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Managing antidepressant discontinuation: a systematic review

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Abbreviations
CBT cognitive behaviour therapy
CI confidence interval
DESS discontinuation emergent signs and symptoms scale
DSM-IV Diagnostic and Statistical Manual, version 4
EQ-5D EuroQol 5-dimensional quality of life scale
HMIC Health Management Information Consortium
MBCT mindfulness based cognitive therapy
MAOIs monoamine oxidase inhibitors
PPI Patient and Public Involvement
PROSPERO International Prospective Register of Systematic Reviews
RCT randomised controlled trial
RDC Research Diagnostic Criteria
REDUCE reducing antidepressant use by careful monitoring in everyday practice programme
RR risk ratio
SCID-LIFE Structured Clinical Interview for DSM-IV - Longitudinal Interval Follow-up Evaluation
SSRIs selective serotonin reuptake inhibitors
TCAs tricyclic antidepressants
TIDieR Template for Intervention and Replication
WHO ICTRP World Health Organisation International Clinical Trials Registry Platform

Prior presentation of findings
The main conclusions were presented by Adam Geraghty at the Society for Academic Primary Care Annual Scientific Meeting, London, UK, on Wednesday July 11th 2018, as part of a 10-minute oral presentation called 'REDUCE programme to help people withdraw from inappropriate long-term antidepressant treatment'.

They will also be presented by Tony Kendrick at the National Institute for Health Research School for Primary Care Research showcase conference in London, UK, on Tuesday 13th November, as part of a 15-minute plenary presentation called 'REDUCE programme to help people withdraw from inappropriate long-term antidepressant treatment'.
Abstract

Purpose
To determine the effectiveness of interventions to manage antidepressant discontinuation, and outcomes for patients.

Methods
Systematic review with narrative synthesis and meta-analysis. Sources: MEDLINE, PubMed, Embase, PsycINFO, AMED, Health Management Information Consortium (HMIC), OpenGrey, and WHO International Clinical Trials Registry Platform (ICTRP) to March 2017. Including: randomised controlled trials (RCTs), quasi-experimental, and observational studies assessing interventions to facilitate discontinuation of antidepressants for depression in adults. Primary outcomes: antidepressant discontinuation, and discontinuation symptoms. Secondary outcomes: relapse/recurrence, quality of life, antidepressant reduction, sexual, social, and occupational function.

Results
Of 15 studies included, 12 were in the synthesis (8 RCTs, 2 single-arm trials, 2 retrospective cohort studies). None of the studies was rated high risk for selection or detection bias. Two studies prompting primary care provider (PCP) discontinuation with antidepressant tapering guidance found 6% and 7% of patients discontinued, versus 8% for usual care. Six studies of psychological or psychiatric treatment plus tapering reported cessation rates of between 40% and 95%. Two studies reported a higher risk of discontinuation symptoms with abrupt termination. At 2 years, risk of relapse/recurrence was lower with cognitive behaviour therapy (CBT) plus taper versus clinical management plus taper (15%-25% vs 35%-80%: RR 0.34, 95% CI 0.18 to 0.67; 2 studies). Relapse/recurrence rates were similar for mindfulness based cognitive therapy (MBCT) with tapering and maintenance antidepressants (44%-48% vs 47%-60%; 2 studies).
Conclusions

CBT or MBCT can help patients discontinue antidepressants without increasing the risks of relapse/recurrence, but are resource intensive. More scalable interventions are needed, incorporating psychological support.

(Word count 250)

Introduction

In Western countries, antidepressant prescriptions are rising steadily, doubling over 10 years.\textsuperscript{1-3} The main reason is increasing long-term use,\textsuperscript{4,5} with a median duration greater than five years in the USA,\textsuperscript{6} mostly prescribed by PCPs.\textsuperscript{2,5} While some people need antidepressants to prevent relapse/recurrence, 30 to 50% of long-term users have no evidence-based indication to continue.\textsuperscript{6-8} This exposes them to potentially serious side-effects,\textsuperscript{9,10} and is costly.\textsuperscript{11}

However, stopping antidepressants is frequently associated with withdrawal symptoms, which can be problematic, and mistaken for relapse/recurrence.\textsuperscript{12} To minimise them, the American Psychiatric Association, and National Institute for Health and Care Excellence advise tapering doses over some weeks in most cases.\textsuperscript{13,14} Psychological interventions like cognitive-behaviour therapy (CBT) and mindfulness-based cognitive therapy (MBCT) are potential alternatives to antidepressants in preventing relapse/recurrence.\textsuperscript{15-17}

Current guidelines for antidepressant discontinuation are based on consensus, and non-systematic reviews have identified a need for more controlled data.\textsuperscript{18} There have been two systematic reviews focussing on the incidence of withdrawal symptoms after discontinuation.\textsuperscript{12,19} We conducted a systematic review to address two questions: what interventions are effective in managing antidepressant discontinuation, and what are the outcomes for patients following discontinuation?
Methods

The protocol was registered with the [International Prospective Register of Systematic Reviews (PROSPERO)] in 2017, reference CRD42017072702.

We included primary studies that:

(1) concerned patients aged ≥ 18 years receiving antidepressants except [mono-amine oxidase inhibitors (MAOIs)] (usually prescribed by specialists\textsuperscript{15}, for treatment of a first or recurrent episode of depression (defined by study authors), regardless of duration of use, or level of care (primary, secondary, tertiary) received. We included studies including patients with anxiety disorders, where >50% had depression, or mixed anxiety and depression;

(2) assessed interventions to facilitate discontinuation of antidepressants including [guided review of patients by PCPs, abrupt discontinuation, tapering, psychological therapies, and pharmacological approaches (e.g. switching to liquid fluoxetine during tapering)];

(3) had, when present, a comparator of continuation of antidepressant, alternative discontinuation procedure, usual care, or clinical management, but not placebo;

(4) were: randomised controlled trials (RCTs), cluster RCTs, quasi-experimental (non-randomised studies, before and after studies), or observational studies.

Our a priori primary outcomes were:

- Discontinuation of antidepressants (cessation by the end of the study period)
- Discontinuation symptoms (either measured on the discontinuation emergent signs and symptoms scale (DESS) or other scale\textsuperscript{20} or listed).

A priori secondary outcomes were:
• Relapse/recurrence (defined by study authors): either within six months, or more than six months following discontinuation

• Quality of life

• Antidepressant reduction

• Sexual function

• Other outcomes (e.g. social and occupational function, wellbeing, quality of relationships)

We used the term ‘relapse/recurrence’ to include both relapse, defined through consensus as the return of syndrome-level depression following remission during the first 4-6 months of treatment, and recurrence, defined as a new episode following recovery lasting more than 4-6 months.\(^{21}\) This was because we did not specify a minimum duration of treatment prior to discontinuation, and patients included could have been in remission or recovery.

We excluded studies that:

(1) included patients with bipolar disorder or dementia, unless data were reported separately;

(2) concerned treatment interruption only

(3) were placebo-controlled trials aimed only at testing maintenance antidepressants in preventing relapse/recurrence.

We searched the following databases from inception until March 2017: MEDLINE (Ovid), PubMed, Embase (Ovid), PsycINFO (EBSCOhost), AMED (EBSCOhost), HMI\textsc{C}, OpenGrey, and WHO ICTRP. We searched citations and reference lists for full papers meeting inclusion criteria from initial searches, and contacted pharmaceutical companies and experts.

The MEDLINE search strategy was developed with an experienced health librarian (SD). It included subject headings/text words related to antidepressants, depression, discontinuation, and study
design, and was peer reviewed by three medical librarians. This strategy was then adapted by EM for the remaining databases, except the WHO ICTRP for which keyword combinations were used (Appendix 1).

EM screened all titles and abstracts against inclusion criteria and TK screened a 10% sample. We obtained full papers where titles/abstracts met the inclusion criteria, or where there was uncertainty. EM and TK independently assessed whether full papers met inclusion criteria. Disagreements were resolved by discussion.

Data extraction was performed in a standardised pre-piloted form by EM and was all checked by TK. It included: patient characteristics (e.g. age, sex, duration of antidepressant use); how withdrawal effects were ascertained; whether relapse/recurrence was distinguished from withdrawal; and elements of the Template for Intervention and Replication (TIDieR) checklist. This included physical/informational intervention materials, who delivered it (e.g. PCP, pharmacist, mental health practitioner), and how, where and when it was delivered.

Risk of bias assessment was performed by EM and checked by TK. We used the Cochrane Risk of Bias tool, in accordance with the Cochrane Handbook. For observational studies and single arm trials we used the National Heart Lung and Blood Institute and Research Triangle Institute International tools. Narrative and tabular summaries of key study characteristics, quality assessment and results were undertaken. For each outcome we presented results by study design, separately for studies of patients with depression only, and with mixed depression and anxiety. Where appropriate, based on clinical and statistical heterogeneity, data were combined in meta-analyses. For binary outcomes we
calculated risk ratios, and for continuous outcomes mean differences, with 95% confidence intervals (CIs) using a priori specified random effects models. Statistical heterogeneity was tested using the Chi² test (p<0.1) and I² statistic (I²≥50%).

The meaning of our results was discussed with three patient colleagues providing Patient and Public Involvement input to our team.

Results
The search yielded 4996 records in total, 4694 unique (Figure 1). Of these, 4581 were ineligible after title and abstract review, with 99% agreement in the 10% sample screened by TK. Of the remaining 113, 78 were excluded after assessment of full papers (see table A, appendix 2 for excluded studies). Thirty five papers, reporting 15 studies were therefore included. Of these 15, one was published as an abstract only.

Table B, Appendix 2 shows study characteristics. Twelve were completed, and included in our synthesis. Two were ongoing (both RCTs, one of tapering for two weeks versus one week, and one of guided tapering plus CBT versus maintenance antidepressants in pregnant women.)

Eight of the completed studies were RCTs (one cluster RCT and one with only one relevant study arm), two single arm trials, and two retrospective cohort studies. Numbers of patients ranged from 12 to 2849. Seven included participants with depression and/or anxiety disorder, and five depression only. Criteria used for depression were reported in nine, including the Diagnostic and Statistical Manual (DSM-IV) and Research Diagnostic Criteria (RDC) (Table B).
Twelve named the antidepressants being discontinued. Two concerned discontinuation of a single antidepressant (desvenlafaxine, and paroxetine, one tricyclic antidepressant (TCA) and related antidepressants, one newer antidepressants, one predominantly SSRIs, and seven both older and newer. Inclusion criteria for duration of use were reported in eight and included ≥4 weeks (1), 24 weeks (1), 3 to 5 months (1), ≥6 months (3), ≥9 months (1), and ≥2 years. Mean/median length of antidepressant use was reported in three, ranging from 9.2 months to 9.5 years. Inclusion criteria for length of remission/recovery were reported in four, ranging from 8 weeks to six months. Three studies of MBCT included a significant proportion of patients in partial remission (Table B).

Interventions included: patient specific letter to the PCP with recommendation to discontinue antidepressant and tapering advice; prompted PCP review of condition and medication; CBT with tapering; MBCT with tapering; gradual discontinuation; and one week tapering. Comparators included: maintenance antidepressant treatment; rapid discontinuation; abrupt discontinuation; clinical management plus taper; and usual care (Table B). Apart from sexual function, data were reported for all pre-specified outcomes of interest.

For RCTs, no included study was rated high risk for selection or detection bias. Performance bias was rated either high risk due to the nature of interventions, or unclear (Table C, Appendix 2). Single arm trials had clearly defined, valid, reliable, and consistently implemented outcome measures, and for both observational studies, timeframes were sufficient to see associations between exposure and outcomes (Table D, Appendix 2).

Discontinuation of antidepressants

Eight studies (six RCTs, two single arm) reported on discontinuation (Table 1).
Timepoints ranged from post-intervention to 24 months from baseline, and cessation rates from 6% to 95%. The lowest rate occurred with patient-specific letters to PCPs recommending antidepressant discontinuation, with tapering advice. There was no significant difference in cessation between this (6%) and usual care (8%) after 12 months (relative risk (RR) 0.75, 95% CI 0.22 to 2.53). Patients who discontinued tended to have a shorter duration of use.

The highest cessation rates (87% and 95%) were in two studies comparing CBT plus tapering to clinical management plus tapering, delivered by the same psychiatrist. When results from these were combined in meta-analysis, there was no significant difference in discontinuation after 20 weeks (RR 1.01, 95% CI 0.89 to 1.15; Chi² = 0.49, I² = 0%). Cessation rates in three studies of MBCT with tapering support ranged from 55% to 75%.

**Antidepressant discontinuation symptoms**

One RCT and one retrospective cohort reported on discontinuation symptoms (Table 2). One compared abrupt discontinuation of desvenlafaxine 50 mg/day versus tapering using 25 mg/day for one week. There was significantly lower risk of discontinuation emergent adverse events with one week taper versus abrupt discontinuation (RR 0.76, 95% CI 0.58 to 0.98). There was no statistically significant difference in the risk of discontinuation syndrome. However, the study may have been underpowered to detect a difference, with 140 patients in the tapering, and 148 in the abrupt discontinuation arm.

In a study of clinical records of 385 patients treated with paroxetine for a single episode of major depressive disorder, discontinuation syndrome occurred significantly more frequently in patients who discontinued abruptly (66% of patients reporting discontinuation syndrome compared with 15% of patients not reporting it; RR 7.35, 95% CI 4.05 to 13.35). Patients experiencing discontinuation syndrome were significantly younger (p = 0.016), but more young patients discontinued abruptly.
41 patients experiencing discontinuation syndrome, 36 were re-administered paroxetine and subsequently tapered off at 5mg every 2–4 weeks, with no recurrence of discontinuation syndrome. However, as 10mg tablets were the only form available, patients had to divide them.

Relapse/recurrence within six months

Three studies (one single arm, two retrospective cohorts) reported relapse/recurrence within six months of discontinuation (Table E, Appendix 2). In both cohort studies, attempts were made to differentiate discontinuation symptoms from relapse/recurrence: e.g. in one, inclusion criteria stated patients had to remain euthymic for one week after discontinuation.

One small (n=12), feasibility study of CBT for preventing recurrence in women who wished to discontinue before pregnancy, found two whose depression recurred within 10 weeks of tapering. In a retrospective cohort study, of 41 patients who experienced discontinuation syndrome after stopping paroxetine, none had recurrence following subsequent slower titration (88%) or switch of antidepressants (12%). In a second cohort, median time to recurrence of depressive or panic disorder was more than twice as long after gradual versus rapid discontinuation. Newer antidepressants (SSRIs, bupropion, duloxetine, venlafaxine) were associated with a shorter time to recurrence than TCAs/tetracyclics.

Recurrence after more than six months

Six studies reported late recurrence (Table F, Appendix 2) at time points ranging from 12 months to six years after discontinuation. In one, a score of 5 for two weeks on the Structured Clinical Interview for Depression Longitudinal Interval Follow-up Evaluation (SCID-LIFE) could have included patients experiencing withdrawal affecting mood temporarily, overestimating recurrence.
There was no significant difference in recurrence following patient-specific recommendations to PCPs to discontinue plus tapering guidance, compared to usual care (26% vs 13%; RR 1.95, 95% CI 0.97 to 3.94). Meta-analysis of two CBT studies\textsuperscript{15,32} showed significantly lower risks of recurrence with CBT plus taper compared to clinical management plus taper after two years (15%-25% vs 35%-80%: RR 0.34, 95% CI 0.18 to 0.67; Chi\textsuperscript{2}=0.19, I\textsuperscript{2}=0%), and six years (40%-50% vs 75%-90%: RR 0.55, 95% CI 0.37 to 0.82; Chi\textsuperscript{2}=1.12, I\textsuperscript{2}=11%). Meta-analysis of two MBCT studies showed no difference in recurrence between MBCT with tapering support and maintenance antidepressants at ≥15 months (44%-48% vs 47%-60%: RR 0.90, 95% CI 0.75 to 1.07; Chi\textsuperscript{2}=0.68, I\textsuperscript{2}=0%).\textsuperscript{16,17} The recurrence rate at 15 months was similar (54%) in another study providing MBCT with tapering support in one arm.\textsuperscript{34}

\textit{Quality of Life}

Four studies (three RCTs, one single arm trial) reported on quality of life (Table G, Appendix 2).\textsuperscript{16,17,27,51} In one there was no significant effect on quality adjusted life years.\textsuperscript{27} Meta-analysis was possible for two comparing MBCT with tapering versus maintenance antidepressants.\textsuperscript{16,17} These meta-analyses found no significant difference on the physical domain of the WHO Quality of Life instrument (WHOQOL-BREF), but a statistically significant difference favouring MBCT with tapering support in the psychological and social domains after 1 month; at ≥12 months there was no statistically significant difference for all three domains. In one study there was no statistically significant difference in European Quality of Life five dimensions questionnaire (EQ-5D) scores between MBCT with tapering support and maintenance antidepressants at any assessed timepoints.\textsuperscript{17}

In one single arm CBT study, quality of life scores for participants who did not relapse (9 out of 12), decreased after 16 weeks acute treatment but improved again at 24 weeks after booster treatment.\textsuperscript{34}
Reduction in antidepressant use

Four studies reported reduction in antidepressant use (Table H, Appendix 2). Reduction rates ranged from 13% of patients for PCP review, to 19% with minimum 50% reduction in use following CBT plus tapering.

Discussion

Summary of main findings

We found discontinuation rates varied from only 6%-7% for prompted PCP patient review and guided tapering, to 40%-95% for specialist psychological or psychiatric interventions. Only two studies reported on discontinuation symptoms. One RCT found a lower risk of serious adverse events with one week taper versus abrupt discontinuation of desvenlafaxine, whilst a retrospective cohort study found discontinuation syndrome significantly more common after abrupt paroxetine cessation.

Rates of relapse/recurrence were low in primary care (13%-26%) compared to psychiatric or psychological therapy settings (15%-90%), presumably related to the larger proportion of patients with multiple recurrences and/or partial remission on antidepressants in specialist settings, but there has been very little research in primary care. A primary care placebo-controlled trial of maintenance SSRI treatment to prevent depression recurrence (excluded from this review) found similar rates, of 10% in the continuation arm and 23% in the taper arm over 18 months.

The risk of relapse/recurrence was significantly reduced by combining cognitive behaviour therapy (CBT) with tapering versus clinical management and tapering alone. Mindfulness based cognitive therapy with tapering enabled high rates of discontinuation without increasing relapse/recurrence rates, compared to maintenance antidepressants.
Strengths and limitations
We conducted a sensitive search across several databases, including grey literature, unrestricted by date, language or publication status, to minimise publication and language bias. One researcher performed study selection, data extraction and risk of bias assessment, with extracted data and bias assessments carefully checked by another experienced reviewer. This is time-efficient but may incur more errors than double data extraction.5

Comparison with the literature
Our findings tend to support consensus guidance that antidepressants should be tapered rather than discontinued abruptly, but there is a need for more trials, of slower tapering.18 One ongoing study is comparing one-week with two-week tapering.57 Our findings are consistent with short-term drug interruption studies (also excluded from this review) showing that discontinuation syndrome occurs more often on abrupt cessation of paroxetine, presumably due to its short half-life.60, 61

Discontinuation took place in some studies during ‘continuation’ treatment to prevent relapse within 4-6 months of remission, and in others during ‘maintenance’ treatment to prevent recurrence.62 This is a potentially important distinction, because guidelines recommend 6-9 months continuation treatment for a first episode of depression, and maintenance treatment for two years or more for recurrent episodes,13,14 although the clinical utility of this distinction was questioned by a systematic review which found no clear difference between continuation and maintenance treatment in reducing the risk of relapse/recurrence.63

Implications for practice and research
It is important for PCPs to discuss discontinuation symptoms with patients, at the time of initiation of an antidepressant. This will allow them to make more informed decisions about whether they
want to start an antidepressant in the first place. Patients may also be reassured that relapse rates may be lower in the primary care setting, although more research needs to be done to confirm that.

Discontinuation symptoms are probably reduced by tapering but slow tapering is a challenge given a lack of suitable formulations. One study found most patients could discontinue paroxetine with a taper of 5mg every 2–4 weeks, but patients had to break tablets in half. Switching to fluoxetine, with its longer half-life and availability in liquid form, may enable successful slow tapering, but this does not appear to have been subject to a trial.

Discontinuation symptoms may affect patients’ willingness to stop antidepressants and be confounded with relapse/recurrence, so future studies should distinguish between them. They should also distinguish between discontinuing continuation and maintenance antidepressant treatment.

Providing psychological therapies seems to enable significantly greater discontinuation rates than brief guidance on tapering to PCPs alone. The mechanism could be through providing support to patients to manage fears of withdrawal, relapse and lack of self-efficacy, which are possible barriers to discontinuation. However, it could also be that having an effective therapy for depression/anxiety for which the medication was initially given removes the need for it, without increasing the risk of relapse/recurrence. Access to face-to-face CBT or MBCT is likely to be quite limited however, warranting the exploration of psychologically-informed digital support for discontinuation to complement PCP care, given the high prevalence of people on potentially inappropriate long-term antidepressant treatment.
Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all the authors except Ms Dawson have received funding from the National Institute for Health Research for the REDUCE (REviewing long term anti-DEpressant Use by Careful monitoring in Everyday practice) applied health research programme 2016-2022, which aims to test psychologically-informed digital support for antidepressant discontinuation to complement PCP care (http://www.isrctn.com/ISRCTN15036829); no other financial relationships with any organisations that might have an interest in the submitted work in the previous three years, with the exception of Ms Dawson, who reports personal fees from University of York, personal fees from University College London, personal fees from Maverex, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.
REFERENCES

1. McCarthy M. Antidepressant use has doubled in rich nations in past 10 years. *BMJ* 2013;347:f7261

2. Pratt L, Brody D, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005-2008. NCHS Data Brief 2011. [www.cdc.gov/nchs/data/databriefs/db76.htm](http://www.cdc.gov/nchs/data/databriefs/db76.htm). (Accessed 12 June 2018)

3. Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: Results from the US National Health and Nutrition Examination Survey. *Journal of Clinical Psychiatry* 2014;75:169–77.

4. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. *BMJ* 2009;339:b3999.

