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[Intervention Protocol]

Discontinuation of long-term antidepressant use for depressive and anxiety disorders in adults

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the feasibility and safety of discontinuation of long-term antidepressant use for depressive and anxiety disorders in adults aged over 18 years.

BACKGROUND

Description of the condition

Antidepressant use

Antidepressants can be divided into various classes based on their slightly different mechanisms of action (see [Table 1](#)). They act, with a few exceptions, by enhancing the transmission of the chemical messengers dopamine, noradrenaline (norepinephrine), adrenaline (epinephrine) and serotonin, which are thought to be involved in mood regulation in the brain. However, the exact mechanism of action of antidepressants is still not known ([Harmer 2017](#)).

The consumption of antidepressants has increased significantly in most countries since 2000 and continues to rise ([OECD 2017](#)). The highest use per population in the Convention on the Organisation for Economic Co-operation and Development (OECD) Health Report is seen in Iceland, Australia, Portugal, UK, Sweden, Canada and Belgium ([OECD 2017](#)). About 12.7% of Belgian adults take antidepressants daily ([RIZIV 2014](#)), with similar rates in the UK (16%; [DHSC 2018](#)), and many other European countries ([Gusmão 2013](#)). In the USA the rate is about 12.7% ([Pratt 2018](#)), and in Australia about 16.8% of adults take antidepressants daily ([Brett 2017](#)).

Like most prescribed medicines, antidepressants can have side-effects and adverse effects. Very common (more than 10%) adverse events ('harms') for all antidepressants are sleep disturbance, sexual dysfunction and gastro-intestinal problems. More serious rare adverse effects (0.01% to 0.1%), are higher risk of agitation and suicide at the beginning of the treatment or when increasing dosage, gastro-intestinal bleeding, and in older people, low sodium in the blood with risk of agitation and confusion and an increased risk of fracture ([BCFI/CBIP 2018](#)). Each antidepressant is also associated with side effects related to their mechanism of action. For example, very common side effects (more than 10%) of tricyclic agents (TCA) are blurred vision, constipation, and dry mouth due to the anticholinergic properties of TCAs. Other common problematic anticholinergic effects (1% to 10%), include an increased intra-ocular pressure, urinary retention, postural hypotension, dizziness and a negative impact on cognition in older people. Patients also commonly report adverse effects on mood and emotion, such as feeling emotionally numb and addicted ([Cartwright 2016](#)). Long-term antidepressant use may also impair patients' autonomy and increase their dependence on medical help and medication ([Kendrick 2015](#)). Typical antidepressant withdrawal symptoms or discontinuation symptoms, such as flu-like symptoms, insomnia, nausea, imbalance or vertigo, sensory disturbances, and hyperarousal (anxiety and agitation), can occur when stopping, missing doses or reducing doses of any antidepressant.

A previous Cochrane Review on antidepressant treatment for depression in primary care suggested that, for one person to experience side effects that led the person to stop taking the antidepressant drug (i.e. number needed to treat for an additional harmful outcome (NNTH); [Arroll 2009](#)), between 4 and 30 people needed to be treated with a TCA, and between 20 and 90 people with selective serotonin reuptake inhibitors (SSRI). In older people, antidepressants tend to pose a greater risk of adverse events

because of co-existing disease and drug-drug interactions related to other medications taken regularly ([Kok 2017](#)).

Indications of antidepressants

Depressive disorders

The most prevalent condition that warrants the use of antidepressants in the community and in nursing homes is depression ([Bourgeois 2012](#); [Wong 2016](#)).

According to the *Diagnostic and Statistical Manual of Mental Disorders 5th edition* (DSM-V) classification, a major depressive disorder is defined as a period of at least two weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities, and also at least four additional symptoms from the following: changes in appetite, weight, sleep or psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty concentrating or thinking or making decisions, or recurrent thoughts of death or suicidal ideation or suicide plans or attempts ([APA 2013](#)). The symptoms must persist for most of the day, nearly every day, for at least two consecutive weeks. The episode must be accompanied by clinically significant distress or impairment in social, occupational or other important areas of functioning. A major depressive episode is a period of two weeks or more, characterised by the symptoms of a major depressive disorder ([APA 2013](#)). Severity of the major depressive disorder (mild, moderate, severe) must be based on the number of criterion symptoms, the severity of those symptoms and the extent to which usual social and working activity is limited and not rely simply on counting the number of symptoms ([APA 2013](#)).

Diagnosing depression can be difficult due to these broad and subjective diagnostic criteria and lack of a reliable and valid test for depression in primary care.

