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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.[1-3] The main reason is increasing long-term use,[4,5] with a median duration greater than five years in the USA,[2] mostly prescribed by PCPs.[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.[6-8] This exposes them to potentially serious side-effects,[9,10] and is costly.[11]

However, stopping antidepressants is frequently associated with withdrawal symptoms, which can be problematic, and mistaken for relapse/recurrence.[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.[13,14] Psychological interventions like cognitive-behaviour therapy (CBT) and mindfulness-based cognitive therapy (MBCT) are potential alternatives to antidepressants in preventing relapse/recurrence.[15-17]

Current guidelines for antidepressant discontinuation are based on consensus, and non-systematic reviews have identified a need for more controlled data.[18] There have been two systematic reviews focussing on the incidence of withdrawal symptoms after discontinuation.[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 (MAOI)s (usually prescribed by specialists[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,[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 (EBSCO*host*), AMED (EBSCO*host*), HMIC, 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.[22] 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,[23] in accordance with the Cochrane Handbook.[24] For observational studies and single arm trials we used the National Heart Lung and Blood Institute and Research Triangle Institute International tools.[25]

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 Chi^2 test ($p<0.1$) and I^2 statistic ($I^2 \geq 50\%$).

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,[15-17,26-57] reporting 15 studies were therefore included.[15-17,26,27,32,34,38,42,50,51,53-55,57] Of these 15, one was published as an abstract only.[26]

Table B, Appendix 2 shows study characteristics. Twelve were completed,[15-17,27,32,34,38,42,50,51,53,54] and included in our synthesis. Two were ongoing (both RCTs, one of tapering for two weeks versus one week,[57] and one of guided tapering plus CBT versus maintenance antidepressants in pregnant women.)[55,56]

Eight of the completed studies were RCTs (one cluster RCT[27] and one[34] with only one relevant study arm),[15-17,27,32,34,38,42] two single arm trials,[50,51] and two retrospective cohort studies.[53,54] Numbers of patients ranged from 12 to 2849.[50,51] Seven included participants with depression and/or anxiety disorder,[15-17,27,32,50,53] and five depression only.[34,38,42,51,54] Criteria used for depression were reported in nine, including the Diagnostic and Statistical Manual (DSM-IV) (7)[16,17,34,38,42,53,54] and Research Diagnostic Criteria (RDC) (2),[15,32] (Table B).

Twelve named the antidepressants being discontinued. Two concerned discontinuation of a single antidepressant (desvenlafaxine,[38] and paroxetine[54]), one tricyclic antidepressant (TCA) and related antidepressants,[15] one newer antidepressants,[51] one predominantly SSRIs,[42] and seven both older and newer.[16,17,27,32,34,50,53] Inclusion criteria for duration of use were reported in eight and included ≥4 weeks (1),[51] 24 weeks (1),[38] 3 to 5 months (1),[15] ≥6 months (3),[16,34,42] ≥9 months (1),[27] and ≥ 2 years.[50] Mean/median length of antidepressant use was reported in three,[24,50,54] ranging from 9.2 months[54] to 9.5 years.[27] Inclusion criteria for length of remission/recovery were reported in four,[32,34,42,51] ranging from 8 weeks[42] to six months[51.] Three studies of MBCT included a significant proportion of patients in partial remission[16,17,34] (Table B).

Interventions included: patient specific letter to the PCP with recommendation to discontinue antidepressant and tapering advice;[27] prompted PCP review of condition and medication;[50] CBT with tapering;[15,32,42,51] MBCT with tapering;[16,17,34] gradual discontinuation;[53,54] and one week tapering.[38] 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).[15-17,27,32,34,42,50]

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.[27] 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.[15,32] 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; $Chi^2 = 0.49$, $I^2 = 0\%$). Cessation rates in three studies of MBCT with tapering support ranged from 55% to 75%.[16,17,34]

Antidepressant discontinuation symptoms

One RCT and one retrospective cohort reported on discontinuation symptoms (Table 2).[38,54] One compared abrupt discontinuation of desvenlafaxine 50 mg/day versus tapering using 25 mg/day for one week.[38] 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).[38] 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.[38]

In a study of clinical records of 385 patients treated with paroxetine for a single episode of major depressive disorder,[54] 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. Of

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).[51,53,54] 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.[53]

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.[51] 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%).[54] In a second cohort, median time to recurrence of depressive or panic disorder was more than twice as long after gradual versus rapid discontinuation.[53] Newer antidepressants (SSRIs, bupropion, duloxetine, venlafaxine) were associated with a shorter time to recurrence than TCAs/tetracyclics.[53]

Recurrence after more than six months

Six studies reported late recurrence (Table F, Appendix 2)[15-17,27,32,34] 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.[18]

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).[27] Meta-analysis of two CBT studies[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^2=0.19, I^2=0%), and six years (40%-50% vs 75%-90%: RR 0.55, 95% CI 0.37 to 0.82; Chi^2=1.12, I^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^2=0.68, I^2=0%).[16,17] The recurrence rate at 15 months was similar (54%) in another study providing MBCT with tapering support in one arm.[34]

Quality of Life

Four studies (three RCTs, one single arm trial) reported on quality of life (Table G, Appendix 2).[16,17,27,51] In one there was no significant effect on quality adjusted life years.[27] Meta-analysis was possible for two comparing MBCT with tapering versus maintenance antidepressants.[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.[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.[51]

Reduction in antidepressant use

Four studies reported reduction in antidepressant use (Table H, Appendix 2).[17,34,42,50] Reduction rates ranged from 13% of patients for PCP review, to 19% with minimum 50% reduction in use following CBT plus tapering.[50,42]

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[38] found a lower risk of serious adverse events with one week taper versus abrupt discontinuation of desvenlafaxine, whilst a retrospective cohort study[54] 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.[58]

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.[59]

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.[54] Switching to fluoxetine, with its longer half-life and availability in liquid form, may enable successful slow tapering,[18] 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.[64] 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.