5. Kendrick T, Stuart B, Newell C, Geraghty AWA, Moore M. Did NICE guidelines and the Quality Outcomes Framework change GP antidepressant prescribing in England? Observational study with time trend analyses 2003-2013. *Journal of Affective Disorders* 2015;186:171-77. doi:10.1016/j.jad.2015.06.052

6. Cruickshank G, MacGillivray S, Bruce D, Mather A, Matthews K, Williams B. Cross-sectional survey of patients in receipt of long-term repeat prescriptions for antidepressant drugs in primary care. *Mental Health in Family Medicine* 2008;5:105–9

7. Ambresin G, Palmer V, Densley K, Dowrick C, Gilchrist G, Gunn JM. What factors influence long-term antidepressant use in primary care? Findings from the Australian diamond cohort study. *Journal of Affective Disorders* 2015;176:125–32 doi: /10.1016/j.jad.2015.01.055

8. Piek E, Kollen BJ, van der Meer K, Penninx BWJH, Nolen WA. Maintenance Use of Antidepressants in Dutch General Practice: Non-Guideline Concordant. *PLoS ONE* 2014;9(5): e97463. doi:10.1371/journal.pone.0097463
9. Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Primary Care Companion to Journal of Clinical Psychiatry* 2001;3:22–7.

10. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551 doi: 10.1136/bmj.d4551

11. Vasiliadis HM, Latimer E, Dionne PA, Préville M. The costs associated with antidepressant use in depression and anxiety in community-living older adults. *Canadian Journal of Psychiatry* 2013;58:201-9

12. Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychotherapy and Psychosomatics* 2015;84:72-81 (DOI:10.1159/000370338)

13. American Psychiatric Association. *Treatment of patients with major depressive disorder. 3rd ed*. [http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx](http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx). Accessed June 12, 2018.

14. National Collaborating Centre for Mental Health. *Depression: The NICE guideline on the treatment and management of depression in adults (updated edition). National clinical practice guideline 90*. National Institute for Health and Clinical Excellence, 2010.

15. Fava GA, Grandi S, Zielezny M, Canestrari R. Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. *American Journal of Psychiatry* 1994;9:1295–99.

16. Kuyken, W., Byford, S., Taylor, RS, Watkins, E., Holden, E., White, K., et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *Journal of Consulting and Clinical Psychology* 2008;76:966–78

17. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: Results of a
randomised controlled trial (The PREVENT study). *Health Technology Assessment* 2015;19(73):1-123.

18. Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. *Therapeutic Advances in Psychopharmacology* 2015;5:357-368.

19. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive Behaviors* 2018. [https://doi.org/10.1016/j.addbeh.2018.08.027](https://doi.org/10.1016/j.addbeh.2018.08.027)

20. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological Psychiatry* 1998;44:77-87.

21. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Remission, recovery, relapse, and recurrence. Archives of General Psychiatry* 1991;48:851-855.

22. Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687

23. Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials *BMJ* 2011;343 :d5928

24. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration. [http://handbook.cochrane.org/](http://handbook.cochrane.org/)

25. National Heart Lung and Blood Institute and Research Triangle Institute International. *Study Quality Assessment Tools*. National Heart Lung and Blood Institute, 2014. [https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools](https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)
26. Dan IA, Simu M. The “discontinuation syndrome” in depressed patients successfully treated with sertraline (abstract). *Eur Neuropsychopharmacology* 2000;10 (Suppl 3): S273-274.

Abstract no. 136

27. Eveleigh R. *Inappropriate long-term antidepressant use in primary care: a challenge to change* [PhD thesis]. Radboud University Nijmegen, 2015.

28. Muskens E, Eveleigh R, Lucassen P, van Weel C, Speijker J, Verhaak P, et al. Prescribing ANtiDepressants Appropriately (PANDA): a cluster randomized controlled trial in primary care. *BMC Fam Pract* 2013;14:6.

29. Eveleigh R, Grutters J, Muskens E, Oude Voshaar R, van Weel C, Speckens A, Lucassen P. Cost-utility analysis of a treatment advice to discontinue inappropriate long-term antidepressant use in primary care. *Family Practice* 2014;31:578–584

30. Fava GA, Grandi S, Zielezny M, Rafanelli C, Canestrari R. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *American Journal of Psychiatry* 1996;153(SUPPL.):945-7.

31. Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *American Journal of Psychiatry* 1998;155(10):1443-5.

32. Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P. Prevention of recurrent depression with cognitive behavioral therapy: Preliminary findings. *Archives of General Psychiatry* 1998;55(9):816-20.

33. Fava GA, Ruini C, Rafanelli C, Finos L, Conti S, Grandi S. Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *American Journal of Psychiatry* 2004;161(10):1872-6.

34. Huijbers MJ, Spinhoven P, Spijker J, Ruhe HG, Van Schaik DJF, Van Oppen P, et al. Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for
recurrent depression: Randomised controlled non-inferiority trial. *British Journal of Psychiatry* 2016;208(4):366-73.

35. Huijbers MJ, Spijker J, Donders ART, van Schaik DJF, van Oppen P, Ruhe HG, et al. Preventing relapse in recurrent depression using mindfulness-based cognitive therapy, antidepressant medication or the combination: Trial design and protocol of the MOMENT study. *BMC Psychiatry* 2012;12 (1) (no pagination)(125).

36. Huijbers MJ, Spinhoven P, Van Schaik DJF, Nolen WA, Speckens AEM. Patients with a preference for medication do equally well in mindfulness-based cognitive therapy for recurrent depression as those preferring mindfulness. *Journal of Affective Disorders* 2016;195:32-9.

37. Speckens AEM. Mindfulness Based Cognitive Therapy and Antidepressant Medication in Recurrent Depression. https://clinicaltrials.gov/ct2/show/NCT00928980, 2009. [Accessed 08-02-18]

38. Khan A, Musgnung J, Ramey T, Messig M, Buckley G, Ninan PT. Abrupt discontinuation compared with a 1-week taper regimen in depressed outpatients treated for 24 weeks with desvenlafaxine 50 mg/d. *Journal of Clinical Psychopharmacology* 2014;34(3):365-8.

39. Ninan PT, Musgnung J, Messig M, Buckley G, Guico-Pabia CJ, Ramey TS. Incidence and timing of taper/posttherapy-Emergent adverse events following discontinuation of desvenlafaxine 50 mg/d in patients with major depressive disorder. *Primary Care Companion to the Journal of Clinical Psychiatry* 2015;17(1).

40. Pfizer. Study Comparing Discontinuation Symptoms Of DVS SR In Subjects With MajorDepressive Disorder (MDD). https://clinicaltrials.gov/ct2/show/NCT01056289, 2010. [Accessed 08-02-18]

41. Kuyken W. Trial platform: preventing depression relapse in the National Health Service practice using Mindfulness-Based Cognitive Therapy. http://www.isrctn.com/ISRCTN12720810, 2006. [Accessed 08-02-18]
42. Klein NS, van Rijsbergen GD, ten Doesschate MC, Hollon SD, Burger H, Bockting CLH. Beliefs about the causes of depression and recovery and their impact on adherence, dosage, and successful tapering of antidepressants. *Depression and Anxiety* 2017;34(3):227-35.

43. Bockting CL, Elgersma HJ, van Rijsbergen GD, de Jonge P, Ormel J, Buskens E, et al. Disrupting the rhythm of depression: Design and protocol of a randomized controlled trial on preventing relapse using brief cognitive therapy with or without antidepressants. *BMC Psychiatry* 2011;11 (no pagination)(8).

44. Bockting C. Imagine your mood: a step towards personalized relapse prevention in depression. http://www.isrctn.com/ISRCTN15472145, 2016.[Accessed 08-02-18]

45. Kuyken W, Byford S, Byng R, Dalgleish T, Lewis G, Taylor R, et al. Study protocol for a randomized controlled trial comparing mindfulness-based cognitive therapy with maintenance anti-depressant treatment in the prevention of depressive relapse/recurrence: The PREVENT trial. *Trials* 2010;11 (no pagination)(99).

46. Kuyken W, Byford S, Byng R, Dalgleish T, Lewis G, Taylor R, et al. Update to the study protocol for a randomized controlled trial comparing mindfulness-based cognitive therapy with maintenance anti-depressant treatment depressive relapse/recurrence: The PREVENT trial. *Trials* 2014;15 (1) (no pagination)(217).

47. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): A randomised controlled trial. *The Lancet* 2015;386(9988):63-73.

48. Anonymous. Erratum: Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial (The Lancet (2015) 386(9988) (63-73) (S0140673614622224) (10.1016/S0140-6736(14)62222-4)). *The Lancet*. 2016;388(10052):137
49. Kuyken W. Preventing depressive relapse/recurrence in NHS settings through mindfulness based cognitive therapy (MBCT). http://www.isrctn.com/ISRCTN26666654, 2009. [Accessed 08-02-18]

50. Johnson CF, Macdonald HJ, Atkinson P, Buchanan Al, Downes N, Dougall N. Reviewing long-term antidepressants can reduce drug burden: a prospective observational cohort study. *British Journal of General Practice* 2012;62(604):e773-9.

51. Psaros C, Freeman M, Safren SA, Barsky M, Cohen LS. Discontinuation of antidepressants during attempts to conceive: a pilot trial of cognitive behavioral therapy for the prevention of recurrent depression. *Journal of Clinical Psychopharmacology* 2014;34(4):455-60.

52. Psaros C, Freeman M, Safren S, Barsky M, Cohen L. Cognitive-behavioral therapy in women discontinuing antidepressant in anticipation of pregnancy. *Neuropsychopharmacology* 2011;36:S347.

53. Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness following rapid versus gradual discontinuation of antidepressants. *American Journal of Psychiatry* 2010;167(8):934-41.

54. Himei A, Okamura T. Discontinuation syndrome associated with paroxetine in depressed patients: a retrospective analysis of factors involved in the occurrence of the syndrome. *CNS Drugs* 2006;20(8):665-72.

55. Molenaar NM, Brouwer ME, Bockting CLH, Bonsel GJ, van der Veere CN, Torij HW, et al. Stop or go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: Study protocol of a pragmatic multicentre non-inferiority randomized controlled trial. *BMC Psychiatry* 2016;16(1) (no pagination).

56. Lambregtse-Van Den Berg M, Burger H, Bockting CL, Bonsel GJ, Duvekot JJ, Torij HW. Stop or go? Tapering antidepressants in pregnancy: A pragmatic multicenter RCT to investigate risk and benefits for mother and child. *Archives of Women’s Mental Health* 2015;18 (2):403-4. [NTR4694]
57. Dunlop BW. Tapering Off Antidepressants. https://clinicaltrials.gov/ct2/show/NCT02661828, 2016. [Accessed 08-02-18]

58. Mangin, D., Dowson, C., Mulder, R., Wells, E., Toop, L., Dowell, T., & Arroll, B. (2015). The effectiveness of maintenance SSRI treatment in primary care depression to prevent recurrence: Multicentre double-blinded placebo controlled RCT. Proceedings of the North American Primary Care Research Group (NAPCRG) 43rd Annual Meeting, http://www.napcrg.org/Conferences/PastMeetingArchives/2015AnnualMeetingArchives/SearchEducationalSessions?m=6&s=14867 (accessed 8th October, 2018)

59. Buscemi N, Hartling L, Vandermeer B, Tjosvold L, Klassen TP. Single data extraction generated more errors than double data extraction in systematic reviews. Journal of Clinical Epidemiology 2006; 59: 697-703.

60. Tint A, Haddad PM, Anderson IM. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. Journal of Psychopharmacology 2008;22:330-332.

61. Montgomery S, Kennedy S, Burrows G, Lejoyeux M, and Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. International Clinical Psychopharmacology 2009;19:271–280.

62. Paykel ES. Continuation and maintenance therapy in depression. British Medical Bulletin 2001; 57: 145–159. https://doi.org/10.1093/bmb/57.1.145

63. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention in antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361: 653–661.

64. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. Drugs Aging 2013;30:793–807.
Table 1: Studies reporting successful discontinuation of antidepressants

| Study (design) | Time point – from baseline | Intervention (cessation rate) | Comparator (cessation rate) | Risk ratio (95% CI) |
|----------------|----------------------------|------------------------------|------------------------------|--------------------|
| **Depression (exclusion or non-reporting of anxiety comorbidities)** |
| Klein 2017 \(^1\) (RCT) \(^1\) | 6 months | CBT+ taper (34/85 = 40%) | m-ADM (n/a) | n/a |
| Huijbers 2016 \(^2\) (Single arm from RCT) \(^2\) | 6 months; after 6 months | MBCT-TS (68/128 = 53%; 70/128 = 55%) | n/a | n/a |
| **Depression and/or anxiety disorders** |
| Eveleigh 2015 \(^3\) (RCT) \(^3\) | 12 months | Letter to PCP with recommendation + tapering advice (4/67 = 6%) | Usual care (6/75 = 8%) | 0.75 (0.22 to 2.53); 1 study |
| Fava 1994 \(^4\) (RCT) | 20 weeks | CBT + taper (20/21 = 95%) | CM + taper (20/22 = 91%) | 1.01 (0.89 to 1.15; \(I^2 = 0\%\)); 2 studies |
| Fava 1998 \(^4\) (RCT) | 20 weeks | CBT + taper (20/23 = 87%) | CM + taper (20/22 = 91%) | n/a |
| Kuyken 2008 \(^4\) (RCT) \(^3\) | 6 months | MBCT-TS (46/61 = 75%) | m-ADM (n/a) | n/a |
| Kuyken 2015 \(^4\) (RCT) \(^4\) | 24 months | MBCT-TS (124/176 = 70%) | m-ADM (n/a) | n/a |
| Johnson 2012 \(^5\) (single arm) | Post-intervention | Guided PCP review (199/2849 = 7%) | n/a | n/a |

\(^1\) 3 arm RCT, but only 2 arms are relevant for this review, ITT analysis; \(^2\) 2 arm RCT but only 1 arm is relevant for this review (second arm: MBCT + m-ADM); ITT analysis; \(^3\) ITT analysis; \(^4\) per protocol analysis (completed 4 sessions of MBCT, 83% of those randomised to intervention arm)  
CM clinical management; CBT cognitive behavioural therapy; m-ADM maintenance antidepressant medication; MBCT-TS Mindfulness based cognitive therapy with support to taper; n/a not applicable; PCP Primary Care Provider
Table 2: Studies reporting antidepressant discontinuation symptoms

| Study (design) | Time point | Intervention (event rate) | Comparator (event rate) | Risk ratio (95% CI) |
|---------------|------------|---------------------------|-------------------------|-------------------|
| Depression (exclusion or non-reporting of anxiety comorbidities) |            |                           |                         |                   |
| Khan 2014 (RCT) Incidence of taper/post-therapy emergent adverse event\(^1\) | Double-blind phase: Baseline (Study Day 168) up to Week 4 | 1 week taper (54/139=39%) | Abrupt discontinuation (75/146=51%) | 0.76 (0.58 to 0.98); 1 study |
| Proportion of patients with discontinuation syndrome\(^2\) | Double-blind phase: Baseline (Study Day 168) up to Week 4 | 1 week taper (30/139=22%) | Abrupt discontinuation (31/146=21%) | 1.02 (0.65 to 1.59); 1 study |
| Himei 2006 (Retrospective cohort) | Patients with discontinuation syndrome (n=41, abrupt (n=27) or gradual (n=14) withdrawal of paroxetine (10mg reduction every 2 weeks)) \(^3\) compared to patients with non-discontinuation syndrome (n=344, abrupt (n=53) or gradual (n=291) withdrawal of paroxetine) | | | 7.35 (4.05 to 13.35); 1 study |

\(^1\) adverse events that started or increased in severity during the double blind phase; \(^2\) an increase of 4 or more points in DESS between baseline and mean score during the first 2 weeks of the double blind phase; \(^3\) diagnosis in medical records, and reconfirmation of diagnosis according to the criteria for the SSRI discontinuation syndrome proposed by Black et al., 2000 (i.e.: (i) the symptoms of the discontinuation syndrome appear within 3 days following cessation/reduction in the dosage of paroxetine; (ii) two or more of the following symptoms are present: dizziness, light-headedness, headache, nausea, paraesthesia, loss of balance, irritability, agitation and insomnia; (iii) the symptoms cannot be explained as a relapse of depression or as any other medical condition; and (iv) the symptoms cause significant distress or impairment in social, occupational and other important areas of functioning).
Figure 1: Flowchart of study selection

Records identified through database searching (n = 4996)

Records identified through other sources (n = 18)

Records after duplicates removed (n = 4694)

Records screened (n = 4694)

Records excluded (n = 4581)

Full-text articles assessed for eligibility (n = 113)

Full-text articles excluded, (n = 78)

Studies included in Review (n = 15; 35 papers)

Studies included in synthesis (n=14)
## APPENDIX 1 - SEARCH STRATEGIES

**MEDLINE**

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R)

Daily and Ovid MEDLINE(R) 1946 to 23 March 2017

| Search ID# | Query                                                                 | Items found |
|------------|-----------------------------------------------------------------------|-------------|
| 1          | exp ANTIDEPRESSIVE AGENTS/                                           | 133782      |
| 2          | exp NEUROTRANSMITTER UPTAKE INHIBITORS/                               | 133192      |
| 3          | (psychotrop* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*).ti,kf,hw. | 136112      |
| 4          | (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfetubamone or Amineptine or Amitriptylin* or Amitriptylin oxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin* or Caroxazone or Chlopopixin or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or Chloropamine or 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| 5          | (Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idoxanoxan or Impiramin* or Iprindole* or Iproniazid* or Ipsapirone or Impiraminoxido or Isocarboxazid* or Lesopitron or Levomilnacipran or Lithium or Lofepramine or (Lu AA21004 or Vortioxetine) or Lu AA24530 or LY2216684 or Maprotoline or Medifoxamine or Melitracan or Metapramine or Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirazazapine or Moclobemide or Monocrotaphos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Nuxiptilin*).ti,kf,hw. | 67830      |
| 6          | (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Piridamol or Pirilindole or Pivagabine or Pizotyline or Propizepine or (Protirypylin* or Perotfrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Teniloxine or Tetindole or Thiazesim or Thoazolinone or Tianepin* or Toloxatone or Tramicyl柝orine or Trazimipramine or 5 Hydroxytryptophan or 5 HT or Tryptophan or Hydroxytryptophan or Venflaxaxine or Viloxazine or Vilazodone or Viquaine or Zalospirone or Zimeldine).ti,kf,hw. | 72802      |
| 7          | 1 or 2 or 3 or 4 or 5 or 6                                           | 328279      |
| 8          | MOOD DISORDERS/ or DEPRESSIVE DISORDER/ or DEPRESSION, POSTPARTUM/ or DEPRESSIVE DISORDER, MAJOR/ or DEPRESSIVE DISORDER, TREATMENT-RESISTANT/ | 106670      |
| 9          | DEPRESSION/                                                          | 95781      |
| 10         | ADJUSTMENT DISORDERS/                                               | 4180        |
| 11         | (mixed anxiety adj2 depression).ti,ab,kf.                           | 222        |
| 12         | (mixed anxiety adj2 depressive disorder).ti,ab,kf.                  | 85        |
| 13         | 8 or 9 or 10 or 11 or 12                                            | 195538      |
| 14         | (cease or cessation* or discontinu* or interrupt or interruption or taper* or reduce or drug holiday or post withdraw* or postwithdraw* or (stop* adj (taking or using)) or | 909991      |
withdraw* or terminat* or deprescrib* or de prescrib* or deprescrip* or de prescrip*).ti,ab,kf.
15 (prevent* adj3 relaps*).ti,ab,kf. 8318
16 (prevent* adj3 recurr*).ti,ab,kf. 17925
17 SECONDARY PREVENTION/ 17455
18 14 or 15 or 16 or 17 943451
19 controlled clinical trial.pt. 93357
20 randomized controlled trial.pt. 456910
21 (randomi#ed or randomi#ation).ti,ab. 516857
22 random#y.ab. 276324
23 trial.ti,ab. 487920
24 groups.ab. 1701672
25 (control* adj3 (trial* or study or studies)).ti,ab. 422582
26 RANDOMIZED CONTROLLED TRIAL/ or PRAGMATIC TRIAL/ 457032
27 (quasi adj (experimental or random$)).ti,ab. 12796
28 ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab. 4446
29 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 2645649
30 EPIDEMIOLOGIC STUDIES/ 7454
31 exp CASE CONTROL STUDIES/ 850134
32 exp COHORT STUDIES/ 1651640
33 Case control.tw. 101281
34 (cohort adj (study or studies)).tw. 135409
35 Cohort analy$.tw. 5537
36 (Follow up adj (study or studies)).tw. 43887
37 (observational adj (study or studies)).tw. 71418
38 Longitudinal.tw. 189339
39 Retrospective.tw. 387610
40 Cross sectional.tw. 249383
41 CROSS-SECTIONAL STUDIES/ 239537
42 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 2415411
43 Case series.tw. 53257
44 CASE REPORT/ 1866965
45 Case* report*.tw. 316198
46 case* stud*.tw. 78415
47 43 or 44 or 45 or 46 2061422
48 29 or 42 or 47 6302954
49 7 and 13 and 18 and 48 2967
50 remove duplicates from 49 2802
51 (rodent* or rat or rats or mouse or mice or animal model*).ti. 1271813
52 (smoking or tobacco or nicotine).ti. or smoking cessation.mp. 109483
53 (antibiotic* or antimicrob* or antifung* or statin*).ti. 155057
54 (comment or editorial or meta-analysis or practice-guideline or review).pt. 3279247
55 51 or 52 or 53 or 54 4744048
56 50 not 55 2212
### PubMed