An untreated depressive episode typically lasts about four to six months on average ([NICE 2016](#); [Solomon 1997](#)). Although approximately half of the people who become depressed will only have a single episode of depression in their lifetimes, approximately 50% will have multiple episodes or persistent depressive disorders ([Eaton 2008](#); [Moffit 2010](#)). Recurrence is common; there is a 50% chance of recurrence after a first episode, rising to 70% and 90% after a second or third episode respectively ([NICE 2016](#)). Therefore it is recommended that treatment should focus not only on improving symptoms of the acute episode, but also on prevention of relapse (return of symptoms of the original depressive episode) and recurrence (development of a subsequent episode) ([NICE 2016](#)).

There are three distinct phases in the treatment of depressive disorder: acute, continuation and maintenance treatment ([APA 2010](#)). Acute therapy is the treatment phase focused on treating the patient to remission and typically lasts six to 12 weeks. The continuation phase is the treatment phase during the first six months after having achieved remission and aims to prevent recurrence of the original depressive episode. The maintenance treatment is treatment to prevent recurrence of depression or a new depressive episode after remission ([Frank 1991](#)).

Acute treatment

Antidepressants have been shown to be efficacious in adults, compared to placebo, in the acute treatment of major depressive disorder in the short term, although the effect is small ([Cipriani](#)

2018). In a previous Cochrane Review, authors found that, for depression in primary care, between 7 and 8 people needed to be treated with a SSRI and between 7 and 16 people with a TCA for 1 person to experience improvement of depression due to the antidepressant use (i.e. number needed to treat for an additional beneficial outcome (NNTB); Arroll 2009). However, there is also increasing criticism about the lack of evidence for effectiveness of antidepressants in the acute treatment of mild to moderate depressive disorders, due to important limitations of the available evidence base (McCormack 2018; Munkholm 2019). There is insufficient evidence to support or to contest the efficacy of antidepressant medication for subthreshold and mild depressive disorder (Cameron 2014).

Continuation and maintenance treatment

Evidence suggests that continuation of antidepressant treatment is effective as it reduces the risk of relapse and recurrence by 50% to 70% (Geddes 2003; Glue 2010; Kaymaz 2008; NICE 2016), although almost all trials on which this conclusion was based were conducted in secondary care and are probably not representative of primary-care patients (Aroll 2017). The evidence for treatment durations of more than nine months is relatively limited, with a lack of long-term trials in which participants were randomised six months after remission to determine the effects of treatment after this time (Kaymaz 2008). A previous Cochrane Review on continuation and maintenance trials for older people with depressive disorders found that the long-term benefits and harms of continuing antidepressant medication in the prevention of recurrence of depression are not clear and no firm treatment recommendations can be made (Wilkinson 2016). Moreover, evidence showed no association between relapse rates and duration of treatment (Geddes 2003), and there was no evidence to justify the defined clinical distinction between continuation treatment (six to nine months) and maintenance treatment (for two years or longer; Kaymaz 2008). Another Cochrane Review of trials in people with persistent depressive disorder found that it is uncertain whether continued or maintained pharmacotherapy (or both) with antidepressant agents is a robust treatment for preventing relapse and recurrence due to moderate or high risk of bias (Machmutow 2019).

Guidelines have underlined the importance of giving antidepressants for a sufficient period of time. The recommended duration of continuation treatment varies from four months to 12 months in depression guidelines after remission (APA 2010; CANMAT 2016; Declercq 2017; NHG 2012; NICE 2016; WHO 2017). Continuation treatment should be continued for at least two years after remission in those at high risk of relapse (APA 2010; CANMAT 2016; Declercq 2017; NHG 2012; NICE 2016; WHO 2017), which is defined as patients having two or more episodes, residual symptoms and severe previous episodes, as these factors are related to a poorer prognosis overall (Geddes 2003). People with depression on long-term maintenance treatment should be regularly re-evaluated. Due to the lack of evidence for the optimal duration of continuation and maintenance treatment, most guidelines are based on expert opinion.

Anxiety disorders

After depression, anxiety disorders (e.g. generalised anxiety disorder, panic disorders or any other anxiety disorder) are the most frequent indication for which antidepressants are

prescribed (Wong 2016). Cognitive behavioural therapy (CBT) and antidepressants are both first-line options for the treatment of anxiety disorders with proven effectiveness (Batelaan 2017; NICE 2011). Antidepressant treatment duration of up to one year results in lower relapse rates among responders compared with treatment discontinuation in anxiety disorders, irrespective of type of anxiety disorder (Batelaan 2017). However, long-term trials are scarce. International guidelines are therefore consensus-based and advise continuation of treatment for variable durations (6 to 24 months; Baldwin 2014; NICE 2011).

