308	GP	6	MADRS and CGI	Yes
Hollyman *et al.*[28]	Heterogeneous	18–64	75 mg up to 175 mg	141	Psychiatrist	6	HAM-D	No
Lecrubier *et al.*[16]	Heterogeneous	NR	25–150 mg	229	Psychiatrist	12	MADRS and CGI	Yes
Mynors-Wallis *et al.*[29]	MDD	18–65	50–150 mg	91	1 Psychiatrist and 2 GPs	12	HAM-D ≤ 7	No†
Philipp *et al.*[30]	Moderate DD	Mean 47	50–100 mg	263	GP	8	HAM-D ≥ 50%	Yes
Thompson and Thompson[20]	Heterogeneous	NR	75 mg	52	GP	4	HAM-D	Yes
Thomson *et al.*[21]	Heterogeneous	Median 33	75–150 mg	115	GP & Psychiatrist	12	HAM-D ≤ 4	Yes
SSRI								
Bjerkenstedt *et al.*[14]	MDD	18–70	Fluoxetine	115	?Psychiatrist	4	Ham-D 21	Yes
Doogan and Langdon[27]	MDD	> 18	Sertraline 50–100 mg	308	GP	6	MADRS and CGI	Yes
Gastpar *et al.*[15]	MDD	18–70	Citalopram 20 mg	257	GPs	4	HAM-D 17	Yes
Hergl *et al.*[18]	MDD	> 18	Sertraline 50–200 mg	166	Psychiatrist	10	HAM-D 17	Yes
Lepola *et al.*[11]	MDD	18–65	Escitalopram 10–20 mg or Citalopram 20–40 mg	471	Investigators? Psychiatrist	8	50% MADRS	Yes
Malt *et al.*[31]	Heterogeneous	Mean 48	Sertraline 50–200 mg	372	GP	24	50% MADRS	Yes
Wade *et al.*[32]	MDD	40/41	Escitalopram 10 mg	380	Unclear	8	50% MADRs	Yes
Venlafaxine	**SNRI**							
Lecrubier *et al.*[16]	Heterogeneous	NR	150 mg	229	Psychiatrist	12	MADRS and CGI	Yes
Mianserin								
Brink[33]	Heterogeneous	18–65	30–60 mg	52	GP	4	HAMD 21	No
Malt *et al.*[31]	Heterogeneous	Mean 48	30–120 mg	372	GP	24	50% MADRs	Yes

* 'Up to' means starting at a lower dose and increasing up to the higher dose as needed.
† Company supplied drug and placebo but did not fund the study.
'?Psychiatrist' means not clear if this was done by a psychiatrist.
MDD, Major Depressive Disorder; HAM-D, Hamilton Depression Scale; MADRS, Montgomery Asberg depression rating scale; Heterogeneous, depression as diagnosed by a primary care clinician on a clinical basis alone; Moderate DD, moderate depressive disorder; NR, not reported; CGI, Clinical Global Impression; GP, general practitioner; SSRI, serotonin selective reuptake inhibitors; SNRI, serotonin–norepinephrine reuptake inhibitor; 50%, 50% reduction in the baseline score as a measure of response.

Table 1 shows the characteristics of each of the studies by their drug class categories. Both TCAs and SSRIs were significantly effective compared with placebo for dichotomous scores of response/remission (Figures 2 and 3). The RR for benefit was 1.23 (95% CI, 1.01–1.48) for TCAs, and 1.33 (95% CI, 1.20–1.48) for SSRIs. By using the pooled RR, the NNT for TCA (based on the median control event rate [MCER]) was 8.5, with a range of 7 to 16. The NNT for SSRI (based on the [MCER] was 6.5, with a range of 9 to 42. We are reporting a range of NNTs based on the range of control event rates, and it is not a confidence interval. Results for continuous outcomes were also significant for the TCA standard mean difference (SMD) = −0.26 (95% CI, −0.5 to −0.02) and for the SSRI group SMD = −0.27 (95% CI, −0.38 to −0.16). For participants on low doses of TCAs (≤ 100 mg per day), the SMD was −0.27 (95% CI −0.38 to −0.16). A SMD of 0.5 is considered a moderate effect size, so that SMDs reported here would be small. For studies longer than 8 weeks, the results were not statistically significant for TCAs but they were for SSRIs. There was significant heterogeneity for the TCA drugs (I^2 = 77%) but not for the SSRI (I^2 = 0).