PubMed, inception to 23 March 2017

| Search ID# | Query                                                                 | Items found |
|------------|----------------------------------------------------------------------|-------------|
| #53        | Search (#47 NOT #52)                                                 | 1162        |
| #52        | Search (#48 OR #49 OR #50 OR #51)                                    | 4216683     |
| #51        | Search (((Editorial[PT] or Guideline[PT] or Meta-Analysis[PT] or Review[PT]))) | 2690893     |
| #50        | Search ((((antibiotic*[TI] or antimicrob*[TI] or antifung*[TI] or statin*[TI]))) | 152759      |
| #49        | Search ((((smoking[TI] or tobacco[TI] or nicotine[TI]) or smoking cessation[ALL]))) | 108342      |
| #48        | Search ((((rodent*[TI] or rat[TI] or rats[TI] or mouse[TI] or mice[TI] or animal model*[TI] or rabbit[TI]))) | 1326349     |
| #47        | Search (#7 AND #12 AND #17 AND #46)                                  | 1554        |
| #46        | Search (#29 OR #41 OR #45)                                           | 6335149     |
| #45        | Search (#42 OR #43 OR #44)                                           | 1869485     |
| #44        | Search Case reports [PT]                                             | 1825701     |
| #43        | Search Case reports [MESH: NOEXP]                                     | 141         |
| #42        | Search Case series [TIAB]                                            | 52191       |
| #41        | Search (#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40) | 2281136     |
| #40        | Search Cross sectional [TIAB]                                        | 243232      |
| #39        | Search Retrospective [TIAB]                                          | 378173      |
| #38        | Search Longitudinal [TIAB]                                           | 185722      |
| #37        | Search (((observational study[TIAB] or observational studies[TIAB]))) | 69599       |
| #36        | Search (((Follow up study[TIAB] or follow up studies[TIAB])))         | 43627       |
| #35        | Search Cohort analy*[TIAB]                                           | 5903        |
| #34        | Search (((cohort study[TIAB] or cohort studies[TIAB])))               | 132794      |
| #33        | Search Case control [TIAB]                                           | 99475       |
| #32        | Search cohort studies [MESH]                                         | 1602115     |
| #31        | Search Case-control studies [MESH]                                   | 826296      |
| #30        | Search Epidemiologic studies [MESH: NOEXP]                           | 7274        |
| #29        | Search (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28) | 2968202     |
| #28        | Search (((waitlist*group [TIAB] or wait* list*group[TIAB] or treatment as usual group[TIAB] or TAU group[TIAB]))) | 582         |
| #27        | Search (((waitlist* control [TIAB] or wait* list*control[TIAB] or treatment as usual control[TIAB] or TAU control[TIAB]))) | 6811        |
| #26        | Search (((quasi experimental[TIAB] or quasi random*[TIAB])))          | 12445       |
| #25        | Search ((RANDOMIZED CONTROLLED TRIAL[MESH:NOEXP] or PRAGMATIC CLINICAL TRIAL[MESH:NOEXP]))) | 107877      |
| #24        | Search (((control* trial*[TIAB] or control* study[TIAB] or control* studies[TIAB]))) | 691375      |
| #23        | Search groups [TIAB]                                                | 1688863     |
| #22        | Search trial [TIAB]                                                 | 459756      |
| #21        | Search Randomly [TIAB]                                               | 268179      |
| #20        | Search (((randomized[TIAB] or randomised[TIAB] or randomization[TIAB] or randomisation[TIAB]))) | 490603      |
| #19        | Search randomized controlled trial [PT]                              | 430440      |
| #18        | Search controlled clinical trial [PT]                               | 516899      |
| #17        | Search (#13 OR #14 OR #15 OR #16)                                    | 296571      |
| #16        | Search SECONDARY PREVENTION [MESH: NOEXP]                            | 16781       |
#15 Search (prevent* recur* [TIAB]) 62250
#14 Search (prevent* relaps* [TIAB]) 21759

#13 Search (((cease [TIAB] or cessation* [TIAB] or discontinu* [TIAB] or interrupt [TIAB] or interruption [TIAB] or taper* [TIAB] or reduce [TIAB] or drug holiday [TIAB] or post withdraw* [TIAB] or postwithdraw* [TIAB] or stop* taking [TIAB] or stop* using [TIAB] or withdraw* [TIAB] or terminat* [TIAB] or deprescrib* [TIAB] or de prescrib* [TIAB] or deprescrip* [TIAB] or de prescrip* [TIAB]))) 210433

#12 Search (#8 OR #9 OR #10 OR #11) 189000
#11 Search mixed anxiety [TIAB] 358
#10 Search ADJUSTMENT DISORDERS [MESH:NOEXP] 4057
#9 Search DEPRESSION [MESH:NOEXP] 151804
#8 Search (((MOOD DISORDERS [MESH:NOEXP] or DEPRESSIVE DISORDER [MESH:NOEXP] or DEPRESSION, POSTPARTUM [MESH:NOEXP] or DEPRESSIVE DISORDER, MAJOR [MESH:NOEXP] or DEPRESSIVE DISORDER, TREATMENT-RESISTANT [MESH:NOEXP]))) 103027
#7 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 321750
#6 Search (((Opipramol [TIAB] or Oxaflozane [TIAB] or Paroxetine [TIAB] or Phenelzine [TIAB] or Pheniprazine [TIAB] or Pipofezin* [TIAB] or Piripedia [TIAB] or Piriuedol [TIAB] or Pivagamine [TIAB] or Pizotyline [TIAB] or Propizepine [TIAB] or Protriptyl* [TIAB] or Perlotrine [TIAB] or Quinupramine [TIAB] or Quipazine [TIAB] or Reboxetine [TIAB] or Ritanserin [TIAB] or Rolipram [TIAB] or Scopolamine [TIAB] or Selegiline [TIAB] or Sertraline [TIAB] or (Setiptiline [TIAB] or Teciptiline [TIAB]) or Tandospirone [TIAB] or Teniloxine [TIAB] or Tetrindole [TIAB] or Thiazesim [TIAB] or Thozalinone [TIAB] or Tianeptin* [TIAB] or Toloxatone [TIAB] or Tranylcypromine [TIAB] or Trazodone [TIAB] or Trimipramine [TIAB] or 5 Hydroxytryptophan [TIAB] or 5 HT [TIAB] or Tryptophan [TIAB] or Hydroxytryptophan [TIAB] or Venlafaxine [TIAB] or Viloxazine [TIAB] or Vilazodone [TIAB] or Vivaline [TIAB] or Zalospirone [TIAB] or Zimeldine [TIAB]))) 104458
#5 Search (((Harmaline [TIAB] or Harmine [TIAB] or Hyperforin [TIAB] or Hypericum [TIAB] or Idazoxan [TIAB] or Imipramin* [TIAB] or Iprindole [TIAB] or Iproniiazid* [TIAB] or Ispaiprione [TIAB] or Imipramoxide [TIAB] or Isocarboxazid* [TIAB] or Lesopiton [TIAB] or Levomilnacipran [TIAB] or Lithium [TIAB] or Lofepramin* [TIAB] or (Lu AA21004 [TIAB] or Vortioxetine [TIAB])) or Lu AA24530 [TIAB] or LY2216684 [TIAB] or Maprotiline [TIAB] or Medifoxamine [TIAB] or Melitracen [TIAB] or Metapramine [TIAB] or Methylphenidate [TIAB] or Mianserin [TIAB] or Milnacipran [TIAB] or Minaprine [TIAB] or Mirtazapine [TIAB] or Moclobemide [TIAB] or Monocrotophos [TIAB] or Nefazodone [TIAB] or Nialamide [TIAB] or Nitroxazepine [TIAB] or Nomifensine [TIAB] or Norfenfluramine [TIAB] or Nortryptiline [TIAB] or Noviptiline* [TIAB]))) 68598
#4 Search (((Agomelatine [TIAB] or Alaproclate [TIAB] or Alnespirone [TIAB] or Amoxapine [TIAB] or Amersergide [TIAB] or Amfetamone [TIAB] or Amiflamine [TIAB] or Aminoantipyrine [TIAB] or Aminopropyl [TIAB] or Amitriptylin* [TIAB] or Amitriptylinoxide [TIAB] or Amoxapine [TIAB] or Aripiprazole [TIAB] or Atomoxetine [TIAB] or Tomoxetine [TIAB] or Befloxacone [TIAB] or Benactyzine [TIAB] or Binospirone [TIAB] or Brofaromine [TIAB] or Bupropropion [TIAB] or Butriptylin* [TIAB] or Caroxazone [TIAB] or Chloroxatine [TIAB] or Cianopramine [TIAB] or Cilobamine [TIAB] or Cilosamine [TIAB] or Cimoxatone [TIAB] or Citalopram [TIAB] or (Chlorimipramin* [TIAB] or Clomipramin* [TIAB] or Clomipramin* [TIAB] or Clorimipramine [TIAB] or Clorgyline [TIAB] or Clovoxamine [TIAB] or Dapoxetine [TIAB] or Deanol [TIAB] or Dibenzepin [TIAB] or Demexiptilin* [TIAB] or Deprenyl [TIAB] or Desipramine [TIAB] or Desvenlafaxine [TIAB] or Dibenzenip [TIAB] or Diclofenosin* [TIAB] or Dimetacrin* [TIAB] or (Dosulepin [TIAB] or Dothiepin [TIAB]) or Droxpin [TIAB] or Duloxetine [TIAB] or DVS 233 [TIAB] or Enilospirone [TIAB] or Eptapinone [TIAB] or Escitalopram [TIAB] or Etoperidone [TIAB] or Femoxetine [TIAB] or Fenfluramin* [TIAB] or Fluvoxamine [TIAB] or Fluoxetin [TIAB] or Fluparoxan [TIAB] or Furanfluramine [TIAB])) 46087
#3 Search (((psychotropic* [TIAB] or antidepress* [TIAB] or anti depress* [TIAB] or ((serotonin [TIAB] or norepinephrine [TIAB] or noradrenaline [TIAB] or nor epinephrine [TIAB] or nor adrenaline [TIAB] or neurotransmitt* [TIAB] or dopamine* [TIAB]))) 144261
and (uptake[TA] or reuptake[TA] or re-uptake[TA]) or noradrenerg*[TA] or antiadrenerg*[TA] or anti adrenerg*[TA] or SSRI*[TA] or SNRI*[TA] or TCA*[TA] or tricyclic*[TA] or tetracyclic*[TA] or heterocyclic*[TA]))

| #  | Search                                      | # Matches |
|----|---------------------------------------------|-----------|
| #2 | Search NEUROTRANSMITTER UPTAKE INHIBITORS[MESH] | 25774     |
| #1 | Search ANTIDEPRESSIVE AGENTS[MESH]           | 52011     |
| Search ID# | Query                                                                 | Items found |
|-----------|----------------------------------------------------------------------|-------------|
| 1         | Psychopharmacology/                                                  | 27419       |
| 2         | Psychotropic Agent/                                                  | 28452       |
| 3         | exp Antidepressant Agent/                                           | 376797      |
| 4         | Serotonin Receptor Affecting Agent/ or Serotonin Uptake Inhibitor/   | 48677       |
| 5         | Dopamine Receptor Affecting Agent/ or Dopamine Uptake Inhibitor/     | 1521        |
| 6         | Adrenergic Receptor Affecting Agent/ or Noradrenaline Uptake Inhibitor/ | 4222      |
| 7         | Neurotransmitter Uptake Inhibitors/                                 | 160         |
| 8         | (antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp. | 293136      |
| 9         | (Agomelatine or Alaproclate or Alinespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Aminieptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binoispine or Brofaromine or Bupropion or Butriptylin* or Caroxazone or Chlopxiten or Cianopramine or Cilobamine or Cillosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dopoxetine or Deanol or Dibenzepin or Demexipitin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or (Dosulepin or Dothiepin) or Dosepin or Duloxetine or DVS 233 or Enilopride or Eptapirone or Escitalopram or Etoperidine or Fenofibrate or Fluoxetine or Fluoxetin or Fluparoxan or Flurazoliddone or Fluvoxamine).ti,kw,hw. | 151125      |
| 10       | (Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idazoxan or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Impriaminoxide or Isocarboxazid* or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or LY2216684 or Mapirotiline or Medifoxamine or Medipramine or Metapramine or Methylphenidate or Mianserin or Minipramine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Nootkodiazepine).ti,kw,hw. | 164343      |
| 11       | (Opipramol or Oxaffizone or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirindoline or Pivagabine or Pizotyline or Propizepine or (Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritalserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Tectipiline) or Tandospirone or Teniloxine or Tetrindole or Thiazemis or Thozalinone or Thianeptin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or 5 Hydroxytryptophan or 5 HT or Tryptophan or Hydroxytryptophan or Venlafaxine or Vilexetine or Vilazodone or Vicalaine or Zalospirone or Zimeldine).ti,kw,hw. | 172971      |
| 12       | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11                 | 663092      |
| 13       | DEPRESSION/ or AGITATED DEPRESSION/ or ATYPICAL DEPRESSION/ or ENDOGENOUS DEPRESSION/ or INVOLUTATIONAL DEPRESSION/ or MAJOR DEPRESSION/ or MASKED DEPRESSION/ or MELANCHOLIA/ or ORGANIC DEPRESSION/ or PUERPERAL DEPRESSION/ or REACTIVE DEPRESSION/ or "mixed anxiety and depression"/ | 355577      |
| 14       | (cease or cessation* or discontinu* or interrupt or interruption or taper* or reduce or drug holiday or post withdraw* or postwithdraw* or (stop* adj (taking or using)) or withdraw* or terminat* or deprescrib* or de prescrib* or deprescrip* or de prescrip*).ti,ab,kw. | 985146      |
| 15       | (prevent* adj3 relaps*).ti,ab,kw.                                   | 12176       |
| 16       | (prevent* adj3 recurrs*).ti,ab,kw.                                  | 24142       |
| 17       | secondary prevention/                                               | 26698       |
18 14 or 15 or 16 or 17
19 randomized controlled trial.de.
20 randomi#ed.ti,ab.
21 randomly.ab.
22 factorial$.ti,ab.
23 (control$ adj3 (trial$ or study or studies or group$)).ti,ab.
24 (quasi adj (experimental or random$)).mp.
25 19 or 20 or 21 or 22 or 23 or 24
26 Clinical study/
27 case control study/
28 Longitudinal study/
29 Retrospective study/
30 Prospective study/
31 Cohort analysis/
32 (Cohort adj (study or studies)).mp.
33 (Case control adj (study or studies)).tw.
34 (follow up adj (study or studies)).tw.
35 (observational adj (study or studies)).tw.
36 (epidemiologic$ adj (study or studies)).tw.
37 (cross sectional adj (study or studies)).tw.
38 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39 exp case study/
40 (case$ and series).tw.
41 case report/
42 (case$ adj2 report$).tw.
43 (case$ adj2 stud$).tw.
44 39 or 40 or 41 or 42 or 43
45 25 or 38 or 44
46 12 and 13 and 18 and 45
47 remove duplicates from 46
48 (rodent* or rat or rats or mouse or mice or animal model*).ti.
49 (smoking or tobacco or nicotine).ti. or smoking cessation.mp.
50 (antibiotic* or antimicrob* or antifung* or statin*).ti.
51 (book or editorial or review).pt.
52 48 or 49 or 50 or 51
53 47 not 52
| Search Id# | Query                                                                 | Items found |
|-----------|----------------------------------------------------------------------|-------------|
| S47       | S40 NOT S46                                                          | 346         |
| S46       | S41 OR S42 OR S43 OR S44 OR S45                                      | 295014      |
| S45       | Ti (editorial or review or guideline)                               | 153362      |
| S44       | Ti (rodent* or rat or rats or mouse or mice or animal model*)        | 112419      |
| S43       | Ti (smoking or tobacco or nicotine)                                  | 27214       |
| S42       | smoking cessation                                                    | 16116       |
| S41       | (TI (antibiotic* or antimicrob* or antifung* or statin*))           | 941         |
| S40       | S11 AND S15 AND S20 AND S39                                         | 396         |
| S39       | S27 OR S34 OR S38                                                   | 22229       |
| S38       | S35 OR S36 OR S37                                                   | 55044       |
| S37       | (TI (case N1 report*)) or (AB (case N1 report*)) or (KW (case N1 report*)) | 42544       |
| S36       | DE "Case Report"                                                     | 22681       |
| S35       | (TI (case N1 series)) or (AB (case N1 series)) or (KW (case N1 series)) | 4044       |
| S34       | S28 OR S29 OR S30 OR S31 OR S32 OR S33                              | 73783       |
| S33       | (TI (cross sectional N1 (study or studies))) or (AB (cross sectional N1 (study or studies))) or (KW (cross sectional N1 (study or studies))) | 22502       |
| S32       | (TI (follow up N1 (study or studies))) or (AB (follow up N1 (study or studies))) or (KW (follow up N1 (study or studies))) | 12995       |
| S31       | (TI (cohort N1 (study or studies))) or (AB (cohort N1 (study or studies))) or (KW (cohort N1 (study or studies))) | 17312       |
| S30       | (TI (case N1 control)) or (AB (case N1 control)) or (KW (case N1 control)) | 10801       |
| S29       | (TI (observational N1 (study or studies))) or (AB (observational N1 (study or studies))) or (KW (observational N1 (study or studies))) | 904         |
| S28       | (TI (epidemiologic* N1 (study or studies))) or (AB (epidemiologic* N1 (study or studies))) or (KW (epidemiologic* N1 (study or studies))) | 12443       |
| S27       | S21 OR S22 OR S23 OR S24 OR S25 OR S26                              | 10595       |
| S26       | (AB (waitlist* or wait* list* or treatment as usual or TAU) N3 (control or group))) | 5909         |
| S25       | (TI (quasi N1 {experimental OR randomi*}) or (AB (quasi N1 {experimental OR randomi*}) | 85          |
| S24       | (TI (control* N3 (trial* or study or studies)) or (AB (control* N3 (trial* or study or studies))) | 72623       |
| S23       | (TI (controlled N1 trial*)) or (AB (controlled N1 trial*))           | 32638       |
| S22       | (TI (random* control* trial*)) or (AB (random* control* trial*))     | 33209       |
| S21       | (TI (clinic* N1 trial*)) OR (AB (clinic* N1 trial*))                 | 26774       |
| S20       | S16 OR S17 OR S18 OR S19                                            | 453         |
| S19       | (TI (prevent* N3 relaps*)) or (AB (prevent* N3 relaps*)) OR (KW (prevent* N3 relaps*)) | 5697        |
| S18       | (TI (prevent* N3 recurrr*)) or (AB (prevent* N3 recurrr*)) OR (KW (prevent* N3 recurrr*)) | 1163        |
| S17       | (TI (deprescrib* or de prescrib* or deprescrip* or de prescrip*)) or (AB (deprescrib* or de prescrib* or deprescrip* or de prescrip*)) or (KW (deprescrib* or de prescrib* or deprescrip* or de prescrip*)) | 463         |
| S16       | (TI (cease or cessation* or discontinu* or interrupt or interruption or taper* or reduce or drug holiday or stop or stopping or withdraw* or terminat* post withdraw* or postwithdraw*)) or (KW (cease or cessation* or discontinu* or interrupt or interruption or taper* or reduce or drug holiday or stop or stopping or withdraw* or terminat* post withdraw* or postwithdraw*)) | 38818     |
interrupt or interruption or taper* or reduce or drug holiday or stop or stopping or withdraw* or termint* post withdraw* or postwithdraw*) or (KW (cease or cessation* or discontinu* or interrupt or interruption or taper* or reduce or drug holiday or stop or stopping withdraw* or termint* post withdraw* or postwithdraw*)) or (MJ (cease or cessation* or discontinu* or interrupt or interruption or taper* or reduce or drug holiday or stop or sto ...Show Less