Long-term antidepressant use

Long-term antidepressant prescription is driving much of the rise in antidepressant use (Brett 2017; Kjosavik 2016; Mars 2017). In the Netherlands, approximately 30% of people taking antidepressants take them for more than one year (Meijer 2004). In the UK, nearly half of the antidepressant users (8% of the total population) have been taking them for more than two years (Johnson 2012), and in the USA half of the antidepressant users (7% of the total population) have been taking them for more than five years (Mojtabi 2014). In Australia, the average duration of treatment with antidepressants is about four years (Kjosavik 2016). High antidepressant use has also been reported in people living in nursing homes. About 40% of Belgian nursing-home residents take antidepressants daily (Bourgeois 2012), with similar rates seen in other European countries (Janus 2016), and the USA (Karkare 2011).

Antidepressants that, despite initially being appropriate, are not discontinued after the recommended treatment period, can lead to long-term unnecessary medication. A recent trial described inappropriate duration of antidepressants, for example, for longer than needed, as "legacy prescribing" (Mangin 2018).

Trials suggest that the motives and barriers of patients and physicians to continue or discontinue antidepressants are numerous and complex (Bosman 2016; Maund 2018). A recent review synthesised 49 barriers and facilitators in nine themes related to patients' perspectives: psychological and physical capabilities, perception of antidepressants, fears of relapse and/or recurrence, intrinsic motivators and goals, the physician as a navigator to maintenance or discontinuation, perceived cause of depression, aspects of information that support decision-making, significant others (a help or a hindrance) and support from other health professionals (Maund 2018). A key barrier was the patient's belief that the physician was responsible for initiating discussions about discontinuation. Other identified barriers are related to the availability of supportive non-pharmacological guidance during discontinuation, the personal circumstances of the patient and the underlying considerations and knowledge of the patients and physicians (Bosman 2016). Patients continued using antidepressants because of fear of relapse, a perceived biological cause for their depressive symptoms and their experience of improved functioning. It was also easier for physicians to prescribe antidepressants for depression as they are more accessible than psychological treatment. In one open, single-arm trial with older patients from nursing homes, resistance to discontinuing antidepressants largely came from the relatives and not the carers of the older individuals (Lindstrom 2007).

Discontinuing antidepressant treatment can be complicated by the potential for patients to experience withdrawal symptoms. Discontinuation symptoms refer to physical and psychological

symptoms that occur when stopping, missing doses or reducing doses (even with gradual tapering) of any antidepressant (APA 2013). Symptoms generally begin two to four days after abrupt discontinuation of antidepressants that had been taken continuously for at least one month (APA 2013). Late onset or longer persistence, lasting weeks to months, has also occurred (Davies 2019). Antidepressant withdrawal reactions are widespread. A recent review suggests incidence rates from 27% to 86%, with an average incidence of 56%, and with up to half of those experiencing withdrawal symptoms having severe reactions (Davies 2019).

Withdrawal symptoms are often very similar to symptoms of relapse or recurrence and may sometimes be misleading and misdiagnosed as depressive recurrence, leading to unnecessary continuation of antidepressant use. If the same or a similar drug is restarted, the withdrawal symptoms will usually resolve fully within one to three days and subsequently the antidepressant can be withdrawn more cautiously (Haddad 2007). Withdrawal symptoms can be distinguished from relapse of the original disorder by their rapid onset after stopping antidepressants. Whereas relapse is uncommon in the first weeks after stopping, the rapid response after reintroducing the original antidepressant and the presence of somatic and psychological withdrawal symptoms is different from the original depressive or anxiety disorder (Haddad 2007; Horowitz 2019). However, many withdrawal variations after discontinuation are possible including late onset of the symptoms (sometimes after several months) making misdiagnosis of withdrawal possible. Additionally, one of the more serious withdrawal reactions can be anxiety symptoms. As antidepressants have been widely prescribed for anxiety disorders, it is a challenge to distinguish withdrawal from relapse of the original anxiety disorder (Davies 2019; Fava 2015). The risk of discontinuation symptoms is higher with antidepressants with a shorter half-life (the time taken for blood concentration to be reduced by 50%), where high doses have been prescribed, and in cases where rapid tapering occurs (APA 2013). The risk also appears to be higher for those who have taken antidepressants for eight weeks or longer (APA 2013).