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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[42] (RCT)[1]	6 months	CBT+ taper (34/85 = 40%)	m-ADM (n/a)	n/a
Huijbers 2016[34] (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[27] (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[15] (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[32] (RCT)	20 weeks	CBT + taper (20/23 = 87%)	CM + taper (20/22 = 91%)	
Kuyken 2008[16] (RCT)[3]	6 months	MBCT-TS (46/61 = 75%)	m-ADM (n/a)	n/a
Kuyken 2015[17] (RCT)[4]	24 months	MBCT-TS (124/176 = 70%)	m-ADM (n/a)	n/a
Johnson 2012[50] (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

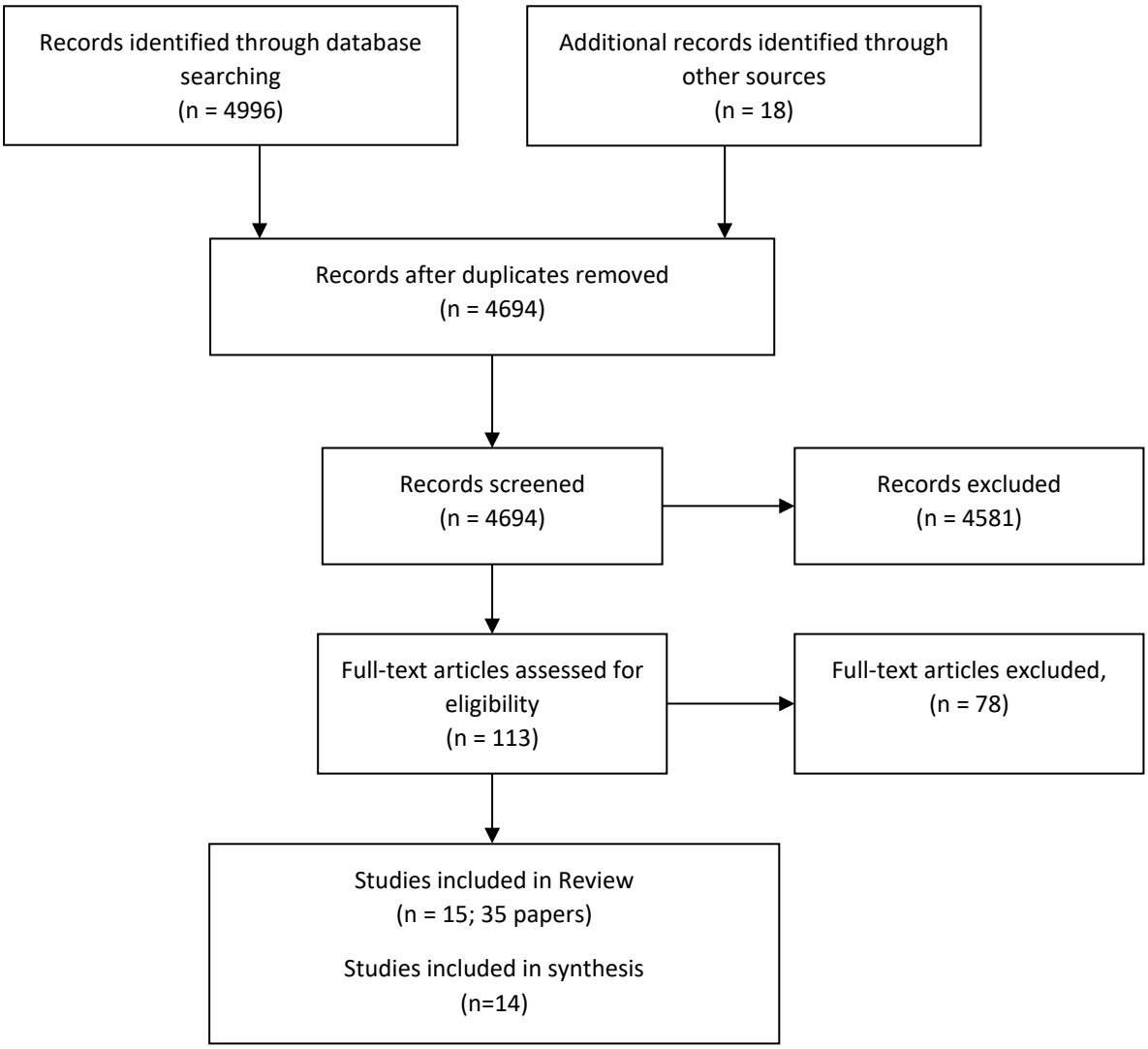
Table 2: Studies reporting antidepressant discontinuation symptoms

Study (design)	Time point	Intervention (event rate)	Comparator (event rate)	Risk ratio (95% CI)
Depression (exclusion or non-reporting of anxiety comorbidities)				
Khan 2014[38] (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[54] (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).