S15 S12 OR S13 OR S14 111656
S14 (TI (mixed anxiety N2 depressive disorder)) OR (AB (mixed anxiety N2 depressive disorder)) OR (KW (mixed anxiety N2 depressive disorder)) 363
S13 (TI (mixed anxiety N2 depression)) OR (AB (mixed anxiety N2 depression)) OR (KW (mixed anxiety N2 depression)) 1214
S12 DE "Major Depression" OR DE "Postpartum Depression" OR DE "Treatment Resistant Depression" OR DE "Late Life Depression" OR DE "Recurrent Depression" OR DE "Reactive Depression" OR DE "Endogenous Depression" OR DE "Atypical Depression" 110816
S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 96482
S10 (TI (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirindole or Pivagabine or Pizotyline or Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Teniloxine or Tetindole or Thiazesim or Thozalinone or Tianepin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or 5 Hydroxytryptophan or 5 HT or Tryptophan or Hydroxytryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone or Zimeldine)) or (KW (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirindole or Pivagabine or Pizotyline or Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Teniloxine or Tetindole or Thiazesim or Thozalinone or Tianepin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or 5 Hydroxytryptophan or 5 HT or Tryptophan or Hydroxytryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone or Zimeldine)) or (MJ (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirindole or Pivagabine or Pizotyline or Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Teniloxine or Tetindole or Thiazesim or Thozalinone or Tianepin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or 5 Hydroxytryptophan or 5 HT or Tryptophan or Hydroxytryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone or Zimeldine)) or (TI (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirindole or Pivagabine or Pizotyline or Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Teniloxine or Tetindole or Thiazesim or Thozalinone or Tianepin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or ...Show Less
S9 (TI (Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idazoxan or Imipramin* or Iprindole or Iproniazid* or Ispapirone or Imipraminoxide or Isocarboxazid* or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or LY2216684 or Maprotiline or Medifoxamine or Melitracen or Metapramine or Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitrooxepine or Nomifensine or Norfenfluramine or Nortriptylpine or Noxiptilin*)) or (KW (Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idazoxan or Imipramin* or Iprindole or Iproniazid* or Ispapirone or Imipraminoxide or Isocarboxazid* or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or LY2216684 or Maprotiline or Medifoxamine or Melitracen or Metapramine or Methylphenidate or Mianserin or Milnacipran or Minaprine 15681
or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or 
Nitrooxazepine or Nomifensine or Norfvenfluramine or Nortriptyline or Noxiptilin*) or (MJ 
(Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idazoxan or 
Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Imipraminoxide or 
Isocarboxazid*or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or (Lu AA21004 or 
Vortioxetine) or Lu AA24530 or LY2216684 or Maprotiline or Medifoxamine or 
Melitracen or Metapramine or Methylenidate or Mianserin or Milnacipran or Minaprine 
or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or 
Nitrooxazepine or Nomifensine or Norfvenfluramine or Nortriptyline or Noxiptilin*)|TI 
(Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idazoxan or 
Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Imipraminoxide or 
Isocarboxazid*or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or (Lu AA21004 or 
Vortioxetine) or Lu AA24530 or LY2216684 or Maprotiline or Medifoxamine or 
Melitracen or Metapramine or Methylenidate or Mianserin or Milnacipran or Minaprine 
or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or 
Nitrooxazepine o...Show Less
| Term | Database Examples |
|------|------------------|
| S7   | (TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*)) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*)) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*)) or (TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*)) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*))) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)))) | 59965 |
| S6   | DE "Tricyclic Antidepressant Drugs" OR DE "Amitriptyline" OR DE "Chlorimipramine" OR DE "Desipramine" OR DE "Doxepin" OR DE "Imipramine" OR DE "Maprotiline" OR DE "Nortriptyline" | 8847 |
| S5   | DE "Serotonin Reuptake Inhibitors" OR DE "Citalopram" OR DE "Fluoxetine" OR DE "Fluvoxamine" OR DE "Paroxetine" OR DE "Zimeldine" | 13283 |
| S4   | DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" | 1525 |
| S3   | DE "Neurotransmitter Uptake Inhibitors" | 326 |
| S2   | DE "Antidepressant Drugs" | 17567 |
| S1   | DE "Psychopharmacology" or DE "Neuropsychopharmacology" | 9416 |
| Search ID# | Query | Items found |
|-----------|-------|-------------|
| S35       | S6 AND S10 AND S15 AND S34 | 21          |
| S34       | S22 OR S30 OR S33           | 21001       |
| S33       | S31 OR S32                  | 4389        |
| S32       | (TI (case N1 report*)) or (AB (case N1 report*)) or (KW (case N1 report*)) | 4079        |
| S31       | (TI (case N1 series) or (AB (case N1 series)) or (KW (case N1 series)) | 343         |
| S30       | S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 | 5541        |
| S29       | (TI (cross sectional N1 (study or studies))) or (AB (cross sectional N1 (study or studies))) OR (KW (cross sectional N1 (study or studies))) | 1925        |
| S28       | (TI (follow up N1 (study or studies))) or (AB (follow up N1 (study or studies))) OR (KW (follow up N1 (study or studies))) | 760         |
| S27       | (TI (cohort N1 (study or studies))) or (AB (cohort N1 (study or studies))) OR (KW (cohort N1 (study or studies))) | 1839        |
| S26       | (TI (case N1 control)) or (AB (case N1 control)) OR (KW (case N1 control)) | 708         |
| S25       | (TI (observational N1 (study or studies))) or (AB (observational N1 (study or studies))) OR (KW (observational N1 (study or studies))) | 132         |
| S24       | (TI (observational N1 (study or studies))) or (AB (observational N1 (study or studies))) OR (KW (observational N1 (study or studies))) | 132         |
| S23       | (TI (epidemiologic* N1 (study or studies))) or (AB (epidemiologic* N1 (study or studies))) OR (KW (epidemiologic* N1 (study or studies))) | 532         |
| S22       | S16 OR S17 OR S18 OR S19 OR S20 OR S21 | 12226       |
| S21       | (AB (waitlist* or wait* list* or treatment as usual or TAU) N3 (control or group))) | 355         |
| S20       | (TI (quasi N1 (experimental OR randomi*)) or (AB (quasi N1 (experimental OR randomi*))) | 387         |
| S19       | (TI (control* N3 (trial* or study or studies))) or (AB (control* N3 (trial* or study or studies))) | 9141        |
| S18       | (TI (controlled N1 trial*)) or (AB (controlled N1 trial*)) | 5597        |
| S17       | (TI (randomi* control* trial*)) or (AB (randomi* control* trial*)) | 5803        |
| S16       | (TI (clinical N1 trial*)) OR (AB (clinical N1 trial*)) | 3644        |
| S15       | S11 OR S12 OR S13 OR S14 | 8964        |
| S14       | (TI (prevent* N3 relaps*)) or (AB (prevent* N3 relaps*)) or (KW (prevent* N3 relaps*)) | 22          |
| S13       | (TI (prevent* N3 recurr*)) OR (AB (prevent* N3 recurr*)) OR (KW (prevent* N3 recurr*)) | 31          |
| S12       | (TI (deprescrib* or de prescrib* or deprescrip* or de prescrip*)) OR (AB (deprescrib* or de prescrib* or deprescrip* or de prescrip*)) OR (KW (deprescrib* or de prescrib* or deprescrip* or de prescrip*)) | 22          |
| S11       | (TI (cease or cessation* or discontinue* or interrupt or interruption or taper* or reduce or drug holiday or stop or stopping or withdraw* or terminat*)) or (AB (cease or cessation* or continuation or discontinue* or interrupt or interruption or taper* or reduce or drug holiday or stop or stopping or withdraw* or terminat*)) or (KW (cease or cessation* or continuation or discontinue* or interrupt or interruption or taper* or reduce or drug holiday or stop or stopping or withdraw* or terminat*)) | 89          |
| S10       | S7 OR S8 OR S9 | 6074        |
| S9        | (TI (depressive disorder or depression or mixed anxiety)) or (AB (depressive disorder or depression or mixed anxiety)) or (KW (depressive disorder or depression or mixed anxiety)) | 604         |
| S8        | (DE "ADJUSTMENT DISORDERS") | 15          |
| S7        | (DE "DEPRESSION") OR (DE "DEPRESSIVE DISORDER") OR (DE "DEPRESSIVE DISORDERS") | 2988        |
| S6        | S1 OR S2 OR S3 OR S4 OR S5 | 2046        |
| S5        | (TI (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or | 142          |
TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*)) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*)) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*)) or (TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*)) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (AB (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (KW (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))) or (TI (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*)) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or antiadrenergic or SSRI* or SNRI* or TCA* or tricylic* or tetracyclic* or heterocyclic*))).
| noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt*… | Show Less |
|---------------------------------------------------------------|-----------|
| S1 (DE "antidepressive agents")                              | 313       |
| Search ID# | Query | Items found |
|----------|-------|-------------|
| 1        | "PSYCHOPHARMACOLOGY"/ | 42          |
| 2        | "PSYCHOTROPIC DRUGS"/ | 135         |
| 3        | exp "ANTI DEPRESSANTS"/ | 389         |
| 4        | exp "SELECTIVE SEROTONIN REUPTAKE INHIBITORS"/ | 35          |
| 5        | (psychotropic* OR antidepress* OR anti depress* OR ((serotonin OR norepinephrine OR noradrenaline OR nor epinephrine OR nor adrenaline OR neurotransmitt* OR dopamine*) AND (uptake OR reuptake OR re-uptake)) OR noradrenerg* OR antiadrenergic OR antiadrenergic OR SSRI* OR SNRI* OR TCA* OR tricyclic* OR tetracyclic* OR heterocyclic*) | 929         |
| 6        | (Agomelatine OR Alaproclate OR Alnesprone OR Amoxapine OR Amersergide OR Amfebutamone OR Amiflamine OR Aminopentine OR Amitriptylin* OR Amitriptylinoxide OR Amoxapine OR Aripiprazole OR Atomoxetine OR Befloxatone OR Benactyzine OR Bino Pivin OR Brofaromine OR Buproprion OR Butriptylin* OR Caroxzone OR Chlopxiten OR Cianopramine OR Cilobamine OR Cilozamine OR Cimoxatone OR Citalopram OR Chlorimipramin* OR Clomipramin* OR Clomipramine OR Clorimipramine OR Clogryline OR Cloxoxamine OR Dopoxetine OR Deanol OR Demexiptilin* OR Deprenyl OR Desipramine OR Desvenlafaxine OR Dibenzepin OR Diclofenasin* OR Dimetacin* OR Dosulepin OR Dothiepin OR Doxepin OR Droxetine OR DVS 233 OR Enilosiprione OR Eptapirone OR Escitalopram OR Etorperidone OR Fencetin* OR Fluoxetine OR Fluvoxamine).ti,ab | 220         |
| 7        | (Harmaline OR Harmine OR Hyperforin OR Hypericum OR John* Wort OR Idazoxan OR Imipramin* OR Iprindole OR Iproniazid* OR Ispapirone OR Imapriminoxide OR Isocarboxazid* OR Lesopitron OR Levomilnacipran OR Lithium OR Lofepramin* OR Lu AA21004 OR Vortioxetine OR Lu AA24530 OR LY2216684 OR Maprotline OR Medifoxamine OR Mellitracen OR Metapramine OR Methylphenidate OR Mianserin OR Milnacipran OR Minaprine OR Mitazapine OR Moclobemide OR Monocrotrophos OR Nefazodone OR Nialamide OR Nortryptine OR Norfluoxetine OR Norfluoxetine OR DVS 233 OR Enilosiprione OR Eptapirone OR Escitalopram OR Etorperidone OR Fencetin* OR Fluoxetine OR Fluvoxamine).ti,ab | 126         |
| 8        | (Opipramol OR Oxaflozane OR Paroxetine OR Phenelzine OR Pheniprazine OR Pipofezin* OR Pirandamine OR Pirbedil OR Pirilindole OR Pivagabine OR Pizotyline OR Propizepine OR Protriptylin* OR Perto frane OR Quinupramine OR Quipazine OR Reboxetine OR Ritalan OR Rolipram OR Scopolamine OR Serelgine OR Sertaline OR Setiptiline OR Teciptiline OR Tandospirone OR Teniloxine OR Tetindrole OR Thiazisim OR Thozalinone OR Tianeptin* OR Tolaxotane OR Tranilycypromine OR Trazodone OR Trimipramine OR 5 Hydroxytryptophan OR 5 HT OR Tryptophan OR Hydroxytryptophan OR Venlafaxine OR Viloxamine OR Vilazodone OR Viqualine OR Zalosiprone OR Zimeldine).ti,ab | 99          |
| 9        | (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8) | 1307        |
| 10       | "MOOD DISORDERS"/ | 90          |
| 11       | "DEPRESSION"/ | 2608        |
| 12       | (depressive disorder OR depression OR mixed anxiety).ti,ab | 4422        |
| 13       | (10 OR 11 OR 12) | 4909        |
| 14       | (cease OR cessation* OR discontinu* OR interrupt OR interruption OR taper* OR reduce OR drug holiday OR stop OR stopping OR withdraw* OR terminat* OR deprescrib* OR de prescrib* OR deprescrib* OR de prescrib*).ti,ab | 14611       |
| 15       | (prevent* ADJ3 relaps*).ti,ab | 144         |
| 16       | (prevent* ADJ3 recur*).ti,ab | 91          |
| 17       | (14 OR 15 OR 16) | 14771       |
"RANDOMISED CONTROLLED TRIALS"/
(randomised OR randomisation).ti,ab (randomly).ab (trial).ti,ab trial.ti,ab (groups).ab (control* ADJ3 (trial* OR study OR studies)).ti,ab (control* adj3 (trial* or study or studies)).ti,ab (quasi ADJ (experimental OR random*)).ti,ab (quasi adj (experimental or random*)).ti,ab ((waitlist* OR wait* list* OR treatment as usual OR TAU) ADJ3 (control OR group)).ab (18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25) (18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25)
"COHORT STUDIES"/
"PROSPECTIVE STUDIES"/
"LONGITUDINAL STUDIES"/
(Case control).ti,ab (Cohort analy*).ti,ab (Follow up ADJ (study OR studies)).ti,ab (observational ADJ (study OR studies)).ti,ab (epidemiologic* ADJ (study OR studies)).ti,ab (Longitudinal).ti,ab (Retrospective).ti,ab (Cross sectional).ti,ab (27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38) (Case series).ti,ab (Case* report*).ti,ab (Case* stud*).ti,ab (40 OR 41 OR 42) (26 OR 39 OR 43) (9 AND 13 AND 17 AND 44) (rodent* OR rat OR rats OR mouse OR mice OR animal model*).ti (smoking OR tobacco OR nicot ine).ti (smoking OR tobacco OR nicotine).ti (smoking cessation).ti,ab (antibiotic* OR antimicrob* OR antifung* OR statin*).ti (46 OR 47 OR 48 OR 49) 45 NOT 50
**OpenGrey**

OpenGrey (http://www.opengrey.eu/), inception to 24 March 2017

| Query                                                                 | Items found |
|-----------------------------------------------------------------------|-------------|
| (antidepressant* OR SSRI* OR serotonin reuptake inhibitor* OR SNRI* OR noradrenaline reuptake inhibitor* OR norepinephrine reuptake inhibitor* or tricyclic antidepressant*) AND (trial* OR RCT* OR observational OR cohort* OR case series OR case report*) | 28          |

**WHO International Clinical Trials Registry platform (WHO ICTRP).**

WHO ICTRP (http://apps.who.int/trialsearch/default.aspx), inception to 24 March 2017

| Query                                                                 | Items found |
|-----------------------------------------------------------------------|-------------|
| Depression AND prevent* AND relapse                                    | 110         |
| Depression AND prevent* AND recurr*                                   | 33          |
| Antidepressant* AND cease                                             | 1           |
| Antidepressant* AND cessation                                         | 3           |
| Antidepressant* AND discontinuation                                    | 13          |
| Antidepressant* AND taper*                                             | 11          |
| Antidepressant* AND reduce                                            | 6           |
| Antidepressant* AND stop*                                              | 4           |
| Antidepressant* AND withdraw*                                          | 8           |
| Antidepressant* AND terminat*                                          | 3           |
| Antidepressant* AND deprescrib*                                       | 3           |
| SSRI* AND cease                                                       | 0           |
| SSRI* AND cessation                                                    | 0           |
| SSRI* AND discontinuation                                              | 1           |
| SSRI* AND taper*                                                       | 3           |
| SSRI* AND reduce                                                       | 3           |
| SSRI* AND stop*                                                        | 1           |
| SSRI* AND withdraw*                                                    | 1           |
| SSRI* AND terminat*                                                    | 0           |
| SSRI* AND deprescrib*                                                  | 0           |
| SNRI* AND cease                                                       | 0           |
| SNRI* AND cessation                                                    | 0           |
| SNRI* AND discontinuation                                              | 0           |
| SNRI* AND taper*                                                       | 1           |
| SNRI* AND reduce                                                       | 0           |
| SNRI* AND stop*                                                        | 0           |
| SNRI* AND withdraw*                                                    | 0           |
| SNRI* AND terminat*                                                    | 0           |
| SNRI* AND deprescrib*                                                  | 0           |
| TCA AND cease                                                         |             |
| Only brought up records for non-psychiatric indications e.g. diabetes, stem cells, transplantations, cancer |             |
| TCA AND cessation | See above |
|-------------------|-----------|
| TCA AND discontinuation | See above |
| TCA AND taper* | See above |
| TCA AND reduce | See above |
| TCA AND stop* | See above |
| TCA AND withdraw* | See above |
| TCA AND terminat* | See above |
| TCA AND deprescrib* | See above |
| tricyclic antidepressant* AND cease | 0 |
| tricyclic antidepressant* AND cessation | 1 |
| tricyclic antidepressant* AND discontinuation | 0 |
| tricyclic antidepressant* AND taper* | 1 |
| tricyclic antidepressant* AND reduce | 2 |
| tricyclic antidepressant* AND stop* | 0 |
| tricyclic antidepressant* AND withdraw* | 1 |
| tricyclic antidepressant* AND terminat* | 0 |
| tricyclic antidepressant* AND deprescrib* | 1 |
| citalopram AND cease | 0 |
| citalopram AND cessation | 0 |
| citalopram AND discontinuation | 4 |
| citalopram AND taper* | 2 |
| citalopram AND reduce | 2 |
| citalopram AND stop* | 1 |
| citalopram AND withdraw* | 0 |
| citalopram AND terminat* | 0 |
| citalopram AND deprescrib* | 0 |
| escitalopram AND cease | 0 |
| escitalopram AND cessation | 1 |
| escitalopram AND discontinuation | 6 |
| escitalopram AND taper* | 2 |
| escitalopram AND reduce | 1 |
| escitalopram AND stop* | 0 |
| escitalopram AND withdraw* | 2 |
| escitalopram AND terminat* | 2 |
| escitalopram AND deprescrib* | 0 |
| fluoxetine AND cease | 0 |
| fluoxetine AND cessation | 1 |
| fluoxetine AND discontinuation | 1 |
| fluoxetine AND taper* | 1 |
| fluoxetine AND reduce | 2 |
| fluoxetine AND stop* | 2 |
| Drug          | Action          | Count |
|--------------|-----------------|-------|
| fluoxetine   | withdraw*       | 0     |
| fluoxetine   | terminat*       | 0     |
| fluoxetine   | deprescrib*     | 0     |
| fluvoxamine  | cease           | 0     |
| fluvoxamine  | cessation       | 0     |
| fluvoxamine  | discontinuation | 0     |
| fluvoxamine  | taper*          | 1     |
| fluvoxamine  | reduce          | 0     |
| fluvoxamine  | stop*           | 0     |
| fluvoxamine  | withdraw*       | 0     |
| fluvoxamine  | terminat*       | 0     |
| fluvoxamine  | deprescrib*     | 0     |
| paroxetine   | cessation       | 0     |
| paroxetine   | discontinuation | 1     |
| paroxetine   | taper*          | 0     |
| paroxetine   | reduce          | 0     |
| paroxetine   | stop*           | 0     |
| paroxetine   | withdraw*       | 1     |
| paroxetine   | terminat*       | 0     |
| paroxetine   | deprescrib*     | 0     |
| sertraline   | cease           | 3     |
| sertraline   | cessation       | 0     |
| sertraline   | discontinuation | 1     |
| sertraline   | taper*          | 1     |
| sertraline   | reduce          | 6     |
| sertraline   | stop*           | 4     |
| sertraline   | withdraw*       | 0     |
| sertraline   | terminat*       | 1     |
| sertraline   | deprescrib*     | 0     |
| duloxetine   | cease           | 0     |
| duloxetine   | cessation       | 0     |
| duloxetine   | discontinuation | 0     |
| duloxetine   | taper*          | 1     |
| duloxetine   | reduce          | 2     |
| duloxetine   | stop*           | 0     |
| duloxetine   | withdraw*       | 0     |
| duloxetine   | terminat*       | 0     |
| duloxetine   | deprescrib*     | 0     |
| venlafaxine  | cease           | 0     |
| venlafaxine  | cessation       | 0     |
| venlafaxine  | discontinuation | 0     |
| venlafaxine  | taper*          | 5     |
| venlafaxine  | reduce          | 1     |
| venlafaxine  | stop*           | 0     |
| Query                                      | Hits |
|--------------------------------------------|------|
| venlafaxine AND withdraw*                  | 1    |
| venlafaxine AND terminat*                  | 0    |
| venlafaxine AND deprescrib*                | 0    |
| mirtazapine AND cease                      | 1    |
| mirtazapine AND cessation                  | 0    |
| mirtazapine AND discontinuation            | 0    |
| mirtazapine AND taper*                     | 0    |
| mirtazapine AND reduce                     | 1    |
| mirtazapine AND stop*                      | 2    |
| mirtazapine AND withdraw*                  | 2    |
| mirtazapine AND terminat*                  | 0    |
| mirtazapine AND deprescrib*                | 0    |
| **Total number of hits**                   | **278** |
APPENDIX 2 - TABLES A-H
### TABLE A: EXCLUDED STUDIES