Description of the intervention

Guidelines recommend discontinuation of antidepressant drugs after successful treatment (NICE 2016). Abrupt discontinuation of antidepressants may lead to temporary withdrawal symptoms.

A common strategy is to taper (gradually reduce the dose) antidepressants over weeks to reduce the risk of withdrawal symptoms (NICE 2016). The National Institute for Health and Care Excellence (NICE) recommends gradually reducing the antidepressant dose every one to two weeks, over a four-week period, although some people may require longer periods, particularly with drugs with a shorter half-life (such as paroxetine and venlafaxine; NICE 2016). However, there is a lack of evidence regarding strategies for discontinuation of antidepressants and the optimal method of stopping antidepressants is currently unknown; withdrawal symptoms can always occur despite a slow taper approach (Horowitz 2019). It is important that patients are informed at the time of initiation of an antidepressant of the intention to stop treatment when their condition has improved, and that this may present a risk of withdrawal symptoms.

Psychological interventions in combination with discontinuation of antidepressants could support the process of discontinuation.

- CBT focuses on the cognitive content of negative thinking and on learning a repertoire of coping skills appropriate to the target thoughts, beliefs or problem areas (NICE 2016). Patients work with a therapist, either face to face or via telecommunication technologies (online therapy) and CBT can be delivered individually or in group. A meta-analysis on the sequential integration of pharmacotherapy and psychotherapy in major depressive disorder suggests that participants receiving CBT after antidepressant discontinuation were significantly less likely to relapse compared to continued pharmacotherapy (Guidi 2016). A recent review of two trials found that the risk of relapse or recurrence was lower with CBT plus tapering compared to clinical management plus tapering after two years (Maund 2019).
- Mindfulness-based cognitive therapy (MB-CT) is a group-based clinical intervention programme designed to reduce relapse or recurrence of major depressive disorder by means of systematic training in mindfulness meditation combined with cognitive-behavioral methods (Piet 2011). MB-CT is a manualised, group-based skills training programme intended to teach people skills to deal with their negative feelings and thoughts as a part of their lives through becoming aware of negative cognitive patterns (Piet 2011). A meta-analysis of six trials showed that MB-CT reduces the 12-month relapse/recurrence risk compared with usual care or placebo, with a relative risk reduction of 43%, in patients with a history of three or more episodes of depression (Huijbers 2016; Piet 2011). A recent systematic review about the effectiveness of interventions to manage antidepressant discontinuation found in two trials that relapse or recurrence rates were similar for MB-CT in combination with tapering and for maintenance antidepressants (Maund 2019).
- Low-intensity psychosocial interventions may use simple approaches that are less complex to undertake than CBT or MB-CT. Contact with people is generally briefer than in other forms of therapy and can be delivered by para-professionals or peer supporters using non-traditional methods such as telephone or the internet. There is no clear definition of low-intensity psychosocial intervention for depression or anxiety in the literature (NICE 2016; Rodgers 2012). The NICE guideline found evidence on three main forms of low-intensity psychosocial interventions in the acute treatment of depression: individual, guided self-help based on the principles of CBT, computerised CBT and a structured group physical activity programme (NICE 2016). However, low-intensity psychosocial interventions can also be used as relapse prevention. One trial suggested that the combination of a self-help intervention with a self-help book and weekly guidance in primary care could prevent relapse of depression in participants with recurrent depressive episodes (Biesheuvel 2015). Antidepressant discontinuation can also be supported by a letter with patient-specific discontinuation advice (Eveleigh 2017). This was based on previous evidence where a letter with discontinuation advice was sent to long-term benzodiazepine users in family practice followed by a follow-up consultation (Gorgels 2005). Online low-intensity interventions could offer online modules and information to patients and practitioners to support antidepressant discontinuation (ISRCTN15036829).

These findings suggest that cognitive therapy and MB-CT in combination with discontinuation of antidepressants are potential alternatives to antidepressants for preventing relapse or recurrence. However, CBT and MB-CT are resource intensive and

access to these psychological interventions is often limited. Low-intensity psychosocial interventions have the potential to reach more people.

Pharmacological treatment with benzodiazepines is suggested, by some experts, as short-term treatment to counteract insomnia associated with withdrawal (Haddad 2007; NHG 2018). However, benzodiazepines may contribute to a risk of dependence, especially in older people, and prescribing long-term benzodiazepines is not appropriate as a substitute for unnecessary antidepressant treatment (Pottie 2018; Wilson 2010).