FIGURES

Figure 1: Flowchart of study selection



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	(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*).ti,kf,hw.	136112
4	(Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine).ti,kf,hw.	44215
5	(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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Noxiptilin*).ti,kf,hw.	67830
6	(Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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).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	randomly.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] 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 Pirandamine [TIAB] or Piribedil[TIAB] or Pirlindole[TIAB] or Pivagabine[TIAB] or Pizotyline[TIAB] or Propizepine[TIAB] or (Protriptylin*[TIAB] or Pertofrane[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 Viqualine[TIAB] or Zalospirone[TIAB] or Zimeldine[TIAB]))	104458
#5	Search (((Harmaline[TIAB] or Harmine[TIAB] or Hyperforin[TIAB] or Hypericum[TIAB] or John* Wort [TIAB] or Idazoxan[TIAB] or Imipramin*[TIAB] or Iprindole[TIAB] or Iproniazid*[TIAB] or Ipsapirone[TIAB] or Imipraminoxide[TIAB] or Isocarboxazid*[TIAB] or Lesopitron[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 Nortriptyline[TIAB] or Noxiptilin*[TIAB]))	68596
#4	Search (((Agomelatine[TIAB] or Alaproclate[TIAB] or Alnespirone[TIAB] or Amoxapine[TIAB] or Amersergide[TIAB] or Amfebutamone[TIAB] or Amiflamine[TIAB] or Amineptine[TIAB] or Amitriptylin*[TIAB] or Amitriptylinoxide[TIAB] or Amoxapine[TIAB] or Aripiprazole [TIAB] or Atomoxetine[TIAB] or Tomoxetine[TIAB] or Befloxatone[TIAB] or Benactyzine[TIAB] or Binospirone[TIAB] or Brofaromine[TIAB] or Bupropion[TIAB] or Butriptylin*[TIAB] or Caroxazone[TIAB] or Chlopoxiten[TIAB] or Cianopramine[TIAB] or Cilobamine[TIAB] or Cilosamine[TIAB] or Cimoxatone[TIAB] or Citalopram[TIAB] or (Chlorimipramin*[TIAB] or Clomipramin*[TIAB] or Chlomipramin*[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 Dibenzepin[TIAB] or Diclofensin*[TIAB] or Dimetacrin*[TIAB] or (Dosulepin[TIAB] or Dothiepin[TIAB]) or Doxepin[TIAB] or Duloxetine[TIAB] or DVS 233[TIAB] or Enilospirone [TIAB] or Eptapirone[TIAB] or Escitalopram[TIAB] or Etoperidone[TIAB] or Femoxetine[TIAB] or Fenfluramin*[TIAB] or Fluotracen [TIAB] or Fluoxetine[TIAB] or Fluparoxan[TIAB] or Furazolidone[TIAB] or Fluvoxamine[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[TIAB] or reuptake[TIAB] or re-uptake[TIAB])) or noradrenerg*[TIAB] or antiadrenergic[TIAB] or anti adrenergic[TIAB] or SSRI*[TIAB] or SNRI*[TIAB] or TCA*[TIAB] or tricyclic*[TIAB] or tetracyclic*[TIAB] or heterocyclic*[TIAB]))	
#2	Search NEUROTRANSMITTER UPTAKE INHIBITORS[MESH]	25774
#1	Search ANTIDEPRESSIVE AGENTS[MESH]	52011

Embase

Embase (Ovid), 1974 to 22 March 2017

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/ or Serotonin Noradrenalin Reuptake Inhibitor/ or Triple Reuptake inhibitor/	48677
5	Dopamine Receptor Affecting Agent/ or Dopamine Uptake Inhibitor/	1521
6	Adrenergic Receptor Affecting Agent/ or Noradrenalin 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 Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofensin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone 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 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 Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Noxiptilin*).ti,kw,hw.	164343
11	(Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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).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 INVOLUTIONAL 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 recurr*).ti,ab,kw.	24142
17	secondary prevention/	26698

18	14 or 15 or 16 or 17	1038745
19	randomized controlled trial.de.	486141
20	randomi#ed.ti,ab.	678999
21	randomly.ab.	349380
22	factorial$.ti,ab.	29959
23	(control$ adj3 (trial$ or study or studies or group$)).ti,ab.	1059738
24	(quasi adj (experimental or random$)).mp.	15035
25	19 or 20 or 21 or 22 or 23 or 24	1745321
26	Clinical study/	285135
27	case control study/	127053
28	Longitudinal study/	110299
29	Retrospective study/	544323
30	Prospective study/	405475
31	Cohort analysis/	321284
32	(Cohort adj (study or studies)).mp.	194800
33	(Case control adj (study or studies)).tw.	104374
34	(follow up adj (study or studies)).tw.	54788
35	(observational adj (study or studies)).tw.	107273
36	(epidemiologic$ adj (study or studies)).tw.	91152
37	(cross sectional adj (study or studies)).tw.	138593
38	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	1930183
39	exp case study/	96920
40	(case$ and series).tw.	208351
41	case report/	2214717
42	(case$ adj2 report$).tw.	617208
43	(case$ adj2 stud$).tw.	249088
44	39 or 40 or 41 or 42 or 43	2705244
45	25 or 38 or 44	5827853
46	12 and 13 and 18 and 45	3560
47	remove duplicates from 46	3421
48	(rodent* or rat or rats or mouse or mice or animal model*).ti.	1472370
49	(smoking or tobacco or nicotine).ti. or smoking cessation.mp.	134529
50	(antibiotic* or antimicrob* or antifung* or statin*).ti.	192464
51	(book or editorial or review).pt.	2907167
52	48 or 49 or 50 or 51	4636647
53	47 not 52	2670

PsycINFO

PsycINFO (EBSCO*host*), inception to 23 March 2017

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 (randomi* control* trial*)) or (AB (randomi* 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 recurr*)) or (AB (prevent* N3 recurr*)) OR (KW (prevent* N3 recurr*))	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*)) or (MJ (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*))(TI (cease or cessation* or discontinu* or	38818

	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*)) 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 Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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 Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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 Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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))(TI (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or ...Show Less	16625
S9	(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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Noxiptilin*)) or (KW (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 Methylphenidate or Mianserin or Milnacipran or Minaprine	15681

	or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine 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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine 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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine o ...Show Less	
S8	(TI (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofenasin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine)) or (KW (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofenasin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine)) or (MJ (Agomelatine or Alnespirone or Alprocolate or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofenasin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine))(TI (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxa ...Show Less	14679

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*)))(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* ...Show Less	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

The Allied and Complementary Medicine Database (AMED)

AMED (EBSCO*host*), inception to 23 March 2017

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 (clinic* N1 trial*)) OR (AB (clinic* 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 discontinu* 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 discontinu* 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 discontinu* 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

	Pirandamine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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 Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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 Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* 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))(TI (Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine 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 Tetrindole or Thiazesim or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or ...Show Less	
S4	(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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Noxiptilin*)) or (KW (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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine 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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine 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 Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Monocrotophos or Nefazodone or Nialamide or Nitroxazepine o ...Show Less	436