| Reference | Reason for exclusion |
|-----------|----------------------|
|Anonymous. Home-based programme significantly reduces depressive symptoms and improves health status in chronically ill older adults with minor depression or dysthymia. *Evidence-Based Healthcare and Public Health* 2004;8(5):257-58. doi: http://dx.doi.org/10.1016/j.hbpc.2004.08.035 | Population has minor depression or dysthymia |
|Apil SRA, Spinhoven P, Haffmans PMJ, et al. Two-year follow-up of a randomized controlled trial of stepped care cognitive behavioral therapy to prevent recurrence of depression in an older population. *International Journal of Geriatric Psychiatry* 2014;29(3):317-25. doi: http://dx.doi.org/10.1002/gps.4010 | Intervention is not aimed at antidepressant reduction/discontinuation. |
|Aronson TA, Shukla S. Long-term continuation antidepressant treatment: A comparison study. *Journal of Clinical Psychiatry* 1989;50(8):285-89. | Population included some bipolar patients (>10%) |
|Baldwin DS, Cooper JA, Huusom AKT, et al. A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. *International Clinical Psychopharmacology* 2006;21(3):159-69. doi: http://dx.doi.org/10.1097/01.yic.0000194377.88330.1d | Intervention is not aimed at antidepressant reduction/discontinuation (interruption study) |
|Bialos D, Giller E, Jatlow P, et al. Recurrence of depression after discontinuation of long-term amitriptyline treatment. *American Journal of Psychiatry* 1982;139(3):325-9. doi: https://dx.doi.org/10.1176/ajp.139.3.325 | Intervention is not aimed at antidepressant reduction/discontinuation |
|Bieling PJ, Hawley LL, Bloch RT, et al. Treatment-specific changes in decentering following mindfulness-based cognitive therapy versus antidepressant medication or placebo for prevention of depressive relapse. *Journal of Consulting and Clinical Psychology* 2012;80(3):365-72. doi: http://dx.doi.org/10.1037/a0027483 | Outcomes were cognitive changes (neither a primary nor secondary outcome of the review) |
|Bockting CLH, Schene AH, Koeter HWJ, et al. Preventing relapse/recurrence in recurrent depression with cognitive therapy: A randomized controlled trial. *Journal of Consulting and Clinical Psychology* 2005;73(4):647-57. doi: http://dx.doi.org/10.1037/0022-006X.73.4.647 | Intervention is not aimed at antidepressant reduction/discontinuation |
|Bockting CLH, Smid NH, Koeter MWJ, et al. Enduring effects of Preventive Cognitive Therapy in adults remitted from recurrent depression: A 10 year follow-up of a randomized controlled trial. *Journal of Affective Disorders* 2015;185:188-94. doi: http://dx.doi.org/10.1016/j.jad.2015.06.048 | Intervention is not aimed at antidepressant reduction/discontinuation |
|Bockting CLH, Spinhoven P, Koeter MWJ, et al. Differential predictors of response to preventive cognitive therapy in recurrent depression: A 2-year prospective study. *Psychotherapy and Psychosomatics* 2006;75(4):229-36. doi: http://dx.doi.org/10.1159/000092893 | Intervention is not aimed at antidepressant reduction/discontinuation |
|Bockting CLH, Ten Doesschate MC, Spijker J, et al. Continuation and maintenance use of antidepressants in recurrent depression. *Psychotherapy and Psychosomatics* 2008;77(1):17-26. doi: http://dx.doi.org/10.1159/000110056 | Observational study not concerning reduction/discontinuation of antidepressants |
|Curtin F, Schulz P. Relapse prevention and antidepressants. *Lancet* 2003;361(9375):2158-59; author reply 59. | Letter concerning a systematic review |
|Dallal A, Chouinard G. Withdrawal and rebound symptoms associated with abrupt discontinuation of venlafaxine. *Journal of Clinical Psychopharmacology* 1998;18(4):343-44. doi: 10.1097/00004714-199808000-00017 | Study design was case series |
| Dobson KS, Hollar SD, Dimidjian S, et al. Randomized Trial of Behavioral Activation, Cognitive Therapy, and Antidepressant Medication in the Prevention of Relapse and Recurrence in Major Depression. *Journal of Consulting and Clinical Psychology* 2008;76(3):468-77. doi: http://dx.doi.org/10.1037/0022-006X.76.3.468 | Intervention is not aimed at antidepressant reduction/discontinuation |
| Number | Reference | Title | Keywords |
|--------|-----------|-------|----------|
| 15     | Fava GA, Rafanelli C, Cazzaro M, et al. | Well-being therapy. A novel psychotherapeutic approach for residual symptoms of affective disorders. *Psychological Medicine* 1998;28(2):475-80. doi: http://dx.doi.org/10.1017/S0033291798006363 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 16     | Flint AJ, Rifat SL. | Recurrence of first-episode geriatric depression after discontinuation of maintenance antidepressants. *American Journal of Psychiatry* 1999;156(6):943-5. doi: https://dx.doi.org/10.1176/ajp.156.6.943 | Study of relapse prevention, not antidepressant discontinuation. |
| 17     | Frank E, Kuperl DJ, Perel JM. | Early recurrence in unipolar depression. *Archives of General Psychiatry* 1989;46(5):397-400. doi: http://dx.doi.org/10.1016/j.bpj.2010.04.006 | Study of relapse prevention, not antidepressant discontinuation. |
| 18     | Godfrin KA, van Heeringen C. | The effects of mindfulness-based cognitive therapy on recurrence of depressive episodes, mental health and quality of life: A randomized controlled study. *Behaviour Research and Therapy* 2010;48(8):738-46. doi: http://dx.doi.org/10.1016/j.brat.2010.04.006 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 19     | Howell CA, Turnbull DA, Beilby JJ, et al. | Preventing relapse of depression in primary care: a pilot study of the "the blues away" program. *The Medical Journal of Australia* 2008;188(12 Suppl):S138-41. doi: http://dx.doi.org/10.5812/ircmj.8018 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 20     | Huijbers MJ, Spinthon P, Spijker J, et al. | Adding mindfulness-based cognitive therapy to maintenance antidepressant medication for prevention of relapse/recurrence in major depressive disorder: Randomised controlled trial. *Journal of Affective Disorders* 2015;187:54-61. doi: http://dx.doi.org/10.1016/j.jad.2015.08.023 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 21     | Kinser PA, Elswick RK, Korstein S. | Potential long-term effects of a mind-body intervention for women with major depressive disorder: sustained mental health improvements with a pilot yoga intervention. *Arch Psychiatr Nurs* 2014;28(6):377-83. doi: https://dx.doi.org/10.1016/j.apnu.2014.08.014 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 22     | Kuehner C. | An evaluation of the ‘Coping with Depression Course’ for relapse prevention with unipolar depressed patients. *Psychotherapy and Psychosomatics* 2005;74(4):254-59. doi: http://dx.doi.org/10.1159/000085150 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 23     | Ludman E, Katon W, Bush T, et al. | Behavioural factors associated with symptom outcomes in a primary care-based depression prevention intervention trial. *Psychological Medicine* 2003;33(6):1061-70. doi: http://dx.doi.org/10.1017/S003329170300816X | Intervention is not aimed at antidepressant reduction/discontinuation |
| 24     | Ludman E, Von Korff M, Katon W, et al. | The design, implementation, and acceptance of a primary care-based intervention to prevent depression relapse. *International Journal of Psychiatry in Medicine* 2000;30(3):229-45. doi: http://dx.doi.org/10.2190/44LK-28E9-RRJ5-KQVV | Intervention is not aimed at antidepressant reduction/discontinuation |
| 25     | Mago R, Crits-Christoph P. | Prevention of recurrent depression with cognitive behavioral therapy. *Arch Gen Psychiatry* 1999;56(5):479-80. [published Online First: 1999/05/08] | Letter commenting on a study already included in the review |
| 26     | Meadows GN, Shawyer F, Enticott JC, et al. | Mindfulness-based cognitive therapy for recurrent depression: A translational research study with 2-year follow-up. *Australian and New Zealand Journal of Psychiatry* 2014;48(8):743-55. doi: http://dx.doi.org/10.1177/0004867414525841 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 27     | Michelson D, Fava M, Amsterdam J, et al. | Interruption of selective serotonin reuptake inhibitor treatment: Double-blind, placebo-controlled trial. *British Journal of Psychiatry* 2000;176(APR.):363-68. doi: http://dx.doi.org/10.1192/bjp.176.4.363 | Intervention is not aimed at antidepressant reduction/discontinuation (interruption study) |
| 28     | Montgomery SA, Fava M, Padmanabhan SK, et al. | Discontinuation symptoms and taper/poststudy-emergent adverse events with desvenlafaxine treatment for major depressive disorder. *International Clinical Psychopharmacology* 2009;24(6):296-305. doi: http://dx.doi.org/10.1097/YIC.0b013e32832fbb5a | Study design was pooled analysis of prevalence and type of discontinuation symptoms after antidepressant discontinuation during or at the end of placebo controlled trials of treatment of depression |
| 29     | Mourad I, Lejoyeux M, Ades J. | [Prospective evaluation of antidepressant discontinuation]. *Encephale* 1998;24(3):215-22. | Study design was case series |
| 30     | Omidia, Mohammadkhani P, Mohammadi A, et al. | Comparing mindfulness based cognitive therapy and traditional cognitive behavior therapy with treatments as usual on reduction of major depressive disorder symptoms. *Iranian Red Crescent Medical Journal* 2013;15(2):142-46. doi: http://dx.doi.org/10.5812/ircmj.8018 | Intervention is not aimed at antidepressant reduction/discontinuation |
| No. | Author(s) | Title | Journal | doi | Summary |
|-----|-----------|-------|---------|-----|---------|
| 31  | Paykel ES, Scott J, Cornwall PL, et al. | Duration of relapse prevention after cognitive therapy in residual depression: Follow-up of controlled trial. | *Psychological Medicine* 2005;35(1):59-68. | http://dx.doi.org/10.1017/S003329170400282X | Intervention is not aimed at antidepressant reduction/discontinuation |
| 32  | Paykel ES, Scott J, Teasdale JD, et al. | Prevention of relapse in residual depression by cognitive therapy. A controlled trial. | *Archives of General Psychiatry* 1999;56(9):829-35. | http://dx.doi.org/10.1001/archpsyc.56.9.829 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 33  | Perlis RH, Nierenberg AA, Alpert JE, et al. | Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. | *Journal of Clinical Psychopharmacology* 2002;22(5):474-80. | | |
| 34  | Petersen Tj, Pava JA, Buchin J, et al. | The role of cognitive-behavioral therapy and fluoxetine in prevention of recurrence of major depressive disorder. | *Cognitive Therapy and Research* 2010;34(1):13-23. | http://dx.doi.org/10.1007/s10608-007-9166-6 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 35  | Rosenbaum JF, Fava M, Hoog SL, et al. | Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. | *Biological Psychiatry* 1998;44(2):77-87. | http://dx.doi.org/10.1016/S0006-3223(89)800126-7 | Intervention is not aimed at antidepressant reduction/discontinuation (interruption study) |
| 36  | Scott J, Palmer S, Paykel E, et al. | Use of cognitive therapy for relapse prevention in chronic depression: Cost-effectiveness study. | *British Journal of Psychiatry* 2003;182(MAR):221-27. | http://dx.doi.org/10.1192/bjp.182.3.221 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 37  | Segal ZV, Bieling P, Young T, et al. | Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. | *Archives of General Psychiatry* 2010;67(12):1256-64. | http://dx.doi.org/10.1001/archgenpsychiatry.2010.168 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 38  | Shawyer F, Meadows GN, Judd F, et al. | The DARE study of relapse prevention in depression: Design for a phase 1/2 translational randomised controlled trial involving mindfulness-based cognitive therapy and supported self monitoring. | *BMC Psychiatry* 2014;12 [1] (no pagination)[3] | http://dx.doi.org/10.1186/1471-244X-32-3 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 39  | Stanger U, Hilling C, Heidenreich T, et al. | Maintenance cognitive-behavioral therapy and manualized psychoeducation in the treatment of recurrent depression: A multicenter prospective randomized controlled trial. | *American Journal of Psychiatry* 2013;170(6):624-32. | http://dx.doi.org/10.1176/appi.ajp.2013.12060734 | Intervention is not aimed at antidepressant reduction/discontinuation |
| 40  | Stant AD, TenVergert EM, Kluter H, et al. | Cost-effectiveness of a psychoeducational relapse prevention program for depression in primary care. | *J Ment Health Policy Econ* 2009;12(4):195-204. | | |
| 41  | Tang TZ, Derubeis RJ, Hollon SD, et al. | Sudden gains in cognitive therapy of depression and depression relapse/recurrence. | *J Consult Clin Psychol* 2007;75(3):404-8. | http://dx.doi.org/10.1037/0022-006x.75.3.404 [published Online First: 2007/06/15] | Intervention is not aimed at antidepressant reduction/discontinuation |
| 42  | Taylor MP, Reynolds CF, 3rd, Frank E, et al. | Which elderly depressed patients remain well on maintenance interpersonal psychotherapy alone?: report from the Pittsburgh study of maintenance therapies in late-life depression. | *Depress Anxiety* 1999;10(2):55-60. | | |
| 43  | Teasdale JD, Segal ZV, Williams JM, et al. | Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. | *J Consult Clin Psychol* 2000;68(4):615-23. | | |
| 44  | Tint A, Haddad PM, Anderson IM. | The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study.[Erratum appears in *J Psychopharmacol*. 2009 Nov;23(8):1006]. | *Journal of Psychopharmacology* 2008;22(3):330-2. | http://dx.doi.org/10.1177/0269881107087488 | Intervention is not aimed at antidepressant reduction/discontinuation (interruption study) |
| 45  | Ulfvarson J, Adami J, Wredling R, et al. | Controlled withdrawal of selective serotonin reuptake inhibitor drugs in elderly patients in nursing homes with no indication of depression. | *European Journal of Clinical Pharmacology* 2003;59(10):735-40. | http://dx.doi.org/10.1007/s00228-003-0687-y | Population had no history of indication for antidepressant use |
46 van Geffen EC, Hugtenburg JG, Heerdink ER, et al. Discontinuation symptoms in users of selective serotonin reuptake inhibitors in clinical practice: tapering versus abrupt discontinuation. European Journal of Clinical Pharmacology 2005;61(4):303-7. doi: https://dx.doi.org/10.1007/s00228-005-0921-x

Population was not described in terms of indication for antidepressant use. Study authors were contacted for details, but no response was received.

47 Von Korff M, Katon W, Rutter C, et al. Effect on Disability Outcomes of a Depression Relapse Prevention Program. Psychosomatic Medicine 2003;65(6):938-43. doi: http://dx.doi.org/10.1097/01.PSY.0000097336.95046.0C

Intervention is not aimed at antidepressant reduction/discontinuation

48 Wang HN, Wang XX, Zhang RG, et al. Repetitive transcranial magnetic stimulation for the prevention of depressive relapse/recurrence: An assessor blind, randomized controlled trial. Brain Stimulation 2017;10(2):507-08. doi: http://dx.doi.org/10.1016/j.brs.2017.01.482

Outcomes for those patients who discontinued antidepressants were not reported

49 Williams JMG, Crane C, Barnhofer T, et al. Mindfulness-based cognitive therapy for preventing relapse in recurrent depression: A randomized dismantling trial. Journal of Consulting and Clinical Psychology 2014;82(2):275-86. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

50 Williams JMG, Russell IT, Crane C, et al. Staying well after depression: Trial design and protocol. BMC Psychiatry 2010;10 (no pagination)(23) doi: http://dx.doi.org/10.1186/1471-244X-10-23

Intervention is not aimed at antidepressant reduction/discontinuation

51 DRKS00006866. European Comparative Effectiveness Research on Internet-based Depression Treatment. 2014. doi: http://dx.doi.org/10.1186/1471-244X-10-23

Intervention is not aimed at antidepressant reduction/discontinuation

52 NCT02747134. Combining Emotion Regulation and Mindfulness Skills for Preventing Depression Relapse. 2016. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

53 NCT02614326. MemFlex to Prevent Depressive Relapse. 2015. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

54 NCT02029963. Can Magnetic Brain Stimulation Help Prevent Relapse in Depression? 2014. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

55 NCT01807988. Internet-based Relapse Prevention for Partially Remitted Depression. 2013. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

56 NCT01619930. The Effects of Behavioral Activation and Physical Exercise on Depression. 2012. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

57 NCT00427128. Prozac Treatment of Major Depression: Discontinuation Study. 2007. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

58 NCT00218764. Cognitive Therapy Versus Medication Treatment for Preventing Depression Relapse. 2005. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

59 NCT00183664. Cognitive Therapy for Treating Depression and Preventing Relapse. 2005. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

60 NCT00183560. Preventing Depression Relapse With Mindfulness-Based Cognitive Therapy. 2005. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

61 NCT00557577. Prevention of Recurrence in Depression With Drugs and CT. 2003. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

62 JPRN-UMIN000005896. The effect of psychoeducation for the prevent from recurrence of major depression and familial expressed emotion. 2011. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

63 JPRN-UMIN000005555. Family psychoeducation to prevent relapse/recurrent in the maintenance treatment of major depression: a randomized controlled trial. 2011. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

64 ISRCTN68246470. (Cost)effectiveness of a cognitive group prevention module for recurrent depression. 2006. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

65 ISRCTN67561918. Psychotherapy for residual depression following initial treatment: effectiveness, relapse prevention and mechanisms of change. 2007. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

66 ISRCTN64953693. An integrative online self-help program (Deprexis®) versus waitlist control for adults with depressive symptoms. 2009. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

67 ISRCTN68088893. An SMS-assisted mindfulness-based intervention for relapse prevention in depression. 2014. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

68 ISRCTN44812125. Cognitive training as a facilitated self-help relapse prevention for depression. 2010. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

69 ISRCTN15969819. Antidepressants to prevent relapse in depression. 2015. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation

70 ISRCTN12388725. E-COMPaRED - internet-supported CBT for depression. 2015. doi: http://dx.doi.org/10.1037/a0035036

Intervention is not aimed at antidepressant reduction/discontinuation
| Study ID | Title                                                                 | Intervention Aim                        |
|---------|----------------------------------------------------------------------|----------------------------------------|
| IRCT201111298253N1 | Effect of psychological intervention on symptoms and preventing recurrence depression. 2012 | Intervention is not aimed at antidepressant reduction/discontinuation |
| ChiCTR-INR-16007984 | Evaluation of mindfulness-based cognitive therapy (MBCT) in the treatment of depression curative effect and relapse prevention function: A randomized controlled study. 2016 | Intervention is not aimed at antidepressant reduction/discontinuation |
| ACTRN12615001093572 | Timely intervention: Efficacy of a depression symptom monitoring smartphone app to deliver psychological intervention at time of greatest need. 2015 | Intervention is not aimed at antidepressant reduction/discontinuation |
| ACTRN12613001204730 | Opti-Med: A randomised controlled trial of deprescribing to optimise health outcomes for frail older people. 2013 | Intervention is deprescribing of variety of medications |
| ACTRN12611000370909 | Deprescribing in frail older people: a randomised controlled trial. 2011 | Intervention is deprescribing of variety of medications |
| ACTRN12608000613303 | Maintenance antidepressants versus treatment cessation in the prevention of depression recurrence. 2008 | Intervention is not aimed at antidepressant reduction/discontinuation |
| ACTRN12607000166471 | Effectiveness of Mindfulness-Based Cognitive Therapy Compared to Treatment-as-usual for Preventing Depressive Relapse in Subjects at Very High Risk. 2007 | Intervention is not aimed at antidepressant reduction/discontinuation |
| Intervention is not for antidepressant reduction/discontinuation | Intervention is not aimed at antidepressant reduction/discontinuation |
### TABLE 3: STUDY CHARACTERISTICS

**Depression (exclusion or non-reporting of anxiety co-morbidities)**

**RCTs**

| Study details | Inclusion/exclusion criteria | Participant characteristics |
|---------------|-----------------------------|-----------------------------|
| **Kahn 2014**<sup>1</sup> | Inclusion criteria: Male and female adult outpatients, 18 years or older, with a primary diagnosis of single or recurrent MDD without psychotic features based on the criteria from the DSM-IV, using the modified Mini International Neuropsychiatric Interview and depressive symptoms for at least 30 days before the screening visit and a 17-item Hamilton Rating Scale for Depression total score of 14 or greater at baseline. Patients who completed open label phase were then randomised to the 3 study arms (continuation of treatment, tapered discontinuation, abrupt discontinuation) | Age (years), mean (SD): INT: 47.9 (11.2); COMP 1: 47.8 (13.7); COMP 2: 46.7 (11.3) |
| Country: USA Setting: 38 clinical research centres Study design: Phase 4 study with 24 week open label phase (n=480) followed by randomised discontinuation phase (n=361) Funding: Pfizer Full publication: Yes (journal article) Linked publications: Ninan 2015<sup>2</sup>, NCT01056289<sup>3</sup> | Exclusion criteria: Patients were excluded if they had a current diagnosis of an anxiety disorder that was considered to be primary; current psychoactive substance abuse or dependence; unstable hepatic, renal, pulmonary, cardiovascular (including uncontrolled hypertension, unstable angina, or recent myocardial infarction); ophthalmologic or neurologic disorder; or other clinically important medical disease (including uncontrolled diabetes) | Female: INT: 74%; COMP 1: 68%; COMP 2: 67% Depression diagnosis: Major depressive disorder |

| Intervention details | Comparator 1 details | Comparator 2 details |
|----------------------|----------------------|----------------------|
| **Name of intervention:** Tapered discontinuation; N=140 | **Name of intervention:** Abrupt discontinuation; N=148 | **Name of intervention:** Antidepressant continuation; N=73 |
| Description: desvenlafaxine 25 mg per day for 1 week followed by placebo for 3 weeks. Treatment duration (randomised phase): 1 week taper + 3 weeks placebo. Delivery: not reported Provider: not reported | Description: placebo for 4 weeks Treatment duration: 4 weeks Delivery: not reported Provider: not reported | Description: continued desvenlafaxine 50 mg per day treatment for 4 weeks Treatment duration: not applicable Delivery: not reported Provider: not reported |
| Study details | Inclusion/exclusion criteria | Participant characteristics |
|--------------|-------------------------------|-----------------------------|
| Klein 2017   |                               | The data for the Klein paper were drawn from a multi-centre trial (n = 238) i.e. the Bockting trial, and an extension of this trial with additional experience sampling (n = 51). The patient characteristics reported in the Klein paper are for 289 patients (i.e. the Bockting trial + the extension). It is unclear from the Klein paper who the patients in the extension were. The characteristics for the 289 patients were therefore not extracted. |
| Country: Netherlands | **Inclusion criteria:** at least two previous depressive episodes in the past five years; currently in remission according to DSM-IV criteria for longer than 8 weeks and no longer than 2 years; have a current score of <10 in the 17 item Hamilton Rating Scale for Depression; have been remitted on antidepressant treatment; use AD at entry in the study (delivered in primary or secondary care) for at least 6 months | |
| Setting: Mental health care sites | **Exclusion criteria:** current mania or hypomania or a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, alcohol or drug dependency/abuse, predominant anxiety disorder | |
| Study design: Randomised controlled three-arm trial (only two arms (CT + taper versus m-ADM) were relevant as third arm was CT + mADM) | **Full publication:** No (protocol and secondary analysis published only. Study ended 06/2017 and there was no trial report at the time of the review searches) | |
| | **Linked publications:** Bockting 2011 (protocol), ISRCTN15472145 | |
| | **Funding:** Netherlands Organization for Health Research and Development (ZonMw), and Netherlands Organization for Scientific Research (NWO). | |
| | **Intervention details** | **Comparator details** |
| | **Name:** Cognitive therapy with tapering of antidepressant (CT + taper); N=85 | **Name:** continuation of maintenance antidepressant medication (m-ADM); N = not reported. **Antidepressant use:** 87.8% SSRI |
| | **Description:** CT: 8 weekly group sessions. Therapists of the sites will be trained with a CT manual to promote treatment integrity. Patients will be encouraged to do homework as prescribed. Taper: GP’s and psychiatrists will be advised to taper antidepressants in 4 weeks to prevent withdrawal symptoms. In this arm patients will be asked for an intention to taper antidepressants. The patient is allowed to start antidepressants again at any time during the study. | **Description:** GP's and psychiatrists will be advised to continue antidepressant prescription at minimal required adequate used dosage (≥ 20 mg Fluoxetine equivalent; as recommended by national guidelines). Patients will be encouraged to use medications prescribed and doctors/psychiatrists will be encouraged to prescribe therapeutic dosages, as well as discuss problems with adherence frequently. |
| | **Treatment duration:** CT: 8 weekly sessions Taper: 4 weeks | **Treatment duration:** not applicable |
| | **Delivery:** CT: group sessions, Taper: not reported | **Delivery:** not reported |
| | **Provider:** CT: A team of clinical psychologists from the University of Groningen, Rotterdam University and Maastricht University, and psychiatrists from the University of Amsterdam and the University of Groningen. Taper: guided by GPs and psychiatrists. | **Provider:** GP’s and psychiatrists |
**Study details**

| Huijbers 2016 | Inclusion/exclusion criteria | Participant characteristics |
|--------------|-------------------------------|-----------------------------|
| **Country:** Netherlands | **Inclusion criteria:** a history of at least three depressive episodes according to the DSM-IV; in full or partial remission, defined as not currently meeting the DSM-IV criteria for major depressive disorder; currently treated with antidepressants for at least 6 months; 18 years of age or older; and Dutch speaking | **Age (years), mean (SD):** INT: 50.7 (10.6) |
| **Setting:** 12 secondary and tertiary psychiatric out-patient clinics | **Exclusion criteria:** bipolar disorder; any primary psychotic disorder (current and previous); clinically relevant neurological/somatic illness; current alcohol or drug dependency; high dosage of benzodiazepines (42 mg lorazepam equivalents daily); recent electroconvulsive therapy (53 months ago); previous MBCT and/or extensive meditation experience (for example retreats); current psychological treatment with a frequency of more than once per 3 weeks; and inability to complete interviews and self-report questionnaires | **Female: INT: 72%** |
| **Study design:** Parallel two group non-inferiority RCT (only one arm (MBCT-TS) was relevant as second arm was MBCT+ maintenance antidepressant medication) | | **Depression diagnosis at intake: In full remission (IDS-C \( \leq 11 \)):** INT: 70 (55%); **In partial remission (IDS-C >11):** INT: 58 (45%) |
| **Funding:** The Netherlands Organization for Health Research and Development (ZonMW) | | **Antidepressant use: SSRIs:** INT: 92 (72%); TCAs: 26 (20%); **Other (SNRI, mirtazapine, MAOI):** 10 (8%) |
| **Full publication:** Yes (journal article) | | **Duration of antidepressant use: not reported** |
| **Linked publications:** Huijbers 2012, Huijbers 2016, NCT00928980 | | |

**Intervention details**

**Name of intervention:** Mindfulness based cognitive therapy followed by guided discontinuation of maintenance antidepressant medication (MBC-TS), N=128

**Description:** MBCT: MBCT largely based on the protocol by Segal, Williams & Teasdale with some adaptations. The intervention consisted of 8 weekly sessions of 2.5 hours (instead of 2 hours) and 1 day of silent practice between the sixth and seventh session. MBCT included formal meditation exercises, such as the body scan, sitting meditation, walking meditation and mindful movement as well as informal exercises, such as bringing present-moment awareness to everyday activities. Cognitive–behavioural techniques included education, monitoring and scheduling of activities, identification of negative automatic thoughts and devising a relapse prevention plan. Participants were encouraged to practice meditation at home for about an hour a day using CDs.