There was limited but sufficient data to calculate the NNTs for some individual antidepressants (Table 2). This was possible for amitriptyline, sertraline, escitalopram and venlafaxine. We could not report a NNT for imipramine or citalopram, as their pooled estimate was significant on a fixed-effects analysis but not the random-effects analysis. There was insufficient data for dothiepin and paroxetine. We only had continuous data for mianserin, with a SMD of −0.37 (95% CI, −0.62 to −0.13) for the two studies, so while statistically significant, did not allow a NNT to be calculated.

The median withdrawal rate for TCAs was 19% and 14% for the SSRIs. The WFAR was not

Figure 2. Tricyclic antidepressants versus placebo with response/remission as the outcome

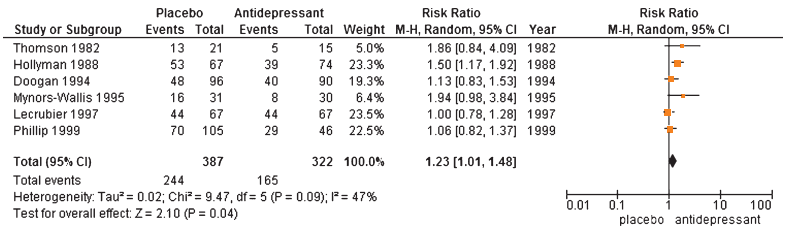


Figure 3. Serotonin selective reuptake inhibitors versus placebo with response/remission as the outcome

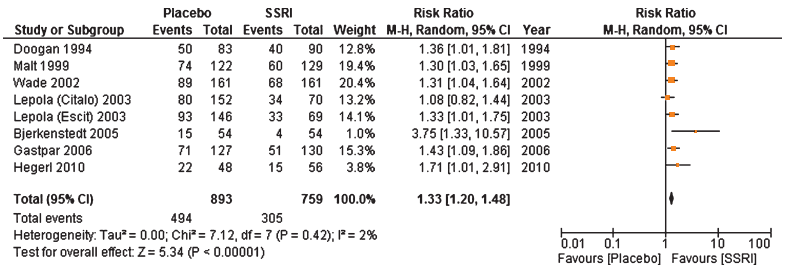


Table 2. Effect size based on numbers needed to treat (NNT) using the pooled relative risk and the median value of the controlled event rates for each study

		NNT calculated on the median control event rate	Range
TCAs as a class		8.5	7–16
SSRIs as a class		6.5	6–42
TCA	Amitriptyline (3 studies)	5	3–7
TCA	Dothiepin (2 studies)	Ns	
TCA	Imipramine (2 studies)	Ns (fixed effects but not random effects) I^2 = 44%	
SSRI	Sertraline (3 studies)	6	6–10
SSRI	Escitalopram (2 studies)	8.5	8–9
SSRI	Paroxetine (1 study)	Ns one study only	
SSRI	Citalopram (2 study)	Two studies (fixed effects but not random effects)	
NaSSA	Mianaserin (2 studies)	Significant on continuous outcome	Cannot calculate
SNRI	Venlafaxine (1 study)	6	Single study

TCA, tricyclic antidepressants; SSRI, serotonin selective reuptake inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin–norepinephrine reuptake inhibitor.

statistically significant for either TCA or SSRI. In a post-hoc sensitivity analysis, where those who withdrew were considered to have not improved, the RRs for TCAs and SSRIs remained non-significant.