How the intervention might work

Discontinuation of antidepressants may decrease the risk of adverse events, risk of drug-drug interactions and minimise the number of medicines whilst making no difference in depressive and anxiety symptoms. However, discontinuation might also cause withdrawal symptoms and recurrence or worsening of the original depressive or anxiety symptoms, which contributes to unsuccessful discontinuation.

The exact therapeutic mechanism of antidepressants is not known (Pringle 2011). Most antidepressants seem to increase the concentrations of monoamine neurotransmitters in the synaptic cleft (Berton 2006). The effect of most antidepressants fully develops after some weeks, indicating that neurophysiological changes of brain tissue (e.g. changes in sensitivity and frequency of receptors) occurring in the presence of a constant level of active ingredients, are necessary for improvement in depressive symptoms (Machmutow 2019). Depending on the active ingredient, antidepressants can have mood-enhancing, anxiolytic or sedative effects and are able to increase or decrease inner drive (Machmutow 2019). The rationale for continuing antidepressant treatment after clinical recovery is that it will sustain the regulation of the monoamine activity (Wilkinson 2016). However, suggesting that a single biochemical deficiency is the cause of depression and that antidepressants work by correcting chemical deficiency is too simplistic (Andrews 2015).

Various explanations for the mechanism of withdrawal symptoms when stopping antidepressants have been proposed (Fava 2015; Horowitz 2019). Daily drug treatment activates receptors, which in turn can affect the availability of several neurotransmitters that can lead to many downstream physiological consequences. When drug treatment abruptly stops, the homeostatic equilibrium is disturbed and the body's adaptive changes take time to recalibrate, resulting in a period of possible withdrawal symptoms (Fava 2015; Horowitz 2019). The neurobiological mechanism of tapering is based on the rationale that biological systems will have more time to adapt to reductions in available ligand, thus reducing the intensity of withdrawal symptoms (Fava 2015).

Additional non-pharmacology treatments can support discontinuation of antidepressants. CBT approaches focus on dysfunctional thoughts, feelings and behaviour, and learning skills (NICE 2016). MB-CT was specifically developed to reduce relapse and recurrence in depression (Piet 2011; Segal 2002). However, the exact mechanisms of preventing relapse and recurrence of psychological interventions remain unclear (Beshai 2011).

Symptoms of discontinuation of antidepressants could be treated by a short treatment of benzodiazepines. Benzodiazepines act

through binding at, and enhancing the effect of gamma-aminobutyric acid (GABA) receptors (Ma 2019). Enhancement of the effect of GABA on this receptor results in sedative, anxiolytic, hypnotic and muscle relaxant effects, thus reducing discontinuation symptoms.

It is important that practitioners should share decision making about discontinuation strategies with the patient and their relatives for successful antidepressant discontinuation.

Why it is important to do this review

Antidepressant use can be accompanied by minor adverse events as well as serious adverse events. While recommendations have underlined the importance of giving antidepressants for a sufficient length of time, there is increasing concern about the overuse of antidepressants (i.e. longer than recommended) for depression, but also for a growing number of other conditions (Kjosavik 2016; Wong 2017). Reviews suggest that 30% to 50% of long-term antidepressant prescriptions had no evidence-based indication supporting their use and that users could try to stop treatment (Ambresin 2015; Cruickshank 2008; Piek 2010).

The effectiveness of interventions aimed at discontinuation of long-term antidepressant use is unknown. Most antidepressant guidelines recommend a slow taper approach over several weeks (APA 2010; CANMAT 2016; NICE 2016). NICE recommendations for stopping antidepressants are to gradually reduce the dose, normally over a four-week period (NICE 2016). Overall, there is a lack of strong evidence supporting how best to discontinue unnecessary antidepressant use (Horowitz 2019).

Therefore we will perform a systematic review of discontinuation in participants using antidepressants for longer than recommended, defined as use of at least six months or more.

A systematic review of discontinuation trials on long-term antidepressants will assist clinicians and patients in shared decision making for an evidence-based choice for appropriate antidepressant prescribing and will have an impact on the guidelines for depressive and anxiety disorder.

OBJECTIVES

To assess the feasibility and safety of discontinuation of long-term antidepressant use for depressive and anxiety disorders in adults aged over 18 years.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), published and unpublished trials, open-label and double-blinded trials, as well as cluster-RCTs. We will include both placebo-controlled and non-placebo-controlled trials. We will exclude cross-over trials.