S3	(TI (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofenasin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine)) or (KW (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofenasin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine)) or (MJ (Agomelatine or Alaprocolate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Diclofenasin* or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenfluramin* or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine))(TI (Agomelatine or Alaproclate or Alnespirone or Amoxapine or Amersergide or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin*or Caroxazone or Chlopoxiten or Cianopramine or Cilobamine or Cilosamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxa ...Show Less	84
S2	(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*)))(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	1546

	noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* ...Show Less	
S1	(DE "antidepressive agents")	313

Health Management Information Consortium (HMIC)

HMIC, inception to 24 March 2017

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 anti adrenergic OR SSRI* OR SNRI* OR TCA* OR tricyclic* OR tetracyclic* OR heterocyclic*).ti,ab	929
6	(Agomelatine OR Alaproclate OR Alnespirone OR Amoxapine OR Amersergide OR Amfebutamone OR Amiflamine OR Amineptine OR Amitriptylin* OR Amitriptylinoxide OR Amoxapine OR Aripiprazole OR Atomoxetine OR Tomoxetine OR Befloxatone OR Benactyzine OR Binospirone OR Brofaromine OR Bupropion OR Butriptylin* OR Caroxazone OR Chlopoxiten OR Cianopramine OR Cilobamine OR Cilosamine OR Cimoxatone OR Citalopram OR Chlorimipramin* OR Clomipramin* OR Chlomipramin* OR Clorimipramine OR Clorgyline OR Clovoxamine OR Dapoxetine OR Deanol OR Demexiptilin* OR Deprenyl OR Desipramine OR Desvenlafaxine OR Dibenzepin OR Diclofenasin* OR Dimetacrin* OR Dosulepin OR Dothiepin OR Doxepin OR Duloxetine OR DVS 233 OR Enilospirone OR Eptapirone OR Escitalopram OR Etoperidone OR Femoxetine OR Fenfluramin* OR Fluotracen OR Fluoxetine OR Fluparoxan OR Furazolidone 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 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 Methylphenidate OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Monocrotophos OR Nefazodone OR Nialamide OR Nitroxazepine OR Nomifensine OR Norfenfluramine OR Nortriptyline OR Noxiptilin*).ti,ab	126
8	(Opipramol OR Oxaflozane OR Paroxetine OR Phenelzine OR Pheniprazine OR Pipofezin* OR Pirandamine OR Piribedil OR Pirlindole OR Pivagabine OR Pizotyline OR Propizepine 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 Tetrindole OR Thiazesim OR Thozalinone OR Tianeptin* 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).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 deprescrip* OR de prescrip*).ti,ab b	14611
15	(prevent* ADJ3 relaps*).ti,ab	144
16	(prevent* ADJ3 recurr*).ti,ab	91
17	(14 OR 15 OR 16)	14771

18	"RANDOMISED CONTROLLED TRIALS"/	2352
19	(randomi#ed OR randomi#ation).ti,ab	6465
20	(randomly).ab	2789
21	(trial).ti,ab trial.ti,ab	6264
22	(groups).ab	23383
23	(control* ADJ3 (trial* OR study OR studies)).ti,ab (control* adj3 (trial* or study or studies)).ti,ab	6624
24	(quasi ADJ (experimental OR random*)).ti,ab (quasi adj (experimental or random*)).ti,ab	410
25	((waitlist* OR wait* list* OR treatment as usual OR TAU) ADJ3 (control OR group)).ab	87
26	(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)	33018
27	"COHORT STUDIES"/	1010
28	"PROSPECTIVE STUDIES"/	198
29	"LONGITUDINAL STUDIES"/	542
30	(Case control).ti,ab	1403
31	(cohort ADJ (study OR studies)).ti,ab	3279
32	(Cohort analy*).ti,ab	134
33	(Follow up ADJ (study OR studies)).ti,ab	633
34	(observational ADJ (study OR studies)).ti,ab	1373
35	(epidemiologic* ADJ (study OR studies)).ti,ab	951
36	(Longitudinal).ti,ab	3139
37	(Retrospective).ti,ab	3045
38	(Cross sectional).ti,ab	4708
39	(27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38)	16417
40	(Case series).ti,ab	114
41	(Case* report*).ti,ab	323
42	(Case* stud*).ti,ab	6076
43	(40 OR 41 OR 42)	6487
44	(26 OR 39 OR 43)	50227
45	(9 AND 13 AND 17 AND 44)	56
46	(rodent* OR rat OR rats OR mouse OR mice OR animal model*).ti	139
47	(smoking OR tobacco OR nicotine).ti (smoking OR tobacco OR nicotine).ti	3936
48	(smoking cessation).ti,ab	1191
49	(antibiotic* OR antimicrob* OR antifung* OR statin*).ti	796
50	(46 OR 47 OR 48 OR 49)	5138
51	45 NOT 50	48

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 norepineprhine 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

fluoxetine AND withdraw*	0
fluoxetine AND terminat*	0
fluoxetine AND deprescrib*	0
fluvoxamine AND cease	0
fluvoxamine AND cessation	0
fluvoxamine AND discontinuation	0
fluvoxamine AND taper*	1
fluvoxamine AND reduce	0
fluvoxamine AND stop*	0
fluvoxamine AND withdraw*	0
fluvoxamine AND terminat*	0
fluvoxamine AND deprescrib*	0
paroxetine AND cessation	0
paroxetine AND discontinuation	1
paroxetine AND taper*	0
paroxetine AND reduce	0
paroxetine AND stop*	0
paroxetine AND withdraw*	1
paroxetine AND terminat*	0
paroxetine AND deprescrib*	0
sertraline AND cease	3
sertraline AND cessation	0
sertraline AND discontinuation	1
sertraline AND taper*	1
sertraline AND reduce	6
sertraline AND stop*	4
sertraline AND withdraw*	0
sertraline AND terminat*	1
sertraline AND deprescrib*	0
duloxetine AND cease	0
duloxetine AND cessation	0
duloxetine AND discontinuation	1
duloxetine AND taper*	1
duloxetine AND reduce	2
duloxetine AND stop*	0
duloxetine AND withdraw*	0
duloxetine AND terminat*	0
duloxetine AND deprescrib*	0
venlafaxine AND cease	0
venlafaxine AND cessation	0
venlafaxine AND discontinuation	0
venlafaxine AND taper*	5
venlafaxine AND reduce	1
venlafaxine AND stop*	0