**Treatment duration:** MBCT: 8 consecutive weeks.

**TS:** Patients were asked and recommended to withdraw gradually from their antidepressants over a period of 5 weeks starting after the seventh session of MBCT. Adherence to the study protocol was defined as attending four or more MBCT sessions, as in previous studies, and having fully discontinued maintenance antidepressant medication before the 6-month follow-up assessment (i.e. within 6 months after baseline and within approximately 3–4 months after the last MBCT session)

**Delivery:** MBCT: Group (8-12 participants). Groups were mixed comprising patients from both treatment groups as well as patients not included in the trial.

**Provider:** MBCT: provided in 12 different centres with a total of 19 teachers and 111 MBCT courses. MBCT teachers were trained in the study protocol for MBCT during a 3-day training retreat in the beginning of the project, as well as at three subsequent training days every 6 months.

**TS:** supervised by psychiatrists.
| Study details | Inclusion/exclusion criteria | Participant characteristics |
|--------------|-----------------------------|-----------------------------|
| **Psaros 2014** | **Inclusion criteria:** aged 18 years or older; planning pregnancy or in the first trimester of pregnancy; independently decided to discontinue their antidepressant; were on treatment with a stable dosage of an antidepressant for at least 4 weeks at the time of the first visit; met stable depression remission criteria for at least 6 months and received a score of less than or equal to 9 on the Hamilton Rating Scale for Depression (HRSD); and had a history of a unipolar major depressive disorder. | **Age (years), mean (SD):** 34 (3.96) |
| **Country:** USA | **Exclusion criteria:** demonstrated significant risk for self-harm or harm to others; had psychotic symptoms; met criteria for a primary diagnosis of schizophrenia, bipolar disorder, active eating disorder, dementia, delirium, or other cognitive disorder according to the Mini-International Neuropsychiatric Interview (MINI); had an active substance and or alcohol abuse disorder within 6 months before study entry; were currently using a mood stabilizer, antipsychotic, or antiepileptic; received CBT or interpersonal therapy within the last year; or had recently been diagnosed with a medical disorder that could mimic depressive symptoms (eg, hypothyroidism). | **Female:** 100% (1 patient pregnant at baseline) |
| **Setting:** Massachusetts General Hospital Center for Women’s Mental Health in Boston or health care provider within the community | | **Depression diagnosis Major unipolar depression:** n=11; **Minor unipolar depression:** n=1 |
| **Study design:** Single arm trial | | **Antidepressant use:** Bupropion: n=3; Sertraline: n=5; Fluoxetine: n=2; Citalopram: n=2 |
| **Full publication:** Yes (journal article) | | **Duration of antidepressant use:** not reported |
| **Linked publications:** Psaros 2011 | | |
| **Funding:** not reported | | |

### Intervention details

**Name:** cognitive behavioural therapy for the prevention of recurrence plus taper (CBT + taper); N=12

**Description:** CBT: The CBT therapy used for this study followed the general principles of CBT with an emphasis on identifying and modifying maladaptive patterns of thinking and behaviour that may trigger or expose vulnerabilities for depression, particularly in the context of trying to conceive. For the acute treatment phase, visits included a baseline assessment, 12 sessions of CBT, and bimonthly independent assessments. The acute phase included 6 modules that focused on the following topics: presentation of the CBT model for depression, motivational interviewing, relaxation strategies, activity scheduling, cognitive restructuring, problem solving, and assertiveness. Participants could complete up to 3 optional monthly CBT booster sessions (with an additional 2 independent assessments) over the follow-up phase.

**Taper:** Drug taper schedules were determined at the baseline visit based on what was clinically appropriate for the medication and the preference of the participant. Typically, doses of medication were tapered at a rate of approximately 25% per week. The mean (SD) for the length of AD taper was 4.3 (2.53) weeks (range, 1–9 weeks).

**Treatment duration:** acute phase (16 weeks), booster phase (12 weeks)

**Delivery:** Face to face

**Provider:** CBT sessions were conducted by a PhD level psychologist specifically trained in CBT.

**Taper:** Drug taper schedules were determined at the baseline visit by participants in collaboration with staff physicians of the MGH Center for Women’s Mental Health;
### Observational studies

| Study details | Inclusion/exclusion criteria | Participant characteristics |
|---------------|-----------------------------|-----------------------------|
| **Himei 2006** | **Inclusion criteria**: had experienced a single episode of MDD diagnosed according to DSM-IV criteria; were given paroxetine as the only pharmacological treatment for their depression; had no comorbid substance dependence or abuse; and were no longer taking paroxetine for the treatment of depression. | **Age (years), mean (SD)**: OUTCOME 1: 40.5 (7.8); OUTCOME 2: mean 37.2 (8.0) (statistical difference between groups) |
| **Country**: Japan | **Exclusion criteria**: patients who were even moderately clinically depressed, anxious, or hypomanic at the time of medication discontinuation as well as those whose rate of discontinuation was uncertain (22.3% of potential antidepressant-treated candidates). | **Female**: OUTCOME 1: n=44%; OUTCOME 2: n=46% |
| **Setting**: The clinical records of patients treated during the previous 5 years in the outpatient units of the Shindrome Abuyama Clinic and Shin-Abuyama Hospital, Osaka. | **Depression**: MDD diagnosed according to DSM IV criteria | |
| **Study design**: Retrospective cohort | **Antidepressant use**: Paroxetine only. | |
| **Full publication**: Yes (journal article) | **Maintenance dose, mean (SD)**: OUTCOME 1: 25.9mg/day (9.9); OUTCOME 2: 26.6mg/day (10.2) | |
| **Linked publications**: None | **Duration of antidepressant use (months)**: OUTCOME 1: mean 9.2 SD 4.1; OUTCOME 2: mean 9.9 SD 4.2 | |
| **Funding**: None | | |

#### Outcome 1 details

**Name**: Non discontinuation syndrome; N=344 (abrupt (n=53) or gradual (n=291) withdrawal of paroxetine (10mg reduction every 2 weeks))

**Description**: clinical records were examined to determine whether patients had been diagnosed as having experienced the discontinuation syndrome on stopping paroxetine. If they had been, this diagnosis was reconfirmed according to the criteria for the SSRI discontinuation syndrome proposed by Black et al. These criteria are: (i) the symptoms of the discontinuation syndrome appear within 3 days following cessation/ reduction in the dosage of paroxetine; (ii) two or more of the following symptoms are present: dizziness, lightheadedness, headache, nausea, paresthesia, loss of balance, irritability, agitation and insomnia; (iii) the symptoms cannot be explained as a relapse of depression or as any other medical condition; and (iv) the symptoms cause significant distress or impairment in social, occupational and other important areas of functioning. The patients had been followed-up to the end of treatment and were assessed for relapse of depression 4 and 8 weeks after medication was stopped.

#### Outcome 2 details

**Name**: Discontinuation syndrome; N=41 (abrupt (n=27) or gradual (n=14) withdrawal of paroxetine (10mg reduction every 2 weeks))

**Description**: clinical records were examined to determine whether patients had been diagnosed as having experienced the discontinuation syndrome on stopping paroxetine. If they had been, this diagnosis was reconfirmed according to the criteria for the SSRI discontinuation syndrome proposed by Black et al. These criteria are: (i) the symptoms of the discontinuation syndrome appear within 3 days following cessation/ reduction in the dosage of paroxetine; (ii) two or more of the following symptoms are present: dizziness, lightheadedness, headache, nausea, paresthesia, loss of balance, irritability, agitation and insomnia; (iii) the symptoms cannot be explained as a relapse of depression or as any other medical condition; and (iv) the symptoms cause significant distress or impairment in social, occupational and other important areas of functioning. The patients had been followed-up to the end of treatment and were assessed for relapse of depression 4 and 8 weeks after medication was stopped.
### Depression and/or anxiety disorders

#### RCTs

| Study details | Inclusion/exclusion criteria | Participant characteristics |
|---------------|-----------------------------|------------------------------|
| **Eveleigh 2015**<sup>1</sup> | **Inclusion criteria:** Long-term antidepressant use (≥9 months). All antidepressants were included, except MAO-inhibitors; written informed consent. | **Age (years), mean (SD):** INT: 56 (12.9); COMP: 56 (14) |
| **Country:** Netherlands | | **Female:** INT: 71%; COMP: 68% |
| **Setting:** 45 general practices | **Exclusion criteria:** Current treatment in a psychiatric in- or outpatient clinic; appropriate use of long-term antidepressants according to the Dutch guidelines for depressive and anxiety disorders (i.e. a history of recurrent depression (≥3 episodes) and/or a recurrent psychiatric disorder with at least two relapses after antidepressant discontinuation); history of psychosis, bipolar disorder, or obsessive compulsive disorder; current diagnosis of substance use disorder (excluding tobacco); non-psychiatric indication for long-term antidepressant usage, e.g. neuropathic pain; hearing impairment and/or insufficient understanding of the Dutch language. | **Life time psychiatric diagnosis:** INT: n=53 (76%); COMP: n=48 (63%); **Depression:** INT: n=39 (57%); COMP: n=38 (46%); **Panic disorder /agoraphobia:** INT: 13 (19%); COMP: 13 (17%); **Generalized anxiety disorder:** INT: 22 (32%); COMP: 13 (17%); **Social phobia:** INT: 16 (23%); COMP: 20 (26%) |
| **Study design:** Two group cluster RCT | | **Antidepressant use:** SSRI: INT: n=57 (81.4%); COMP: n=50 (65.8%); SNRI: INT: n=7 (10%); COMP: n=11 (14.5%); Other (non TCA): INT: n=2 (2.9%); COMP: n=10 (13.2%); TCA: INT: n=4 (5.7%); COMP: n=5 (6.6%) |
| **Funding:** Netherlands Organization for Health Research and Development (ZonMw) | | **Duration of antidepressant use (years), median (range):** INT: 8.0 (1 to 48); COMP: 9.5 (1 to 56) |
| **Full publication:** Yes (PhD thesis) | | **Linked publications:** Muskens 2013<sup>28</sup>, Eveleigh 2014<sup>29</sup> |
| **Linked publications:** Muskens 2013<sup>28</sup>, Eveleigh 2014<sup>29</sup> | | |

#### Intervention details

| Name: Letter to GP disclosing patient does not meet the criteria for a depressive or anxiety disorder in the past six months combined with a (patient-tailored) treatment recommendation to discontinue; N = 22 practices (70 patients) |
| **Description:** The GP receives a letter stating that the patient does not meet the criteria for a depressive or anxiety disorder in the past six months. In addition, he or she receives an information sheet with current guidelines on antidepressant tapering and information about the discontinuation syndrome, including a detailed scheme for tapering for each patient. Duration of tapering was primarily based on the dosage and the half-life of the different antidepressants. No treatment restrictions are imposed on GP or patient in case of relapse or onset of a new psychiatric disorder after discontinuation. |
| **Treatment duration:** Patient consultation with GP to discuss recommendation was approximately 3 months from baseline |
| **Delivery:** Letter to GP + face to face discussion of recommendation between GP and patient |

#### Comparator details

| Name: Usual care; N = 23 practices (76 patients) |
| **Description:** GPs were unaware which patients participated in this study and continued usual care. The control condition will consisted of usual care and did not impose restrictions on GPs to deliver care or to refer to specialised mental health care, including the continuation or discontinuation of psychotropic drugs. |
| **Treatment duration:** not applicable |
| **Delivery:** Face to face |
| **Provider:** GP |

1. Eveleigh, J., Muskens, R., & de Jongh, A. (2015). Impact of informing general practitioners that patients do not meet the criteria for a depressive or anxiety disorder in the past six months: A randomized controlled trial. *International journal of geriatric psychiatry*, 30(6), 678-684.
2. Muskens, R., Eveleigh, J., & de Jongh, A. (2013). Impact of informing general practitioners that patients do not meet the criteria for a depressive or anxiety disorder in the past six months: A randomized controlled trial. *International journal of geriatric psychiatry*, 28(12), 1314-1320.
3. Eveleigh, J., Muskens, R., & de Jongh, A. (2014). Impact of informing general practitioners that patients do not meet the criteria for a depressive or anxiety disorder in the past six months: A randomized controlled trial. *International journal of geriatric psychiatry*, 29(12), 1314-1320.
| Study details | Inclusion/exclusion criteria | Participant characteristics |
|---------------|------------------------------|-----------------------------|
| **Fava 1994**<sup>1</sup> | **Inclusion criteria**: A current diagnosis of primary major depressive disorder according to the Research Diagnostic Criteria (RDC); successful response to 3 to 5 month’s full antidepressant treatment administered by the same psychiatrist according to standardized protocol. After drug treatment, rated as “better” or “much better” according to Kellner’s global rating scale of improvement, in full remission and in stage 3 of primary unipolar depression. | **Age (years), mean (SD)**: INT: 43 (2.3); COMP: 48.5 (3.3) |
| **Country**: Italy | **Exclusion criteria**: history of manic, hypomanic, or cyclothymic features; history of active drug or alcohol abuse or dependence; history of personality disorder according to DSM-III-R criteria; history of antecedent dysthymia, active medical illness; no evidence of depressed mood after treatment, absence of residual symptoms. | **Female**: INT: 60%; COMP: 75% |
| **Setting**: Outpatients referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine in Italy. | | **Depression - residual symptoms after successful treatment**: All patients reported residual symptoms, with a mean of 2.7 (1.2) per patient. The most frequently reported symptoms were: generalized anxiety (73% of patients), somatic anxiety (55%), and irritability (40%). |
| **Study design**: Parallel two group RCT | | **Antidepressant use**: Amitriptyline: INT: n=7 (35%); COMP: n=12 (60%); Desipramine: INT: n=6 (30%); COMP: n=2 (10%); Imipramine: INT: n=5 (25%); COMP: n=4 (20%); Mianserin: INT: n=2 (10%); COMP: n=2 (10%); | |
| **Funding**: Partially supported by Ministero Universita e Ricerca Scientifica e Tecnologica; Consiglio Nazionale delle Ricerche; and Mental Health Project, Istituto Superiore di Sanità, Rome | | **Duration of antidepressant use (months)**: 3 to 5 |
| **Full publication**: Yes (journal article) | | |
| **Linked publications**: Fava 1996, Fava 1998<sup>2</sup> | | |

**Intervention details**

| Comparator details |
|--------------------|
| **Name**: Cognitive behavioural therapy + tapering (CBT + taper); N=21 (tapering was not feasible for n=1, and they were excluded from further participation in the study, but included in analysis) |
| **Description**: Treatment consisted of 10 40-minute sessions once every other week. Antidepressant drugs were tapered at the rate of 25 mg of amitriptyline or its equivalent every other week, and then they were withdrawn completely. Cognitive therapy was conducted as described by Beck, and included strategies and techniques designed to help depressed patients correct their distorted views and maladaptive beliefs. Whenever appropriate, as in the case of residual symptoms related to anxiety, exposure strategies were planned with the patient. Patients already on benzodiazepines were allowed to continue to do so. |
| **Treatment duration**: 20 weeks (10 sessions, 1 every other week) |
| **Delivery**: Face to face |
| **Provider**: 1 psychiatrist, with extensive experience in affective disorders and cognitive behavioural psychotherapy, who had initially treated the patients. The psychiatrist performed treatment in both groups. |

| Comparator details |
|--------------------|
| **Name**: Clinical management + tapering (CM +; N=22 (tapering was not feasible for n=2, and they were excluded from further participation in the study, but included in analysis) |
| **Description**: Treatment consisted of 10 40-minute sessions once every other week. Antidepressant drugs were tapered at the rate of 25 mg of amitriptyline or its equivalent every other week, and then they were withdrawn completely. Clinical management consisted of monitoring medication tapering, reviewing the patient’s clinical status, and providing the patient with support and advice if necessary. Interventions such as exposure strategies, diary work and cognitive restructuring were proscribed. Patients already on benzodiazepines were allowed to continue to do so. |
| **Treatment duration**: 20 weeks (10 sessions, 1 every other week) |
| **Delivery**: Face to face |
| **Provider**: 1 psychiatrist, with extensive experience in affective disorders and cognitive behavioural psychotherapy, who had initially treated the patients. The psychiatrist performed treatment in both groups. |
### Study Details

| Study Details | Inclusion/Exclusion Criteria | Participant Characteristics |
|---------------|-----------------------------|-----------------------------|
| **Country:** Italy | **Inclusion criteria:** A current diagnosis of major depressive disorder according to the RDC for a Selected Group of Functional Disorders; 3 or more episodes of depression, with the immediately preceding episode being no more than 2 1/2 years before the onset of the present episode; a minimum 10-week remission according to RDC (≤2 symptoms present to no more than a mild degree with absence of functional impairment) between the index episode and the immediately preceding episode; a minimum global severity score of 7 for the current episode of depression; and successful response to antidepressant drugs administered by 2 psychiatrists according to a standardized protocol (use of TCAs, with gradual increases in dosages. Patients who could not tolerate TCAs were switched to SSRIs). **Exclusion criteria:** a history of manic, hypomanic, or cyclothymic features (i.e. bipolar depression); a history of active drug or alcohol abuse or dependence or of personality disorder according to DSM-IV criteria; a history of antecedent dysthymia; or active medical illness | **Age (years), mean (SD):** INT: 45.1 (10.3); COMP: 48.7 (12.1) |
| **Setting:** Outpatients referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine in Italy. | | **Female:** INT: 55%; COMP: 65% |
| **Study design:** Parallel two group RCT | | **Depression – Pre-intervention scores for the Clinical Interview for Depression (CID), mean (SD):** INT 30.8, SD (3.3); COMP 29.7 (3.9) |
| **Funding:** Partially supported by the "Mental Health Project," Istituto Superiore di Sanita and the "Ministero dell Universita e della Ricerca Scientifica e Tecnologica" | | **Comorbidities: Generalized anxiety disorder:** INT: n=6 (30%); COMP: n=4 (20%); Agoraphobia: INT: n=3 (15%); COMP: n=3 (15%); Social phobia: INT: n=0 (0%), COMP: n=1 (5%) |
| **Full publication:** Yes (Journal article) | | **Antidepressant use:** Amitriptyline: INT: n=7 (35%); COMP: n=7 (35%); Imipramine: INT: n= 5 (25%); COMP: n=5 (25%); Desipramine: INT: n=5 (25%); COMP: n=6 (30%); Fluoxetine: INT: n=2 (10%); COMP: n=2 (10%); Sertraline: INT: n=1 (5%); COMP: n=0 (0%) |
| **Linked publications:** Fava 2004 | | **Duration of antidepressant use (months):** 3 to 5 |

### Intervention Details

**Name:** Cognitive behavioural therapy + tapering (CBT + taper); **N=23** (tapering was not feasible for n=3 and they were excluded from further participation in the study, but included in analysis)

**Description:** 10 30-minute sessions once every other week. Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline hydrochloride or its equivalent every other week, and then the drugs were withdrawn completely (in the last 2 sessions, all patients were drug free). Cognitive behavioural treatment consisted of the following 3 main ingredients: (1) CBT of residual symptoms of major depression. Cognitive therapy was conducted as described by Beck et al., (2) Lifestyle modification. Patients were instructed that depression is merely the consequence of a maladaptive lifestyle, which does not take life stress, interpersonal friction, excessive work, and inadequate rest into proper account The strategies used technically derived from lifestyle modification approaches that were effective in clinical cardiological studies. (3) Well-being therapy. In the last 2 or 3 sessions, a psychotherapeutic strategy for enhancing well-being was used based on Ryff and Singer’s conceptual model of well-being as the result of self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth. A few patients were taking benzodiazepines at low doses and continued to do so throughout the study.

**Treatment duration:** 20 weeks (10 sessions, 1 every other week)

**Delivery:** Face to Face

**Provider:** 1 psychiatrist, who performed all treatments in both groups.

### Comparator Details

**Name:** Clinical management + tapering (CM + taper); **N=22** (tapering was not feasible for n=2, and they were excluded from further participation in the study, but included in analysis)

**Description:** 10 30-minute sessions once every other week. Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline hydrochloride or its equivalent every other week, and then the drugs were withdrawn completely (in the last 2 sessions, all patients were drug free). Clinical management consisted of monitoring medication tapering, reviewing the patient’s clinical status, and providing the patient with support and advice if necessary. Specific interventions such as exposure strategies, diary work, and cognitive restructuring were prescribed. The patient was encouraged to share the main events that took place in the previous 2 weeks. A few patients were taking benzodiazepines at low doses and continued to do so throughout the study.