Types of participants

Participant characteristics

Trial participants, aged 18 years and older, using long-term antidepressants, prescribed for depressive or anxiety disorder. Long-term is defined as use of at least six months of any

antidepressant treatment. Diagnosis of depressive and anxiety disorder is defined by trial authors. We will include trials with any from the following classes of antidepressants.

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-noradrenaline antidepressants (SNRIs)
- Noradrenaline reuptake inhibitors (NARIs)
- Tricyclic antidepressants (TCAs)
- Noradrenaline-dopamine reuptake inhibitors (NDRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Other antidepressants:
 - * melatonergic antidepressants
 - * noradrenergic and specific serotonergic antidepressants (NASSAs)
 - * serotonin antagonist and reuptake inhibitors
 - * multimodal serotonin reuptake inhibitor and receptor blocker
 - * St. John's Wort (*Hypericum perforatum*) and other natural products

We will not place restrictions on the dose of antidepressant treatment.

In this review, we will use the term 'depression' to refer to the DSM-V diagnosis of major depressive disorder.

Setting

We will include trials in a range of settings (e.g. primary care, outpatient psychiatric hospital, nursing home).

Exclusion criteria

We will exclude trials that include participants with, or with a history of bipolar disorder, obsessive compulsive disorder or psychosis.

We will exclude discontinuation trials in the context of electroconvulsive therapy or hospital admission.

We will exclude discontinuation trials if participants were not treated in line with the recommended duration of treatment. Therefore, we will exclude discontinuation trials if participants have received less than six months of antidepressant treatment.

Types of interventions

We will include trials that compare discontinuation to continued antidepressant use or usual care.

Experimental Intervention

We will define discontinuation of antidepressants as one or more of the following interventions.

- Abrupt discontinuation: abruptly discontinuing an antidepressant either using placebo or no medication
- Tapering: gradually reducing the dose until complete discontinuation of antidepressant use either using placebo or no medication
- Combined intervention (high intensity): one or more high-intensity psychological interventions combined with discontinuation of antidepressants, either abruptly or tapering. Psychological interventions must have been based on a

scientific theory, with at least one contact between therapist and participant, either face to face or via telecommunication technologies. The intervention must have considered the personal needs of the participants or a group of participants. We will consider CBT, MB-CT, behaviour therapy, interpersonal therapy (IPT), behaviour modification/therapy or any other psychologically orientated interventions.

- Combined intervention (low intensity): one or more low-intensity psychosocial interventions combined with discontinuation of antidepressants, either abruptly or tapering. Low-intensity interventions are simple approaches that are less complex to undertake than formal high-intensity psychological interventions; contact with people is generally briefer than in other forms of therapy and can be delivered by para-professionals or peer supporters using non-traditional methods such as telephone or the internet. We will consider individual, guided self-help based on the principles of CBT, computerised CBT, a structured group physical activity programme or any other low-intensity psychosocial interventions.
- Discontinuation, either abruptly or tapering, with pharmacological treatment to counteract antidepressant withdrawal symptoms, for example, benzodiazepines as short-term treatment to support discontinuation and to counteract insomnia associated with discontinuation.

Comparator intervention

- Continuation of antidepressant use
- Usual care or treatment as usual, mostly continuation of antidepressant use, according to clinical judgement

Co-interventions of any kind or any kind of non-pharmacological treatment for discontinuation in the intervention and the control groups are allowed.

Types of outcome measures

We will include trials that meet the above inclusion criteria regardless of whether they report on the following outcomes.

We will use the definitions of diagnosis, response, relapse and recurrence as defined by trial authors. [Appendix 1](#) lists abbreviations of the measuring instruments used in this review.

Primary outcomes

1. Successful discontinuation rate: the proportion (%) of participants who successfully discontinued antidepressants at the end of the trial. We define successful discontinuation as:
 - a. no antidepressant use; and
 - b. absence of depressive or anxiety symptoms or diagnosis, or both; and
 - c. no drop-out before the end of the trial.
2. Relapse rate: the proportion (%) of participants who did not successfully discontinue antidepressants at the end of the

trial due to relapse or recurrence of depressive and/or anxiety symptoms and/or diagnosis. We define relapse rate as:

- a. relapse of depressive and/or anxiety symptoms and/or diagnosis after continuation; or
 - b. relapse of antidepressant use after discontinuation due to presence of depressive and/or anxiety symptoms and/or diagnosis; or
 - c. relapse of depressive and/or anxiety symptoms after discontinuation; or
 - d. dropout from the trial due to relapse to depressive and/or anxiety symptoms and/or diagnosis.
3. The presence of discontinuation symptoms (measured by Discontinuation-Emergent Signs and Symptoms (DESS) Scale (Rosenbaum 1988), symptoms assessment form, unified Parkinson disease rating scale or any relevant instrument).
 4. Any adverse events attributable to the continuation of antidepressant use.