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*	1
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
1	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.ehbc.2004.08.035	Population has minor depression or dysthymia
2	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.
3	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%)
4	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)
5	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
6	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)
7	Bockting CL, Spinhoven P, Wouters LF, et al. Long-term effects of preventive cognitive therapy in recurrent depression: a 5.5-year follow-up study. *Journal of Clinical Psychiatry* 2009;70(12):1621-8. doi: https://dx.doi.org/10.4088/JCP.08m04784blu	Intervention is not aimed at antidepressant reduction/discontinuation
8	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
9	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
10	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
11	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
12	Curtin F, Schulz P. Relapse prevention and antidepressants. *Lancet* 2003;361(9375):2158-59; author reply 59.	Letter concerning a systematic review
13	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
14	Dobson KS, Hollon 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

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/S0033291797006363	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, Kupfer DJ, Perel JM. Early recurrence in unipolar depression. *Archives of General Psychiatry* 1989;46(5):397-400.	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 "Keeping the blues away" program. *The Medical journal of Australia* 2008;188(12 Suppl):S138-41.	Intervention is not aimed at antidepressant reduction/discontinuation
20	Huijbers MJ, Spinhoven 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, Kornstein 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-KQVW	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	Omidi A, 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

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. doi: 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. doi: 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.	Intervention is not aimed at antidepressant reduction/discontinuation
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. doi: 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. doi: http://dx.doi.org/10.1016/S0006-3223%2898%2900126-7	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. doi: 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. doi: 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) doi: http://dx.doi.org/10.1186/1471-244X-32-3	Intervention is not aimed at antidepressant reduction/discontinuation
39	Stangier 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. doi: http://dx.doi.org/10.1176/appi.ajp.2013.12060734	Intervention is not aimed at antidepressant reduction/discontinuation
40	Stant AD, TenVergert EM, Kluiter 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.	Intervention is not aimed at antidepressant reduction/discontinuation
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. doi: 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.	Intervention is not aimed at antidepressant reduction/discontinuation
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.	Intervention is not aimed at antidepressant reduction/discontinuation
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. doi: https://dx.doi.org/10.1177/0269881107087488 https://dx.doi.org/10.1177/0269881107081550	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. doi: 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.	Intervention is not aimed at antidepressant reduction/discontinuation
52	NCT02747134. Combining Emotion Regulation and Mindfulness Skills for Preventing Depression Relapse. 2016.	Intervention is not aimed at antidepressant reduction/discontinuation
53	NCT02614326. MemFlex to Prevent Depressive Relapse. 2015.	Intervention is not aimed at antidepressant reduction/discontinuation
54	NCT02029963. Can Magnetic Brain Stimulation Help Prevent Relapse in Depression? 2014.	Intervention is not aimed at antidepressant reduction/discontinuation
55	NCT01807988. Internetbased Relapse Prevention for Partially Remitted Depression. 2013.	Intervention is not aimed at antidepressant reduction/discontinuation
56	NCT01619930. The Effects of Behavioral Activation and Physical Exercise on Depression. 2012.	Intervention is not aimed at antidepressant reduction/discontinuation
57	NCT00427128. Prozac Treatment of Major Depression: Discontinuation Study. 2007	Intervention is not aimed at antidepressant reduction/discontinuation
58	NCT00218764. Cognitive Therapy Versus Medication Treatment for Preventing Depression Relapse. 2005.	Intervention is not aimed at antidepressant reduction/discontinuation
59	NCT00183664. Cognitive Therapy for Treating Depression and Preventing Relapse. 2005.	Intervention is not aimed at antidepressant reduction/discontinuation
60	NCT00183560. Preventing Depression Relapse With Mindfulness-Based Cognitive Therapy. 2005.	Intervention is not aimed at antidepressant reduction/discontinuation.
61	NCT00057577. Prevention of Recurrence in Depression With Drugs and CT. 2003.	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.	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.	Intervention is not aimed at antidepressant reduction/discontinuation
64	ISRCTN68246470. (Cost)effectiveness of a cognitive group prevention module for recurrent depression. 2006	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.	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.	Intervention is not aimed at antidepressant reduction/discontinuation
67	ISRCTN58808893. An SMS-assisted mindfulness-based intervention for relapse prevention in depression. 2014.	Intervention is not aimed at antidepressant reduction/discontinuation
68	ISRCTN44812125. Cognitive training as a facilitated self-help relapse prevention for depression. 2010	Intervention is not aimed at antidepressant reduction/discontinuation
69	ISRCTN15969819. Antidepressants to prevent relapse in depression. 2015.	Intervention is not aimed at antidepressant reduction/discontinuation
70	ISRCTN12388725. E-COMPARED - internet-supported CBT for depression. 2015.	Intervention is not aimed at antidepressant reduction/discontinuation

71	IRCT201111298253N1. Effect of psychological intervention on symptoms and preventing recurrence depression. 2012.	Intervention is not aimed at antidepressant reduction/discontinuation
72	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
73	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
74	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
75	ACTRN12611000370909. Deprescribing in frail older people: a randomised controlled trial. 2011	Intervention is deprescribing of variety of medications
76	ACTRN12608000613303. Maintenance antidepressants versus treatment cessation in the prevention of depression recurrence. 2008.	Intervention is not aimed at antidepressant reduction/discontinuation
77	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
78	Intervention is not for antidepressant reduction/discontinuation	Intervention is not aimed at antidepressant reduction/discontinuation