**Treatment duration:** 20 weeks (10 sessions, 1 every other week)

**Delivery:** Face to Face

**Provider:** 1 psychiatrist, who performed all treatments in both groups.
| Study details | Inclusion/exclusion criteria | Participant characteristics |
|--------------|-----------------------------|----------------------------|
| **Kuyken 2008**<sup>16</sup> | **Inclusion criteria:** Patients aged 18 years or older; history of three or more previous episodes of depression meeting DSM IV criteria for depression, treated with therapeutic dose of antidepressants over the last 6 months and currently in full or partial remission.  
**Exclusion criteria:** Comorbid diagnoses of current substance dependence; organic brain damage; current/past psychosis; bipolar disorder; persistent antisocial behaviour; persistent self-injury requiring clinical management/therapy; unable to engage with MBCT for physical, practical, or other reasons (e.g., very disabling physical problem, unable to comprehend materials); and formal concurrent psychotherapy | Age (years), mean (SD): INT: 48.95 (10.55); COMP: 49.37 (11.84)  
Female: INT: 77%; COMP: 76%  
Depression diagnosis at intake: In full remission: INT: 69%; COMP: 66%; In partial remission: INT: 31%; COMP: 34%  
Number of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD): INT: 0.83 (0.96); COMP: 1.04 (1.11)  
Antidepressant use: SSRIs: 58%; TCAs: 22%; Combination: 20%  
Duration of antidepressant use (months): ≥ 6 |
| **Country:** UK | | |
| **Setting:** Primary care settings across a range of urban and rural locations in Devon. Patients were identified from computerised practice databases | | |
| **Study design:** Parallel two group RCT, stratified by symptomatic status (HRSD ≥ 8) | | |
| **Funding:** UK Medical Research Council | | |
| **Full publication:** Yes (journal article) | | |
| **Linked publications:** ISRCTN12720810 2006<sup>16</sup> | | |

| Intervention details | Comparator details |
|----------------------|-------------------|
| **Name:** Mindfulness based cognitive therapy + support to taper/discontinue antidepressants (MBCT-TS); N=61  
**Description:** MBCT: 2 hour sessions per week. Sessions content followed treatment protocol (Segal, Williams, & Teasdale, 2002) and included guided mindfulness practices (i.e., body scan, sitting meditation, yoga); inquiry into patients’ experience of these practices; review of weekly homework (i.e., 40 minutes of mindfulness practice per day and generalization of session learning); and teaching/discussion of cognitive—behavioural skills. An adequate dose of MBCT was defined as participation in at least four of the eight MBCT group sessions.  
TS: Study team provided guideline information to physicians and patients about typical tapering/discontinuation regimes and possible withdrawal effects. Patients and physicians prompted to begin discussing a tapering/discontinuation regime after 4–5 weeks of the MBCT groups. At the end of the MBCT groups, they were reminded to ensure a tapering/discontinuation regime was in place.  
Treatment duration: MBCT: 8 consecutive weeks, followed by four follow-up sessions in the following year.  
TS: The research team asked that patients consider tapering/discontinuing their medication as soon following MBCT as they deemed appropriate and within 6 months of the MBCT group ending.  
**Delivery:** Primary care settings with MBCT groups of 9–15 patients  
**Provider:** MBCT: clinical psychologist or occupational therapist. Both therapists had undergone a training program taught by one of the developers of MBCT, had experience of running at least two supervised pilot groups, and had an ongoing personal mindfulness practice.  
TS: Tapering/discontinuation regimes determined by physicians and patients. | **Name:** Maintenance antidepressant medication (m-ADM); N=62  
**Description:** maintenance of the antidepressant medication treatment that was an inclusion criterion for the study. During the maintenance phase, physicians were asked to manage m-ADM in line with standard clinical practice and the British National Formulary. Protocol adherence was defined as continuing to take m-ADM at a therapeutic maintenance dose for the duration of the trial. Changes in medication sometimes occurred during the maintenance treatment stage, but physicians and patients were asked to ensure the dose remained within therapeutic limits.  
Treatment duration: duration of trial (15 months)  
**Delivery:** GPs were asked to meet with patients regularly to review their medication treatment.  
**Provider:** GP |
### Study details

| Name       | Comparator details |
|------------|--------------------|
| Kuyken 2015 | **Inclusion criteria:** Patients aged 18 years or older, with a diagnosis of recurrent major depressive disorder in full or partial remission according to the DSM-IV, a history of three or more previous major depressive episodes in which depression was the primary disorder and it was not secondary to substance abuse, bereavement or a general medical condition, were on a therapeutic dose of ADM, and were open either to continue taking antidepressants for 2 years or to take part in a MBCT class and consider stopping their ADM. | **Participant characteristics** |
| Country: UK | Age (years), mean (SD): INT: 50 (12); COMP: 49 (13) |
| Setting: General practices in urban and rural settings in Bristol, Exeter and East, North, and South Devon | Female: INT: 71%; COMP: 82% |
| Study design: Parallel two group RCT, stratified by locality and symptomatic status (GRID HAMD ≥ 8) | Depression diagnosis at intake: |
| Funding: National Institute for Health Research | Asymptomatic: INT: 77%; COMP: 76% |
| Full publication: Yes (HTA report) | Symptomatic: INT: 23%; COMP: 24% |
| Linked publications: Anonymous 2016, ISRCTN26666654, Kuyken 2010, Kuyken 2014, Kuyken 2015 | No. of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD): INT: 0.5 (0.9); COMP: 0.7 (0.9) |

### Intervention details

**Name:** Mindfulness based cognitive therapy + support to taper/discontinue antidepressants (MBCT-TS); N=212

**Description:** MBCT: 2.25 hour sessions per week. Session content included guided mindfulness practices (i.e. body scan, sitting meditation, movement); inquiry into participants’ experience of these practices; weekly review of home practice (i.e. 40 minutes of mindfulness practice per day with the guidance of a CD, bringing mindfulness into everyday life); and teaching of dialogue around cognitive–behavioural skills. The original MBCT manual was adapted to include more work on developing a relapse/recurrence signature and response plan that explicitly included participants considering reduction/discontinuation of m-ADM. There were an additional four group reunion sessions during the first year of follow-up to provide ongoing support and reinforce the key components of the interventions. An adequate dose of MBCT was defined as participation in at least four of the eight MBCT group sessions.

**TS:** Letters signed by the chief investigator and trial GP were sent to each participant’s GP, copied to the participant, prompting the GP to have a discussion with the participant about a suitable tapering/discontinuation regime after 4–5 weeks of the MBCT-TS group. At the end of the MBCT-TS group another letter was sent reminding the GP to ensure that a tapering/discontinuation regime was in place. Study team wrote to participant and their GP after each follow-up reminding them that the trial was seeking to compare staying on antidepressants with taking part in mindfulness classes and stopping ADM. Participants who experienced a significant deterioration following tapering were encouraged to use the skills developed as part of the MBCT treatment. Actual timeline and regime used to taper were determined by physicians and participants Use of pain killers and sleeping tablets was allowed (% usage was the same in both study arms).

**Treatment duration:** 8 consecutive weeks, followed by four follow-up sessions in the following year.

**Delivery:** one-to-one orientation session with the therapist followed by group sessions.

**Provider:** 4 MBCT therapists (2 clinical psychologists, 2 occupational therapists) with post-qualification experience averaging 19 years, extensive training and experience in leading MBCT groups (min. 4 years). TS: GPs

**Comparator details**

**Name:** Maintenance antidepressant medication (m-ADM); N=212

**Description:** During the maintenance phase, physicians were asked to manage m-ADM in line with standard clinical practice and the British National Formulary (BNF). Trial GPs and psychiatrist provided materials for all participants and participating GPs on m-ADM and ongoing support as required. Participants were encouraged to adhere to medication for the full length of the trial by sending them letters signed by the chief investigator and their GP after each follow-up, reminding them that the trial was seeking to compare staying on antidepressants for 2 years with taking part in mindfulness classes and stopping ADM. Changes in medication sometimes occurred during the maintenance treatment stage but physicians and participants were asked to ensure that the dose remained within therapeutic limits. Use of pain killers and sleeping tablets was allowed (% usage was the same in both study arms).

**Treatment duration:** 24 months

**Delivery:** GPs were asked to meet with patients regularly to review their medication treatment.

**Provider:** GPs
### Study details

| Study details | Inclusion/exclusion criteria | Participant characteristics |
|---------------|-----------------------------|-----------------------------|
| **Johnson 2012** | *Inclusion criteria:* Patients prescribed the same antidepressant for ≥2 years were identified by community health and care partnerships (CHCPs) support staff using a data extraction tool specifically designed, developed and piloted to identify this patient group from individual General Practice Administration System Scotland systems. This tool identified patients prescribed an antidepressant within the previous 3 months and patients prescribed the same antidepressant for 2 years or more. This duration was chosen as current guidelines recommend up to 2 years antidepressant treatment for those at risk of relapse. Amitriptyline was excluded from the search due to its non-mental health uses. Duloxetine was included as an earlier audit of the data found that prescriptions for managing conditions other than depression were sparse. Exclusion criteria: Patients were excluded if aged <18 years, under regular psychiatric care, had a GP face-to-face antidepressant review within the preceding 6 months, or were on the severe mental illness register (practices review this group as part of the Quality Outcomes Framework [QOF]). | **Age (years), mean (SD):** 54.4 (13.4) |
| **Country:** Scotland | | **Female** (Demographic data were available for 94.4% (2691/2849) patients reviewed): 1975/2691 |
| **Setting:** 4 CHCPs containing urban general practices in most deprived areas | | **Indication for antidepressant use (1929/284 (67.7%) had antidepressant indication recorded):** Depression: 65.0%, Mixed anxiety depression: 22%; Anxiety disorder: 10%; Other mental health 1, General medical: 1.5%. |
| **Study design:** Single arm intervention | | **Antidepressant use:** Fluoxetine: 26.8%, Citalopram: 25.8%, Paroxetine: 8.7%, Venlafaxine: 7.3%, Trazodone: 6.7%, Sertraline: 6.2%; Mirtazapine: 6.1%, Dosulepin: 5.0%; Escitalopram: 2.4%; Lofepramine: 2.1%; Duloxetine:1.1%; Other: 1.7% |
| **Funding:** HCP Local Enhanced Service and NHS GG&C Mental Health Collaborative monies. | | **Duration of antidepressant use (years):** mean 5.5, SD 3.0, range 2.0 to 24.8 |
| **Full publication:** Yes (journal article) | | |
| **Linked publications:** None | | |

### Intervention details

**Name of intervention:** GP face to face review with patient of clinical condition and medication; N=2849

**Description:** Practices were asked to review and submit forms for a proportion of all registered patients (equivalent to 30 per 4000 patients). Other than exclusion criteria, GPs were not provided with guidance or a sampling framework from which to select patients, therefore GPs were allowed to prioritise patients for review, permitting flexibility to pragmatically select patients they felt may benefit most, at the expense of introducing selection bias into the study. At review GPs completed a standardised review form recording: date of review, CHCP, practice, name of antidepressant(s), daily dose, changes in antidepressant therapy and any onward referral. Subsequent amendments were made to capture patients’ age, sex, GP-defined indication, and duration of current antidepressant for CHCP-2 to 4.

**Treatment duration:** All practices in the four CHCPs reviewed patients once and CHCP-1 followed-up with a second review within 3 months of the first.

**Delivery:** Face to face

**Provider:** GP
## Observational studies

### Study details

**Baldessarini 2010**

**Country:** Italy  
**Setting:** the Lucio Bini Mood Disorders Center affiliated with the University of Cagliari in Sardinia  
**Study design:** Retrospective cohort  
**Full publication:** Yes (journal article)  
**Linked publications:** No  
**Funding:** Supported in part by the NIH; the Lucio Bini Private Donors Mood Disorders Research Fund; the Bruce J. Anderson Foundation and the McLean Private Donors Psychopharmacology Research Fund.

### Inclusion/exclusion criteria

**Inclusion criteria:** consecutive patients who met the following criteria: diagnosed clinically with DSM-based recurrent major depressive disorder, bipolar I or II disorder, or panic disorder; received a tricyclic antidepressant (or the tricyclic-like tetracyclics maprotiline and mianserin), a modern antidepressant (serotonin reuptake inhibitors or bupropion, duloxetine, or venlafaxine), or more than one antidepressant, with or without a mood stabilizer, following standard clinical practices regarding drug selection and dosing in the study community; recovered from an antidepressant-treated index episode of a major depression or panic disorder, based on clinical euthymia and a score ≤7 on the Hamilton Depression Rating Scale sustained for at least 30 days (including patients with panic disorder evaluated with the same rating scale for consistency); discontinued medication electively for clinical or personal reasons over a known period of time, allowing categorization into groups based on rapid (1–7 days) or gradual (≥2 weeks) discontinuation; remained clinically stable or euthymic for at least 1 week after discontinuing treatment; and remained under prospective observation for at least 1 year, during initial treatment and through a first new episode of major depression or panic disorder that met DSM-IV diagnostic criteria at clinical assessment. Follow-up was censored at 100 months.

**Exclusion criteria:** patients who were even moderately clinically depressed, anxious, or hypomanic at the time of medication discontinuation as well as those whose rate of discontinuation was uncertain (22.3% of potential antidepressant-treated candidates).

### Participant characteristics

**Age (years), mean (SD):** EXP 1: 44.1 (15.4); EXP 2: 39.5, (14.5)  
(Note: Data not reported by diagnosis i.e. data for MDD, panic disorder, BP I and BP II patients were combined)

**Female:** EXP 1: 69%; EXP 2: 61.7% (Note: Data not reported by diagnosis i.e. data for MDD, panic disorder, BP I and BP II patients were combined)

**Psychiatric diagnosis:** Recurrent major depressive disorder  
EXP 1: n=118 (56.2%); EXP 2: 106 (56.4%); Panic disorder: EXP 1: n=38 (18.1%); EXP 2: 37 (19.7%); Bipolar II disorder: EXP 1: 33 (15.7%); EXP 2: 29 (15.4%); Bipolar I disorder: EXP 1: 21 (10.0%); EXP 2: 16 (8.5%)

**Antidepressant use:** TCA and tetracyclics (amprotiline and mianserin): n=249 (62.6%), Modern antidepressants (SSRIs, bupropion, duloxetine or venlafaxine): n=149 (37.4%), Mood stabilisers: n=125 (31.5%), Sedatives: n= 255 (64.1%) (Note: Data not reported by diagnosis i.e. data for MDD, panic disorder, BP I and BP II patients were combined)

**Duration of antidepressant use:** not reported

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### Exposure 1

**Name:** Gradual discontinuation; N=210  
**Description:** Discontinuation ≥ 2 weeks (none of the patients tapered off in the 8 to 14 day range)  
**Treatment duration:** not reported  
**Delivery:** not reported  
**Provider:** Decisions to discontinue treatment were clinical, not experimental; they were decided by the patient in 80.7% of cases and at the advice of the prescribing physician in 19.3% of cases. Gradual discontinuation was slightly more prevalent than rapid (53% compared with 47% of cases). Among study patients, adjunctive psychotropic medications were continued unchanged after discontinuation of antidepressants.

### Exposure 2

**Name:** Rapid discontinuation ; N=188  
**Description:** discontinuation over 1-7 days  
**Treatment duration:** not reported  
**Delivery:** not reported  
**Provider:** Decisions to discontinue treatment were clinical, not experimental; they were decided by the patient in 80.7% of cases and at the advice of the prescribing physician in 19.3% of cases. Stopping abruptly or rapidly was almost always the patient’s decision (94.1% of discontinuations) Among study patients, adjunctive psychotropic medications were continued unchanged after discontinuation of antidepressants.
### Ongoing studies

| Study details | Inclusion/exclusion criteria |
|---------------|-------------------------------|
| **Molenaar 2016** | Inclusion criteria: Women who are less than 16 weeks pregnant and use a SSRI primarily for depressive disorder, and are currently at least in remission or recovered, |
| Country: Netherlands | Exclusion criteria: multiple pregnancy, as these women have a markedly increased obstetric risk, thereby threatening the homogeneity of the study population and thus potentially complicate the statistical analysis; insufficient proficiency in Dutch or English, since intervention is not yet available in other languages; severe medical conditions, such as oncology-related conditions or conditions that need urgent medical interventions, which involve treatment decisions overriding research participation; current mania or hypomania or a history of bipolar illness, suicidality and serious self-harm, any psychotic disorder (current and previous), current alcohol or drug misuse, predominant anxiety disorders and personality disorders that require psychotherapeutic treatment for more than 2 sessions a month. |
| Setting: Not reported | |
| Study design: Pragmatic multi-centre randomized controlled non-inferiority trial | |
| Full publication: Protocol is published as a journal article | |
| Linked publications: Lambregtse-Van Den Berg 2015 | |
| Funding: Netherlands Organization for Health Research and Development and Erasmus Medical Centre, Department of Psychiatry, | |

### Intervention details

**Name:** Guided tapering of SSRI according to protocol with preventive cognitive therapy (STOP)

**Description:** Taper: Women will be referred to a psychiatrist trained in guiding tapering of SSRIs during pregnancy. They will plan and carry out SSRI discontinuation using an expert-based discontinuation protocol. The aim is to taper the use of SSRIs within four weeks, depending on patient preferences and on drug characteristics (e.g., half-life in the body).

Preventive cognitive therapy: Trained psychologists will provide preventive cognitive therapy. This psychological intervention has proven to be effective in relapse prevention and the current manual was evaluated in previous studies. The preventive psychological intervention consists of a minimum of eight weekly VSee sessions. These sessions are led by professional psychologists trained in cognitive behavioural therapy and may occur at any time of the day. The focus of the sessions is on identifying and teaching the participants to challenge dysfunctional beliefs, enhance recall of positive feelings and cognitions and a personal prevention plan is developed in which it is specified how the participant can prevent a depressive episode in the future. For each session the participant will receive some assignments of approximately 10 min per day. There are no restrictions on the use of medication like sleeping pills, paracetamol, and mild tranquillizers.

**Treatment duration:** Taper: aim is to taper the use of SSRIs within four weeks, depending on patient preferences and on drug characteristics (e.g., half-life in the body).

CT: The preventive psychological intervention consists of a minimum of eight weekly VSee sessions

**Delivery:** CT: The intervention will be applied through VSee (http://www.vsee.com), a HIPAA-compliant telehealth app

**Provider:** Taper: psychiatrist trained in guiding tapering of SSRIs during pregnancy

CT: Sessions are led by professional psychologists trained in cognitive behavioural therapy

### Comparator details

**Name:** Continuation of SSRIs - usual care (GO)

**Description:** Women instructed to consult their doctor as they regularly do, in line with the pragmatic nature of the study. All the care that is provided will be monitored.

**Treatment duration:** Not reported

**Delivery:** usual care

**Provider:** usual care
Inclusion criteria: Age 18-75 years; currently taking an FDA-approved antidepressant for at least four weeks on the list of approved medications: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone or vortioxetine), SNRIs (desvenlafaxine, duloxetine, levomilnacipran, venlafaxine) and other classes (amitriptyline, bupropion, desipramine, doxepin, mirtazapine, nefazodone, nortriptyline, phenelzine, selegiline, or tranylcypromine). Clomipramine, a tricyclic antidepressant approved for the treatment of OCD, will also be included, but will be classed as an SSRI for this study because inhibition of the serotonin transporter is its primary therapeutic mechanism; no longer wishes to take the antidepressant medication they are currently prescribed, due to one of the following reasons: 1) ineffective for symptoms; 2) intolerable side effect; 3) improvement of their illness for sufficient duration that it is clinically appropriate to taper the medication; primary psychiatric diagnosis of major depressive disorder, an anxiety disorder, OCD, or PTSD and; ability to read and understand English language.

Exclusion criteria: Has met criteria at any time during their life for a primary psychotic disorder (e.g. schizophrenia), or dementia; meets criteria for DSM-5-defined substance use disorder within three months of the screening visit; currently taking two or more antidepressants; presents with a clinically significant suicide risk, as assessed by a study physician; presence of any unstable or central nervous system-related medical illness that would interfere with cognition or participation; women who are currently pregnant or lactating, or plan to become pregnant during the study.

Intervention details

Name: Two-Week Antidepressant Taper Regimen

Description: Two-Week Taper Regimen to discontinue medication. Days 1-7: 50% of baseline antidepressant dose taken; Days 8-14: 25% of baseline antidepressant dose taken; Day 15: Stop antidepressant.

Treatment duration: 2 weeks

Delivery: not reported

Provider: not reported

Comparator details

Name: One-Week Antidepressant Taper Regimen

Description: One-Week Taper Regimen to discontinue medication. Days 1-3: 50% of baseline antidepressant dose taken; Days 4-7: 25% of baseline antidepressant dose taken; Day 8: Stop antidepressant.