Risk of bias

Most studies used a blinded active drug and placebo, but methods of randomisation or concealment were often not reported. Formal measures of bias would categorise most trials as having an unclear risk of bias; however, this may be unfair given most studies are old and the requirement for more rigid criteria for reporting have only been implemented in recent years. Of greater concern was industry involvement in 13 of the 17 studies; funnel plots indicated there were some small studies with small effect sizes missing for both tricyclics and SSRIs (Appendix 2 and 3).

Discussion

Summary

Our results suggest antidepressants are effective when compared with placebo for depression in primary care. There were four broad medication groups, including TCA, SSRI, SNRI and NaSSA, and all had evidence of efficacy. This includes what we have called heterogeneous depression, which was usually described as patients with a primary care clinical diagnosis of depression. In other studies, it included a diagnosis by structured criteria such as the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.[17] This was often augmented by a threshold from a depression inventory such as the Hamilton Depression Scale (mainly in the older papers), and the Montgomery Asberg Depression Rating Scale (in the more recent papers). The severity of depression and the effectiveness of antidepressants is a contentious issue, owing to concern about publication bias. A meta-analysis of 35 randomised controlled trials obtained from the Food and Drug Administration (which included unpublished data) found antidepressants were clearly effective only in patients with severe levels of depression (Hamilton Depression Rating Scale scores of ≥ 28).[4] In this current review, the majority of participants were in the mild-to-moderate level of severity. While we were able to pool data and show amitriptyline, sertraline and escitalopram were effective in two or more studies, caution is needed in suggesting that these medications should be chosen over others in their classes, given that the choice to study a particular medication is industry-driven.

Strengths and limitations

There were several strengths to this current review. It contains only studies conducted with patients recruited from primary care settings. All medications were compared with placebo and/or with other medications where two medications were being studied. Authors were contacted to see if there were any relevant unpublished articles. This review contains two more papers than the 2015 review by Linde *et al*.[13] and is the most comprehensive record of current papers.[18,19] A key limitation of the review is the high rate of withdrawal from the evaluated studies and the high level of industry involvement. The funnel plot suggests there are some missing small studies with smaller effects for both the TCA and the SSRIs. The funnel plot analyses were limited by the small number of studies in each class. High withdrawal rates observed in the studies is problematic, but mimics what happens in everyday clinical practice. Sensitivity analysis performed, assuming all withdrawals did not respond, did not materially change the effect measures. The types of adverse effects have been reported elsewhere.[6]

Comparison with existing literature

There were notable absences of studies conducted in primary care on agents such as mirtazapine, bupropion and duloxetine, fluvoxamine, milnacipran and reboxetine, all of which have been studied in secondary care settings. Our review reports data in 22 drug versus placebo combinations. This is considerably less than a 30-year review of drug versus placebo studies, which included 121 comparisons.[22] Their review included 19 different medications, while our review included 11. There were 17 studies comparing fluoxetine versus placebo, while our review had only one. The most recent study of an antidepressant versus placebo in primary care was in 2010,[18]

and, while the authors had disclosed involvement with pharmaceutical companies, the study did not seem to be industry-funded. The last medication versus medication study in primary care was published in 2012, and this was not funded by a pharmaceutical company.[23] A recent network meta-analysis looked at both placebo-controlled and other anti-depressant-controlled trials.[13] While this included newer medications, all trials were drug-versus-drug comparisons, which we feel is important due to the controversy of efficacy in mild-to-moderate depression, which predominates in primary care. Another systematic review of anti-depressants found these medications were not effective for mild and sub-threshold depression.[24] This finding reinforces our view there should be a placebo group at least in the short-term.

Implications for practice

There appears to be some evidence to claim that antidepressants are effective for patients in primary care with depression. There was clear evidence for amitriptyline, mianserin, sertraline, escitalopram, venlafaxine, as individual drugs. There is almost certainly a commercial reason as to why particular medications were more studied, and the presence of evidence does not necessarily imply they are better than those with little or no evidence. Of more concern is the evidence of publication bias, as 13 of the 17 studies were funded by industry. We urge caution in their use. While antidepressant medications may be effective in primary care, our review does not answer the question of when they should be used, who should get them or how long primary care clinicians should wait to initiate prescribing.