TABLE B: STUDY CHARACTERISTICS

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

RCTs

Study details	Inclusion/exclusion criteria	Participant characteristics
Kahn 2014[38] *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,[39] NCT01056289[40]	*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) *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)	*Age (years), mean (SD):* INT: 47.9 (11.2); COMP 1: 47.8 (13.7), COMP 2: 46.7 (11.3) *Female:* INT: 74%; COMP 1: 68%; COMP 2: 67% *Depression diagnosis:* Major depressive disorder *Antidepressant use:* desvenlafaxine 50mg per day *Duration of antidepressant use (weeks)*: 24
Intervention details	**Comparator 1 details**	**Comparator 2 details**
Name of intervention: Tapered discontinuation; N=140 *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	*Name of intervention:* Abrupt discontinuation; N=148 *Description:* placebo for 4 weeks *Treatment duration:* 4 weeks *Delivery:* not reported *Provider:* not reported	*Name of intervention:* Antidepressant continuation; N=73 *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[42] *Country:* Netherlands *Setting:* Mental health care sites *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),[43] ISRCTN15472145[44] *Funding:* Netherlands Organization for Health Research and Development (ZonMw), and Netherlands Organization for Scientific Research (NWO).	*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 *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	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.

Intervention details	Comparator details
Name: Cognitive therapy with tapering of antidepressant (CT + taper); N=85 *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. *Treatment duration:* CT: 8 weekly sessions Taper: 4 weeks *Delivery:* CT: group sessions, Taper: 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.	*Name:* continuation of maintenance antidepressant medication (m-ADM); N = not reported. Antidepressant use: 87.8% SSRI *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:* not applicable *Delivery:* not reported *Provider:* GP's and psychiatrists

Single arm trials

Study details	Inclusion/exclusion criteria	Participant characteristics
Huijbers 2016[34] *Country:* Netherlands *Setting*: 12 secondary and tertiary psychiatric out-patient clinics *Study design:* Parallel two group non-inferiority RCT (only one arm (MBCT-TS) was relevant as second arm was MBCT+ maintenance antidepressant medication) *Funding:* The Netherlands Organization for Health Research and Development (ZonMW) *Full publication:* Yes (journal article) *Linked publications:* Huijbers 2012,[35] Huijbers 2016,[36] NCT00928980[37]	*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 *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	*Age (years), mean (SD):* INT: 50.7 (10.6) *Female*: INT: 72% *Depression diagnosis at intake: In full remission (IDS-C ≤11):* INT: 70 (55%); *In partial remission (IDS-C >11):* INT: 58 (45%) *Antidepressant use: SSRIs*: INT: 92 (72%); TCAs: 26 (20%); *Other (SNRI, mirtazapine, MAOI):* 10 (8%) *Duration of antidepressant use*: not reported
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. 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. A protocol for medication tapering developed for this study by two experts in pharmacological treatment of major depressive disorder was provided. For discontinuation a minimum of 3 and a maximum of 12 consultations during the follow-up period were recommended. *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. TS: Face to face. *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[51] *Country:* USA *Setting:* Massachusetts General Hospital Center for Women's Mental Health in Boston or health care provider within the community *Study design:* Single arm trial *Full publication:* Yes (journal article) *Linked publications:* Psaros 2011[52] *Funding:* not reported	*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. *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)	*Age (years), mean (SD):* 34 (3.96) *Female:* 100% (1 patient pregnant at baseline) *Depression diagnosis Major unipolar depression:* n=11*; Minor unipolar depression:* n=1 *Antidepressant use: Bupropion*: n=3; *Sertraline*: n=5; *Fluoxetine*: n=2; *Citalopram*: n=2 *Duration of antidepressant use*: 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[54] *Country:* Japan *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. *Study design:* Retrospective cohort *Full publication:* Yes (journal article) *Linked publications:* None *Funding:* None	*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. *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).	*Age (years), mean (SD):* OUTCOME 1: 40.5 (7.8); OUTCOME 2 : mean 37.2 (8.0) (statistical difference between groups) *Female:* OUTCOME 1: n=44%; OUTCOME 2: n=46% *Depression:* MDD diagnosed according to DSM IV criteria *Antidepressant use:* Paroxetine only. *Maintenance dose, mean (SD):* OUTCOME 1: 25.9mg/day (9.9); OUTCOME 2: 26.6mg/day (10.2) *Duration of antidepressant use (months)*: OUTCOME 1: mean 9.2 SD 4.1; OUTCOME 2: mean 9.9 SD 4.2

Outcome1 details	Outcome 2 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	*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[27] *Country:* Netherlands *Setting:* 45 general practices *Study design:* Two group cluster RCT *Funding:* Netherlands Organization for Health Research and Development (ZonMw) *Full publication:* Yes (PhD thesis) *Linked publications:* Muskens 2013,[28] Eveleigh 2014[29]	*Inclusion criteria:* Long-term antidepressant use (≥9 months). All antidepressants were included, except MAO-inhibitors; written informed consent. *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.	*Age (years), mean (SD):* INT: 56 (12.9); COMP: 56 (14) *Female:* INT: 71%; COMP: 68% *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%) *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%) *Duration of antidepressant use (years), median (range):* INT: 8.0 (1 to 48); COMP: 9.5 (1 to 56)

Intervention details	Comparator 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 *Provider*: GP	*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

Study details	Inclusion/exclusion criteria	Participant characteristics
Fava 1994[15] *Country:* Italy *Setting:* Outpatients referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine in Italy. *Study design:* Parallel two group RCT *Funding:* Partially supported by Ministero Universita e Ricerca Scientifica e Tecnlogica; Consiglio Nazionale delle Ricerche; and Mental Health Project, Istituto Superiore di Sanità, Rome *Full publication:* Yes (journal article) *Linked publications:* Fava 1996,[30] Fava 1998[31]	*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. *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.	*Age (years), mean (SD):* INT: 43 (2.3); COMP: 48.5 (3.3) *Female:* INT: 60%; COMP: 75% *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%). *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%); *Duration of antidepressant use (months):* 3 to 5