Treatment duration: 1 week

Delivery: not reported

Provider: not reported

Abbreviations: COMP comparator; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition; EXP exposure; INT intervention; MDD major depressive disorder; SD standard deviation
|                | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Binding of participants and personnel (performance bias) | Binding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|----------------|---------------------------------------------|------------------------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------------------|----------------------------------------|
| Eveleigh 2015  | ?                                           | ?                                       | ✅                                                       | ✅                                          | ✅                                       | ✅                                      |
| Fava 1994      | ?                                           | ✅                                       | ✅                                                       | ✅                                          | ✅                                       | ✅                                      |
| Fava 1993      | ?                                           | ✅                                       | ✅                                                       | ✅                                          | ✅                                       | ✅                                      |
| Khan 2014      | ?                                           | ✅                                       | ?                                                       | ✅                                          | ✅                                       | ✅                                      |
| Klein 2017     | ?                                           | ✅                                       | ✅                                                       | ✅                                          | ✅                                       | ✅                                      |
| Kuyken 2008    | ✅                                           | ✅                                       | ✅                                                       | ✅                                          | ✅                                       | ✅                                      |
| Kuyken 2015    | ✅                                           | ✅                                       | ✅                                                       | ✅                                          | ✅                                       | ✅                                      |

Selective outcome reporting was not assessed for Klein et al., 2017 as this paper was reporting a secondary analysis.
| 1. Was the research question or objective in this paper clearly stated? | Baldessarini 2010 | Himei 2006 | Johnson 2012 | Huijbers 2016 | Psaros 2014 |
|-------------------------------------------------|----------------|------------|--------------|--------------|-------------|
| Yes - p.934,935                                 | Yes - p.665,666 | Yes - p.773 | Yes - p.366 | Yes - p.3    |

| 2. Was the study population clearly specified and defined? | Baldessarini 2010 | Himei 2006 | Johnson 2012 | Huijbers 2016 | Psaros 2014 |
|-------------------------------------------------|----------------|------------|--------------|--------------|-------------|
| Yes - p.935                                     | Yes - p.666    | Yes - p.773-774 | Yes - p.367 | Yes - p.3    |

| 3. Was the participation rate of eligible persons at least 50%? | Baldessarini 2010 | Himei 2006 | Johnson 2012 | Huijbers 2016 | Psaros 2014 |
|-------------------------------------------------|----------------|------------|--------------|--------------|-------------|
| Not applicable - retrospective study            | Not applicable - retrospective study | Can't determine - out of 96 practices 71 agreed to participate (p.775), however of those patients prescribed long-term antidepressants only 2849 out of 15689 were reviewed and had forms submitted by their GP (p.775). | Not applicable - study was two armed RCT of which one arm was relevant for review. Participation rate of eligible participants in whole RCT was 49% (p.369). | Yes - In total, 15 women were screened from July 2009 to June 2011, and 12 participants were enrolled. Three of the screened participants were ineligible for the study because of failure to establish Major Depressive Disorder (MDD) as the primary Axis I diagnosis (p.5). |

| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Baldessarini 2010 | Himei 2006 | Johnson 2012 | Huijbers 2016 | Psaros 2014 |
|-------------------------------------------------|----------------|------------|--------------|--------------|-------------|
| Can't determine - all patients included in the study had responded well to antidepressant treatment and were evaluated, treated, and followed at the Lucio Bini Mood Disorders Center affiliated with the University of Cagliari in Sardinia (p.935). Unclear over what period of time the patients were selected from. | Yes - patients were treated during the previous five years and were treated in the outpatient clinic of one of two clinics. Unclear if there are important differences between the 2 clinics. However, inclusion criteria were detailed and would mean population was homogenous on important issues such as drug (paroxetine only), and that they had experienced a single episode of MDD (p.666). | Yes - practices came from four of the community health and care partnerships (CHCPs) serving a highly urbanised population within the most deprived areas of Scotland with a high burden of disease and chronic conditions. These four CHCPs were interested in reviewing antidepressant prescribing and were high volume prescribers by defined daily doses (DDDs) per capita from the Prescribing and Information System for Scotland (PRISMS) (p.773-774). | Not applicable - study was two armed RCT of which one arm was relevant for review. Patients were recruited in 12 secondary and tertiary psychiatric out-patient clinics across The Netherlands between September 2009 and January 2012. There were detailed inclusion and exclusion criteria (p.367). | Yes - women were recruited from Massachusetts General Hospital (MGH) Center for Women’s Mental Health in Boston, MA, or via a referral from another health care provider within the community, so there might be differences between these populations (p.3). However, there were detailed inclusion and exclusion criteria (p.3). |
| Study                  | 5. Was a sample size justification, power description, or variance and effect estimates provided? | 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? |
|-----------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Baldessarini 2010      | Not reported                                                                                     | Yes                                                                                                       |
| Himei 2006            | Not reported                                                                                     | Yes                                                                                                       |
| Johnson 2012          | Yes - p.774                                                                                        | Not applicable (review and action taken with antidepressant took place at the same time)                   |
| Huijbers 2016         | Not applicable - study was two armed RCT of which one arm was relevant for review. Sample size calculation for whole RCT was 280 in total (n = 140 per group) (p.4, Huijbers 2012). | Yes                                                                                                       |
| Psaros 2014           | Not reported - but following issues of sample size are mentioned in the paper: 1. "Although significance testing could not be completed because of the small sample size, there were some apparent differences between those participants who did and did not relapse" (p.7). 2. "Although the sample size and study design preclude us from drawing conclusions about this observed relationship, women with infertility or difficulty conceiving may be especially vulnerable to depressive recurrence and, as a result, may require more intensive monitoring and intervention" (p.7). 3. "The nonrandomized design and small sample size do not allow for conclusions around the causality of treatment effects" (p.7). | Yes                                                                                                       |
| Study | Question | Response | Limitations of Study | Notes |
|-------|----------|----------|----------------------|-------|
| Baldessarini 2010<sup>13</sup> | 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes - mean follow up was 2.81 years (SD 3.63). Follow up was every 2-4 months. Follow up was censored at 100 months (p.935) | No - limitations of study in discussion are: "The follow-up reviews by CHCP-1 demonstrated further prescribing reductions could be made. However, the 3-month time period is likely too short to assess sustainability of reductions, especially as common mental health problems are relapsing and remitting in nature. Therefore, a 12-month follow-up period with reviews at 3, 6, and 12 months would be more appropriate to assess long-term sustainability of prescribing changes" (p.777). | Yes - "Patients were asked and recommended to withdraw gradually from their antidepressants over a period of 5 weeks, starting after the seventh session of MBCT...... Adherence to the study protocol was defined as attending four or more MBCT sessions, as in previous studies and having fully discontinued mADM before the 6-month follow-up assessment (i.e. within 6 months after baseline and within approximately 3-4 months after the last MBCT session") (p.367). |
| Himei 2006<sup>14</sup> | | Yes - the groups are based on outcome | | Yes - reports on 24 weeks of trial (p.5) |
| Johnson 2012<sup>20</sup> | | | | |
| Huijbers 2016<sup>24</sup> | | | | |
| Psaros 2014<sup>11</sup> | | | | |
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

| Author | Yes | No | Not applicable |
|--------|-----|----|----------------|
| Baldessarini 2010 | No | - discontinuation was rapid (1-7 days) or gradual (≥2 weeks) | |
| Himei 2006 | Not applicable - groups were based on outcome. In regard to tapering, the clinics only used one type of tapering strategy (a second one was later used to help patients in the discontinuation syndrome group successfully withdraw from paroxetine) | |
| Johnson 2012 | Not applicable | |
| Huijbers 2016 | Yes - data for relevant study arm were provided for intention to treat population and per-protocol population (Adherence to the study protocol was defined as attending four or more MBCT sessions, as in previous studies, and having fully discontinued mADM before the 6-month follow-up assessment (i.e. within 6 months after baseline and within approximately 3–4 months after the last MBCT session) | |
| Psaros 2014 | No applicable | |

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

| Author | Yes | No | Not applicable |
|--------|-----|----|----------------|
| Baldessarini 2010 | Yes - excluded those patients whose rate of discontinuation was uncertain (22.3% of potential antidepressant-treated candidates) (p.935) | |
| Himei 2006 | Not applicable - groups were based on outcome. Outcomes of discontinuation syndrome or non-discontinuation syndrome were clearly defined. | |
| Johnson 2012 | Yes | |
| Huijbers 2016 | Not applicable - study was two armed RCT of which one arm was relevant for review. | |
| Psaros 2014 | Yes | |

10. Was the exposure(s) assessed more than once over time?

| Author | Yes | No | Not applicable |
|--------|-----|----|----------------|
| Baldessarini 2010 | Not applicable | |
| Himei 2006 | Not applicable | |
| Johnson 2012 | No - intervention was 1 GP review | |
| Huijbers 2016 | Not applicable | |
| Psaros 2014 | Yes - For quality assurance, all sessions were audiotaped (p5) | |

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

| Author | Yes | No | Not applicable |
|--------|-----|----|----------------|
| Baldessarini 2010 | Yes - first new episode of major depression or panic disorder that met DSM-IV diagnostic criteria at clinical assessment (p.935) | |
| Himei 2006 | Not applicable - groups were based on outcome. | |
| Johnson 2012 | Yes - GPs had standardised form with outcomes to complete (p.774) | |
| Huijbers 2016 | Yes - "The primary outcome measure was relapse/recurrence as measured with the SCID-I by trained research assistants every 3 months during the follow-up period" (p.367). | |
| Psaros 2014 | Yes - All assessments were performed by a research assistant or trained study clinicians. The research assistants were trained by the study psychologist on how to conduct and assess psychiatric interviews and questionnaires. Assessments were scripted, and training included mock interviews and assessments (p.5) | |
|                                | Baldessarini 2010\(^{13}\) | Himei 2006\(^{14}\) | Johnson 2012\(^{20}\) | Huijbers 2016\(^{16}\) | Psaros 2014\(^{11}\) |
|--------------------------------|-----------------------------|----------------------|-------------------------|--------------------------|----------------------|
| **12. Were the outcome assessors blinded to the exposure status of participants?** | Not reported | Not reported | Not reported | No - "The research assistants conducting the assessments could not be masked to treatment group since they were also involved in the practical organisation of the trial" (p.367). | Not reported |
| **13. Was loss to follow-up after baseline 20% or less?** | Not applicable - retrospective study. | Not applicable - retrospective study. | Not applicable | No - over the course of the trial 28% were lost to follow-up in the relevant study arm (p.369). | Yes - all patients, including 3 women who met study end point completed all relevant sessions and assessments (p.6) |
| **14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?** | Yes - effect of covariates examined (p.938). | Not applicable - but statistical comparison, between those who experienced discontinuation syndrome and those that did not, of age, sex, maintenance and dosage and duration of treatment with paroxetine was made (p.667). | Yes - Analysis by CHCP was performed (There was significant variation between CHCPs in patients continuing, stopping, reducing, increasing, or changing antidepressants ($\chi^2 = 30.89, 12$ df, $P<0.005$). This was attributable to CHCP-1 having fewer patients change antidepressant than CHCPs 2, 3 & 4. There was no significant difference between CHCPs 2, 3 and 4) (p.776) | Yes - depressive symptoms at baseline, and number of depressive episodes in the past (p.368) | Yes - illness characteristics of relapses versus non relapsers were assessed (number of past episodes of depression, number of past failed attempts to discontinue antidepressants) (p.6). |
| 15. Any other forms of bias | Baldessarini 2010[^13] | Himei 2006[^14] | Johnson 2012[^10] | Huijbers 2016[^14] | Psaros 2014[^11] |
|--------------------------------|----------------------|-------------|-------------------|-------------------|------------------|
| Can’t determine - Conflicts of interest and funding were reported - 2 of the authors had research grants and consultan-tships with pharma. Research was funded through in part by NIH grant MH-073579 to Drs. Tondo and Baldessarini; the Lucio Bini Private Donors Mood Disorders Research Fund to Dr. Tondo; and a grant from the Bruce J. Anderson Foundation and the McLean Private Donors Psychopharmacology Research Fund to Dr. Baldessarini (p.940). | No - The authors have no conflicts of interest that are directly relevant to the content of this study and no sources of funding were used to assist in conducting the study (p.672). | No - The authors have declared no competing interests (p.778). | No - The authors have declared no competing interests (p.366). | Can’t determine - Dr Psaros reports personal fees from Bracket Global. Dr Freeman reports grants from Eli Lilly, Forest, and GlaxoSmithKline; consulting with PamLab; an advisory board position with Takeda/Lundbeck and Otsuka; and medical editing for the Diagnostic and Statistical Manual of Mental Disorders nutri-tionals. Dr Safren and Ms Barsky have nothing to disclose. Dr Cohen reports grants from AstraZeneca Pharmaceuticals; Bayer HealthCare Pharmaceuticals; Bristol-Myers Squibb; Cephalon, Inc; Forest Laboratories, Inc; GlaxoSmithKline; National Institute on Aging; National Institute of Mental Health; Ortho-McNeil-Janssen; Pfizer, Inc; and Sunovion Pharmaceuticals, Inc. Dr Cohen also reports consultancy with Eli Lilly and Company (p.8) |

Options: Yes, no, can’t determine, not reported, not applicable

Abbreviations: DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition; mADM maintenance antidepressant medication; MBCT mindfulness-based cognitive therapy; p. page number; SCID Structured Clinical Interview for DSM-IV; SD standard deviation
### Table E: Studies reporting relapse/recurrence within six months of discontinuation

| Study (design) | Definition of relapse/recurrence | Intervention (relapse/recurrence rate) | Comparator (relapse/recurrence rate) | Results |
|----------------|----------------------------------|----------------------------------------|--------------------------------------|---------|
| **Depression (exclusion or non-reporting of anxiety comorbidities)** |
| Psaros 2014[^1] (Single arm) | Criteria for a current depressive episode according to the MINI, or AD treatment re-initiation | CBT + taper (2/12 = 17%) | n/a | 2 participants relapsed 5 weeks and 10 week after completing AD taper; 1 participant reinitiated AD treatment 1 week after completing AD taper although they did not meet full criteria for a major depressive episode |
| Himei 2006[^2] (Retrospective cohort) | DSM-IV criteria | 41 patients with discontinuation syndrome after either abrupt (n=27) or gradual (n=14) withdrawal of paroxetine (10mg reduction every 2 weeks) Subsequently, 36/41 re-administered paroxetine and tapered off by 5mg every 2–4 weeks. 5/41 required change of medication, as unable to tolerate adverse effects of paroxetine. 0/41 relapsed 4 and 8 weeks after paroxetine stopped. |
| **Depression and/or anxiety disorders** |
| Baldessarini 2010[^3] (Retrospective cohort) | DSM-IV-TR criteria | Gradual discontinuation - ≥ 2 weeks Median time to recurrence (months): MDD: 7.60 Panic disorder: 13.2 | Rapid discontinuation – 1-7 days Median time to recurrence (months): MDD: 3.17 Panic disorder: 4.23 | Ratio of occurrence latency (gradual/rapid): MDD: 2.40 Panic disorder: 3.1 |

**Abbreviations:** AD antidepressant; CBT cognitive behavioural therapy; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition; DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; MDD major depressive disorder; MINI The Mini-International Neuropsychiatric Interview; n/a not applicable
Table F: Studies reporting recurrence more than six months after discontinuation

| Study (design) | Definition of recurrence | Timepoint – from baseline | Intervention (recurrence rate) | Comparator (recurrence rate) | Risk ratio (95% CI) |
|----------------|--------------------------|---------------------------|-------------------------------|-------------------------------|-------------------|
| Huijbers 2016^1 (Single arm from RCT) | DSM-IV criteria for depressive episode | 15 months | MBCT-TS (69/128 = 54%) | n/a | n/a |
| Eveleigh 2015^2 (RCT) | Severity of symptoms on BSI-53 and CESD | After 1 year | Letter to PCP with recommendation + tapering advice (18/70 = 26%) | Usual care (10/76 = 13%) | 1.95 (0.97, 3.94; 1 study) |
| Fava 1994^3 (RCT) | RDC defined episode of major depression | 2 years; 4 years; 6 years | CBT + taper (3/20 = 15%; 7/20 = 35%; 10/20 = 50%) | CM + taper (7/20 = 35%; 14/20 = 70%; 15/20 = 75%) | 2 years: 0.34 (0.18, 0.67; I^2 = 0%; 2 studies) |
| Fava 1998^4 (RCT) | RDC defined episode of major depression | 2 years; 6 years | CBT + taper (5/20 = 25%; 8/20 = 40%) | CM + taper (6/20 = 30%; 18/20 = 90%) | 6 years: 0.55 (0.37, 0.82; I^2 = 11%; 2 studies) |
| Kuyken 2008^5 (RCT) | DSM-IV criteria for major depressive disorder | 15 months | MBCT-TS (29/61 = 48%) | m-ADM (37/62 = 60%) | 215months: 0.90 (0.75, 1.07; I^2 = 0%; 2 studies) |
| Kuyken 2015^6 (RCT) | SCID-LIFE score of 5 for 2 consecutive weeks at any time | 24 months | MBCT-TS (94/212 = 44%) | m-ADM (100/212 = 47%) | 215months: 0.90 (0.75, 1.07; I^2 = 0%; 2 studies) |

^1 RCT but only 1 arm is relevant for this review, ITT analysis; ^2 ITT analysis; ^3 complete case analysis (95% and 91% of those randomised to the intervention and comparator arms respectively); ^4 complete case analysis (87% and 91% of those randomised to the intervention and comparator arms respectively).

**Abbreviations:** BSI-53 Brief Symptom Inventory; CESD Centre for Epidemiological Studies Depression Scale; CM clinical management; CBT cognitive behavioural therapy; DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition; ITT intention to treat; m-ADM maintenance antidepressant medication; MBCT-TS Mindfulness based cognitive therapy with support to taper; n/a not applicable; PCP Primary Care Provider; RDC Research Diagnostic Criteria; SCID-LIFE Structured Clinical Interview for DSM-IV - Longitudinal Interval Follow-up Evaluation
| Study (design) | Measure (Timepoints) | Intervention | Comparator | Mean difference (95% CI) |
|---------------|----------------------|--------------|------------|-------------------------|
| **Depression (exclusion or non-reporting of anxiety comorbidities)** | | | | |
| Psaros 2014* (Single arm) | QLESQ Baseline, time of relapse, end of acute phase, at 24 weeks from baseline | CBT + taper | n/a (see text for results) | |
| Eveleigh 2015* (RCT) | QALY (calculated using EQ-5D) 12 months | Letter to PCP with recommendation + tapering advice | Usual care | Mean: 0.70; SE: 0.03; SD: 0.25 N: 70 -0.02 (-0.10, 0.06; 1 study) |
| Kuyken 2008* (RCT)² | WHOQOL-BREF (physical; psychological; social; environmental) 1 month post treatment, 15 months from baseline | MBCT-TS Physical 1 M: mean: 24.08; SD: 5.75; N: 60 15 M: mean: 29.37; SD: 5.28; N: 60 Psychological 1 M: mean: 18.88; SD: 3.97; N: 60 15 M: mean: 18.61; SD: 3.79; N: 60 Social 1 M: mean: 10.09; SD: 2.15; N: 60 15 M: mean: 10; SD: 2.27; N: 60 | m-ADM Physical 1 M: mean: 22.86; SD: 5.78; N: 59 15 M: mean: 22.93; SD: 6.88; N: 59 Psychological 1 M: mean: 17.47; SD: 4.82; N: 59 15 M: mean: 17.36; SD: 5.58; N: 59 Social 1 M: mean: 9.08; SD: 2.74; N: 59 15 M: mean: 9.66; SD: 3.06; N: 59 | ≥12 months from baseline Physical: -0.12 (-1.58, 1.34; $I^2 = 48%$; 2 studies) Psychological: 0.36 (-0.75, 1.47; $I^2 = 45%$; 2 studies) Social: -0.01 (-0.59, 0.58; $I^2 = 0%$; 2 studies) |
| Kuyken 2015* (RCT)³ | EQ-5D, WHOQOL-BREF (Q1 overall perception of health; Q2 overall perception of health; physical; psychological; social; environment) | MBCT-TS Physical 1 M: mean: 14.3; SD: 3.3; N: 174 12 M: mean: 14.1; SD: 3.4; N: 166 Psychological 1 M: mean: 13.4; SD: 2.6; N: 174 12 M: mean: 13.3; | m-ADM Physical 1 M: mean: 14.3; SD: 3.0; N: 173 12 M: mean: 14.7; SD: 3.3; N: 157 Psychological 1 M: mean: 12.6; SD: 2.8; N: 173 12 M: mean: 13.3; | |
| 1 month post treatment, 9, 12, 18 and 24 months from baseline | SD: 2.9; N: 166 |
|---|---|
| Social | 1 M: mean: 13.8; SD: 2.9; N: 174 |
| | 12 M: mean: 13.7; SD: 3.3; N: 169 |
| SD: 2.7; N: 157 |
| Social | 1 M: mean: 13.3; SD: 3.4; N: 173 |
| | 12 M: mean: 13.9; SD: 3.5; N: 167 |

1 ITT analysis; 2 Complete case analysis (1 month post treatment and at 15 months, 98% and 95% of those randomised to the intervention and comparator arms respectively) 3 Complete case analysis (1 month post treatment 82% of those randomised to the intervention and comparator arms, 24 months, 79% and 80% of those randomised to the intervention and comparator arms respectively)

**Abbreviations:** EQ-5D European Quality of Life five dimensions questionnaire; M months; PCP Primary Care Provider; QALY Quality Adjusted Life Years; QLESQ Quality of Life Satisfaction; SD standard deviation; SE standard error; WHOQOL-BREF World Health Organization Quality of Life instrument
Table H: Studies reporting reduction in antidepressant dosage, usage or combination

| Study (design) | Timepoint – from baseline | Intervention (reduction rate) | Comparator (reduction rate) | Other results |
|----------------|---------------------------|-------------------------------|-----------------------------|--------------|
| **Depression (exclusion or non-reporting of anxiety comorbidities)** |
| Klein 2017[^1] (RCT[^1]) | 6 months | CBT + taper (Minimum 50% reduction of ADM use: 16/85 = 19%) | m-ADM (n/a) | n/a |
| Huijbers 2016[^2] (Single arm from RCT[^2]) | Not reported | MBCT-TS (Reduction in ADM: 17/128 = 13%) | n/a | n/a |
| **Depression and/or anxiety disorders** |
| Kuyken 2015[^3] (RCT[^3]) | 24 months | MBCT-TS (Reduction in ADM dose: 29/176 = 16%) | m-ADM (n/a) |  |
| Johnson 2012[^4] (single arm) | Post intervention | Guided PCP review (Reduced dose: 366/2849 = 12.8%) | n/a | 9.5% (95% CI = 9.1% to 9.8% P<0.001) reduction in mean PDD, expressed as DDDs. Estimated 8.1% (£23 320 per annum) reduction in antidepressant prescribing costs. |

[^1]: 3 arm RCT, but only 2 arms are relevant for this review; ITT analysis;[^2]: RCT but only 1 arm is relevant for this review; ITT analysis;[^3]: per protocol analysis (completed 4 sessions of MBCT, 83% of those randomised to intervention arm)

**Abbreviations:** ADM antidepressant medication; CBT cognitive behavioural therapy; DDD defined daily doses; m-ADM maintenance antidepressant medication; MBCT-TS Mindfulness based cognitive therapy with support to taper; n/a not applicable; PCP Primary Care Provider, PDD prescribed daily dose.
| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| 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, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3                 |
| INTRODUCTION  |   |                                                                                                                                                                                                             |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                              | 4                 |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                          | 4                 |
| METHODS       |   |                                                                                                                                                                                                             |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                             | 5                 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                           | 5,6               |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                               | 6,7               |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                               | Appendix 1        |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                       | 5,6,7             |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                     | 7                 |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                           | 7                 |
| 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. | 7                 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                | 7,8               |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.                                                                                | 7,8               |
| Section/topic                  | #   | Checklist item                                                                 | Reported on page # |
|-------------------------------|-----|--------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies   | 15  | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Not reported      |
| Additional analyses           | 16  | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7,8               |
| 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. | 8, flowchart supplementary file |
| Study characteristics         | 18  | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8, 9, Table B in Appendix 2 |
| 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). | 9, Tables C & D Appendix 2 |
| Results of individual studies | 20  | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 10-13, Tables 1 & 2 (pages 25, 26), Tables E-H in Appendix 2 |
| Synthesis of results          | 21  | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 12, Table 1 (page 25), Tables F & G in Appendix 2 |
| Risk of bias across studies   | 22  | Present results of any assessment of risk of bias across studies (see Item 15). | 9, Table C in Appendix 2 |
| Additional analysis           | 23  | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Not applicable |
| DISCUSSION                    |     |                                                                                  |                   |
| Summary of evidence           | 24  | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13, 14-15        |
| Limitations                   | 25  | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14               |
| Conclusions                   | 26  | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 14-15            |
| FUNDING                       |     |                                                                                  |                   |
## PRISMA 2009 Checklist

| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2