Secondary outcomes

1. Depressive symptoms and anxiety symptoms as measured on a scale (measured by the Hamilton Depression Rating Scale (HDRS; Hamilton 1960), the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery 1997), the Beck Depression Inventory (BDI; Beck 1961), the Inventory of Depressive Symptomatology (IDS; Rush 2000), the Patient Health Questionnaire (PHQ; Spitzer 1999), Beck Anxiety Inventory (BAI; Beck 1993), the Hamilton Anxiety Scale (HAM-A) for General Anxiety Disorder (Hamilton 1959; Maier 1988), General Anxiety Disorder (GAD-7; Spitzer 2006), the Panic and Agoraphobia Scale (PAS; Bandelow 1992), or any other instrument)
2. Time to relapse after randomisation (measured in weeks)
3. Quality of life of participants (measured by Short Form 36 (SF-36; Ware 1992), Short Form 12 (SF-12; Gandek 1998), or any other instrument)
4. Social and occupational functioning (measured by Global Assessment of Function Scores (GAFS; APA 2000), Occupational Functioning Scale (OFS; Hannula 2006), or any other instrument)
5. Severity of a patient's illness assessed by a health professional (clinical global impression measured by Clinical Global Impression Change scale (CGI-C; Busner 2007), or any other instrument)

Timing of outcome assessment

We will analyse the effects of discontinuation over the short term (trials with follow-up of four weeks or less), over the titration period used in the trial, over the medium term (trials with follow-up from four weeks to six months) and long term (trials with follow-up of six months or more after discontinuation). We will prioritise outcomes over the medium term (from four weeks to six months) and long term (follow-up 6 months or more).

Hierarchy of outcome measures

We will consider the outcome measurements at the predefined endpoint of the trial.

If trials use different outcome measures, we will include data as per the following rules: in case of available data from both observer-rating scales and self-report questionnaires, we will prioritise data from observer-rating scales. We will use the DSM-V definitions for depressive disorder and anxiety disorder (APA 2013), relapse and

recurrence definitions of Frank 1991, HAM-D scale for depressive symptoms and the HAM-A for anxiety symptoms. In case of several outcome measures of the same hierarchy level used in one trial, we will select the outcome measure most frequently used across all trials. In case of several outcome measures of the same hierarchy level and the same availability across trials, we will randomly select the outcome measure. If trials do not report the HAM-D or HAM-A, where applicable we will select the outcome measure most frequently used across all trials.

Search methods for identification of studies

Cochrane Common Mental Disorders Controlled Trials Register (CCMD-CTR)

Cochrane Common Mental Disorders maintains a specialised register of RCTs, the CCMD-CTR. This register contains over 40,000 reference records (reports of RCTs) for anxiety and depressive disorders, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of this Group. The CCMD-CTR is a partially trials-based register with more than 50% of the reference records tagged to around 12,600 individually PICO-coded trial records. Reports of trials for inclusion in the register are collated from (weekly) generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trials registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) can be found on the Group's website with an example of the core MEDLINE search displayed in Appendix 2.

In 2016 the Group's Specialised Register (CCMD-CTR) became out of date with the Editorial Group's move from Bristol to York.

Electronic searches

The Cochrane Common Mental Disorders' Information Specialist will conduct searches on the following bibliographic databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

- CCMD Specialised Register (CCMD-CTR) all available years;
- Cochrane Central Register of Controlled Trials (CENTRAL; current year and issue);
- Ovid MEDLINE databases (1946 onwards) search strategy listed in Appendix 3;
- Ovid Embase (1974 onwards);
- Ovid PsycINFO (all available years).

We will not apply any restrictions on date, language or publication status to the searches.

We will search international trials registries via the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing trials.

Searching other resources

Grey literature

We will search the grey literature for dissertations and theses, clinical guidelines and regulatory agency reports (where appropriate).

- Open Grey (www.opengrey.eu/);
- ProQuest Dissertations & Theses Global (www.proquest.com/);
- DART-Europe E-theses Portal (www.dart-europe.eu/);
- EThOS - the British Libraries e-theses online service (ethos.bl.uk/);
- Open Access Theses and Dissertations (oatd.org).