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.	*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	Inclusion/exclusion criteria	Participant characteristics
Fava 1998[32] *Country:* Italy *Setting:* Outpatients referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine in Italy. *Study design:* Parallel two group RCT *Funding:* Partially supported by the "Mental Health Project," Istituto Superiore di Sanita and the "Ministero dell Universita e della Ricerca Scientifica e Tecnologica *Full publication:* Yes (journal article) *Linked publications:* Fava 2004[33]	*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 episode5; 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). After drug treatment, rated as “better" or “much better" according to global rating scale of improvement, in full remission and in stage 3 of primary unipolar depression. *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) *Female:* INT: 55%; COMP: 65% *Depression – Pre-intervention scores for the Clinical Interview for Depression (CID), mean (SD):* INT 30.8, SD (3.3); COMP 29.7 (3.9) *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%) *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%) *Duration of antidepressant use (months):* 3 to 5

Intervention details	Comparator 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.	*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 proscribed. 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[16] *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[41]	*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

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	Inclusion/exclusion criteria	Participant characteristics
Kuyken 2015[17] *Country:* UK *Setting:* General practices in urban and rural settings in Bristol, Exeter and East, North, and South Devon *Study design:* Parallel two group RCT, stratified by locality and symptomatic status (GRID HAMD ≥ 8) *Funding:* National Institute for Health Research *Full publication:* Yes (HTA report) *Linked publications*:, Kuyken 2010,[45] Kuyken 2014,[46] Kuyken 2015,[47] Anonymous 2016,[48] ISRCTN26666654[49]	*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. *Exclusion criteria:* Depressed, as assessed using the Structured Clinical Interview for DSM-IV (SCID); had a comorbid diagnosis of current substance abuse (patients with previous substance abuse were eligible for inclusion as long as they were in sustained full remission); organic brain damage; current/past psychosis, including bipolar disorder; displayed persistent antisocial behaviour; engaged in persistent self-injury that required clinical management/therapy; were undergoing formal concurrent psychotherapy.	*Age (years), mean (SD):* INT: 50 (12); COMP: 49 (13) *Female:* INT: 71%; COMP: 82% *Depression diagnosis at intake:* *Asymptomatic:* INT: 77%; COMP: 76% *Symptomatic*: INT: 23%; COMP: 24% *No. of comorbid DSM-IV Axis I psychiatric diagnoses, mean (SD):* INT: 0.5 (0.9); COMP: 0.7 (0.9) *Antidepressant use (weeks prescribed over 24 month follow up period)*: *SSRIs*: 21642.5; *SNRIs*: 2690; *TCAs*: 2586, *Mirtazapine*: 1541; *Agomelatine*: 64; *Others*: 32; *Flupentixo*l: 24; *Moclobemide*: 14 *Duration of antidepressant use:* not reported

Intervention details	Comparator 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 rehearse 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	*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

Single arm trials

Study details	Inclusion/exclusion criteria	Participant characteristics
Johnson 2012[50] *Country:* Scotland *Setting:*4 CHCPs containing urban general practices in most deprived areas *Study design:* Single arm intervention *Funding:* HCP Local Enhanced Service and NHS GG&C Mental Health Collaborative monies. *Full publication:* Yes (journal article) *Linked publications:* None	*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) *Female* (Demographic data were available for 94.4% (2691/2849) patients reviewed)*:* 1975/2691 *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%.* *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% *Duration of antidepressant use (years):* mean 5.5, SD 3.0, range 2.0 to 24.8
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	Inclusion/exclusion criteria	Participant characteristics
Baldessarini 2010[53] *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 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).	*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 (SSRI, 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

Exposure 1	Exposure 2
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.	*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

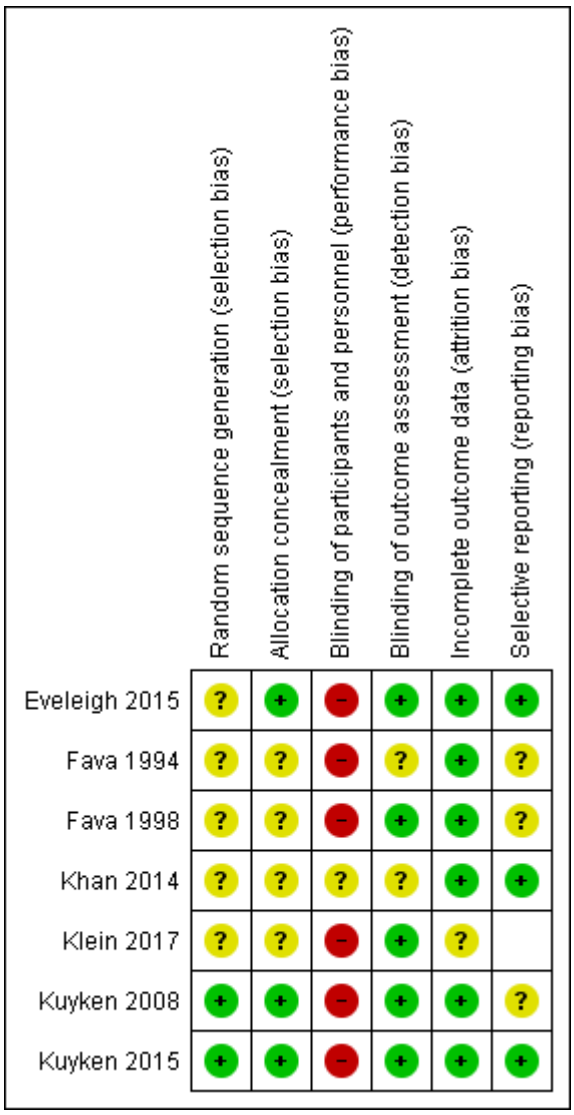
Study details	Inclusion/exclusion criteria
Molenaar 2016[55] *Country:* Netherlands *Setting:* Not reported *Study design:* Pragmatic multi-centre randomized controlled non-inferiority trial *Full publication:* Protocol is published as a journal article *Linked publications:* Lambregtse-Van Den Berg 2015[56] *Funding:* Netherlands Organization for Health Research and Development and Erasmus Medical Centre, Department of Psychiatry.	*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, *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.
Intervention details	**Comparator 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	*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