Implications for research

There is an absence of evidence for the newer antidepressant medications versus placebo in primary care, many of which have been extensively studied in secondary care. This situation needs to be remedied. There also seems to be a trend towards medication-to-medication comparisons without a placebo arm, which may be problematic, as there is a risk that two medications may appear similar in efficacy, but neither is better than placebo. This is important in primary care, as the range of depressive illnesses encountered are mainly in the mild-to-moderate spectrum where antidepressants are generally less effective. Research is needed, which is free from industry funding and of sufficient power and duration, to determine effectiveness over a longer timeframe.

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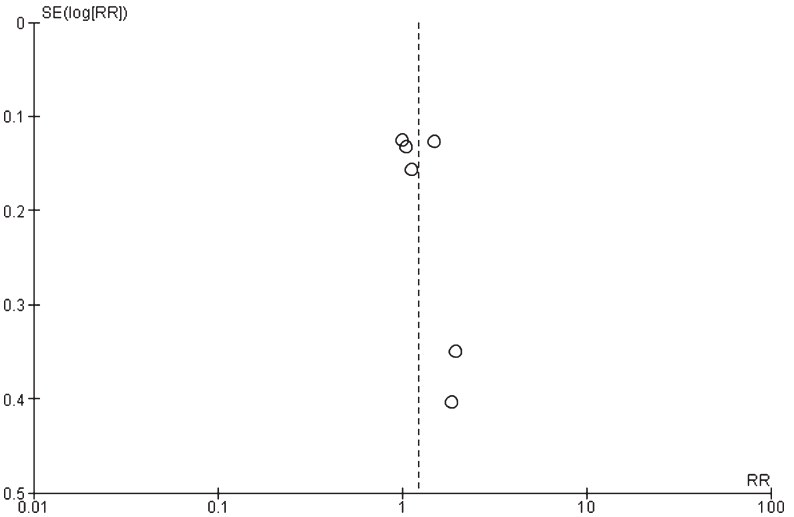
COMPETING INTERESTS
None.

Appendix 1. Data extraction form

Variable	Questions to consider	Adequate? X/√/unclear
Methods	Study design RCT of drug versus placebo Total study duration ……. months	
Participants	Setting % recruited by GPs % assessed by GPs % intervention conducted by GPs Diagnostic criteria (leave for co-ordinator) Country Date of study Setting GP Who did the intervention? Any drug company involvement?	
Intervention	Total number of intervention groups: INTERVENTION Specific intervention dose and dose escalation PLACEBO Specific intervention dose and dose escalation	
Outcome and time	Outcomes and time points 1. Reported when – report only end-of-study outcomes 2. What reported: CGI if no other For each outcome of interest: 1. Outcome definition, eg HAM-D, CGI, Montgomery Asberg 2. Unit of measurement: dichotomous and/or continuous (if you have to estimate say so, eg ruler on a graph)	
Results	1. Number of participants allocated to each intervention group at baseline 2. For each outcome of interest and at end of study 3. Summary data for each intervention group 4. Unit of measurement, eg HAM-D, Montgomery Asberg 5. Serious events (number) 6. Adverse effects number and type (number) 7. Adverse effects leading to withdrawal (number) 8. Withdrawal due to any reason (number)	
Intention-to-treat analysis?	Was analysis performed in accordance with the principle of intention-to-treat?	
Risk of bias (www.cochrane-handbook.org)		
Domain	**Judgement** ***Low risk, high risk, unclear risk***	**Support for judgement**
Adequate random sequence generation?		
Allocation concealment?		
Blinding? (participants and personnel)		
Blinding of outcome assessment?		
Incomplete outcome data?		
Selective reporting?		
Other bias?		
Overall assessment of risk of bias		

RCT, randomised controlled trial; GP, general practitioner; CGI, clinical global impression; HAM-D, Hamilton depression rating scale.

Appendix 2. Funnel plot for tricyclic antidepressants (TCA) versus placebo



Appendix 3. Funnel plot for tricyclic antidepressants (TCA) versus placebo