Study details	Inclusion/exclusion criteria

NCT02661828_2016[57] *Country:* USA *Setting:* Not reported *Study design:* RCT, open label *Full publication:* Clinical trial.gov entry *Linked publications:* None *Funding:* Emory University	*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 consider tapering 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	**Comparator 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	*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

Table C: Risk of bias assessment for RCTs



Selective outcome reporting was not assessed for Klein at el., 2017 as this paper was reporting a secondary analysis

Table D: Risk of bias assessment for single arm trials and observational studies

	Baldessarini 2010[53]	Himei 2006[54]	Johnson 2012[50]	Huijbers 2016[34]	Psaros 2014[51]
1. Was the research question or objective in this paper clearly stated?	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?	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%?	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?	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).

	Baldessarini 2010[53]	Himei 2006[54]	Johnson 2012[50]	Huijbers 2016[34]	Psaros 2014[51]
5. Was a sample size justification, power description, or variance and effect estimates provided?	Not reported	Not reported	Yes - p.774	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).	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).
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Not applicable (review and action taken with antidepressant took place at the same time)	Yes	Yes

	Baldessarini 2010[53]	Himei 2006[54]	Johnson 2012[50]	Huijbers 2016[34]	Psaros 2014[51]
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)	Yes - the groups are based on outcome	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).	Yes - reports on 24 weeks of trial (p.5)

	Baldessarini 2010[53]	Himei 2006[54]	Johnson 2012[50]	Huijbers 2016[34]	Psaros 2014[51]
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)?	No - discontinuation was rapid (1-7 days) or gradual (≥2 weeks)	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)	Not applicable	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) (p.367)	Not applicable
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes - excluded those patients whose rate of discontinuation was uncertain (22.3% of potential antidepressant-treated candidates) (p.935)	Not applicable - groups were based on outcome. Outcomes of discontinuation syndrome or non-discontinuation syndrome were clearly defined.	Yes	Not applicable - study was two armed RCT of which one arm was relevant for review.	Yes
10. Was the exposure(s) assessed more than once over time?	Not applicable	Not applicable	No - intervention was 1 GP review	Not applicable	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?	Yes - first new episode of major depression or panic disorder that met DSM-IV diagnostic criteria at clinical assessment.(p.935)	Not applicable - groups were based on outcome.	Yes - GPs had standardised form with outcomes to complete (p.774)	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).	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[53]	Himei 2006[54]	Johnson 2012[50]	Huijbers 2016[34]	Psaros 2014[51]
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).

	Baldessarini 2010[53]	Himei 2006[54]	Johnson 2012[50]	Huijbers 2016[34]	Psaros 2014[51]
15. Any other forms of bias	Can't determine - Conflicts of interest and funding were reported - 2 of the authors had research grants and consultantships 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 nutritionals. 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[51] (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[54] (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[53] (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)
Depression (exclusion or non-reporting of anxiety comorbidities)				
Huijbers 2016[34] (Single arm from RCT)[1] DSM-IV criteria for depressive episode	15 months	MBCT-TS (69/128 = 54%)	n/a	n/a
Depression and/or anxiety disorders				
Eveleigh 2015[27] (RCT) [2] 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[15] (RCT)[3] 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) 6 years: 0.55 (0.37, 0.82; I^2 = 11%; 2 studies)
Fava 1998[32] (RCT)[4] RDC defined episode of major depression	2 years; 6 years	CBT + taper (5/20 = 25%; 8/20 = 40%)	CM + taper (6/20 = 80%; 18/20 = 90%)	
Kuyken 2008[16] (RCT)[2] DSM–IV criteria for major depressive disorder	15 months	MBCT-TS (29/61 = 48%)	m-ADM (37/62 = 60%)	≥15months: 0.90 (0.75, 1.07; I^2 = 0%; 2 studies)
Kuyken 2015[17] (RCT)[2] SCID-LIFE score of 5 for 2 consecutive weeks at any time	24 months	MBCT-TS (94/212 = 44%)	m-ADM (100/212 = 47%)	

[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

Table G: Studies reporting Quality of Life

Study (design)	Measure (Timepoints)	Intervention	Comparator	Mean difference (95% CI)
Depression (exclusion or non-reporting of anxiety comorbidities)				
Psaros 2014[51] (Single arm)	QLESQ Baseline, time of relapse, end of acute phase, at 24 weeks from baseline	CBT + taper		n/a (see text for results)
Depression and/or anxiety disorders				
Eveleigh 2015[27] (RCT)[1]	QALY (calculated using EQ-5D) 12 months	Letter to PCP with recommendation + tapering advice Mean: 0.70; SE: 0.03; SD: 0.25 N: 70	Usual care Mean: 0.72; SE: 0.03; SD: 0.26; N: 76	-0.02 (-0.10, 0.06; 1 study)
Kuyken 2008[16] (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	**<u>1 month post treatment</u>** Physical: 0.20 (-0.68, 1.08; I^2 = 17%; 2 studies) Psychological: 0.87 (0.33, 1.40; I^2 = 0%; 2 studies) Social: 0.68 (0.15, 1.22; I^2 = 0%; 2 studies) **<u>≥12 months from baseline</u>** 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[17] (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[42] (RCT)[1]	6 months	CBT + taper (Minimum 50% reduction of ADM use: 16/85 = 19%)	m-ADM (n/a)	n/a
Huijbers 2016[34] (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[17] (RCT)[3]	24 months	MBCT-TS (Reduction in ADM dose:29/176 = 16%)	m-ADM (n/a)	
Johnson 2012[50] (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.

PRISMA 2009 Checklist

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

PRISMA 2009 Checklist

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			

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

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