Reference lists

We will check the reference lists of all included trials and relevant systematic reviews to identify additional trials missed from the original electronic searches (for example unpublished or in-press citations).

Correspondence

We will contact trial authors and subject experts for information on unpublished or ongoing trials, or to request additional trial data.

Data collection and analysis

Selection of studies

Two review authors (EVL, KA) will independently screen titles and abstracts for inclusion of all the potential trials we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text trial reports and publications, and two review authors (EVL, KA) will independently screen the full text, identify trials for inclusion, and identify and record reasons for exclusion of the ineligible trials. We will resolve any disagreement through discussion or, if required, we will consult a third review author (MVD). We will identify and exclude duplicate records and we will collate multiple reports that relate to the same trial so that each trial rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram ([Moher 2009](#)), and Characteristics of included and excluded studies tables.

Data extraction and management

We will use a data collection form to extract trial characteristics and outcome data, which we will pilot on at least one trial in the review. Two review authors (EVL, KA) will independently extract trial characteristics and outcome data from included trials. We will extract the following trial characteristics.

- Methods: trial design, total duration of trial, details of any 'run-in' period, number of trial centres and location, trial setting, withdrawals, and date of trial
- Participants: number, mean age, age range, gender, severity of condition, duration of antidepressant treatment before trial, comorbidity, setting (primary care versus outpatient psychiatric hospital versus nursing home), diagnostic criteria, inclusion criteria, and exclusion criteria

- Interventions: intervention inclusive mode of discontinuation (gradually or abruptly), comparison, concomitant treatment (psychological treatment, medications)
- Outcomes: primary and secondary outcomes specified and collected, and time points reported
- Notes: funding for trial, and notable conflicts of interest of trial authors

We will note in the 'Characteristics of included studies' table if trials did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third review author (MVD). One review author (EVL) will transfer data into the Review Manager 5 file ([Review Manager 2014](#)). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the trial reports. A second review author (KA) will spot-check trial characteristics for accuracy against the trial report.

Main planned comparisons

- Abrupt discontinuation versus continued antidepressant use or usual care
- Tapering versus continued antidepressant use or usual care
- Combined intervention (with high-intensity psychological treatment) versus continued antidepressant use or usual care
- Combined intervention (with low-intensity psychosocial treatment) versus continued antidepressant use or usual care
- Discontinuation with pharmacological treatment versus continued antidepressant use or usual care

Co-interventions of any kind of non-pharmacology treatment for discontinuation in the intervention and the control group are allowed.

Assessment of risk of bias in included studies

Two review authors (EVL, KA) will independently assess risk of bias for each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). We will resolve any disagreements by discussion or by involving another review author (MVD). We will assess the risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We will judge each potential source of bias as high, low or unclear and provide a supporting quotation from the trial report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different trials for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with the trial authors, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the trials that contribute to that outcome.

Measures of treatment effect

Dichotomous data

We will analyse dichotomous data as proportions and express the pooled estimates as odds ratios (OR) with 95% confidence intervals (95% CI).

Continuous data

For continuous data we will enter data from various scales, questionnaires and other clinical measures. We will analyse continuous data as means and express the pooled estimate as a mean difference (MD), if the trials used the same scale, or standardised mean difference (SMD), if they used different scales to measure the same outcome, with a standard deviation (SD). We will calculate a 95% CI for each estimate. We will analyse 'time to relapse' as hazard ratios where the data are provided as a time to event.

Unit of analysis issues

Participants in RCTs are the unit of analysis.

Cluster-randomised trials

We plan to incorporate results from cluster-RCTs into the review using generic inverse variance methods (Deeks 2017). With cluster-RCTs, it is important to ensure that data were analysed with consideration of their clustered nature. We will extract the intraclass correlation coefficient (ICC) for each trial. We will adjust for the clustering effect by dividing the clusters by a 'design effect'. We will calculate this using the number of participants or the mean size per cluster and the intraclass correlation coefficient (ICC). If the ICCs are not reported, we plan to request them from trial authors. If these data are not available, we plan to use estimates from similar trials to 'correct' data for clustering when this has not been done (Deeks 2017).

Trials with multiple treatment groups

For trials with two or more active treatment arms, we will undertake the following approach according to whether the outcome is continuous or dichotomous. For a continuous outcome: we will pool means, SDs, and the number of participants for each active treatment group across treatment arms as a function of the number of participants in each arm for comparison against the control group (Deeks 2017). For a dichotomous outcome: we plan to combine active treatment groups into a single arm for comparison against the control group (in terms of numbers of people with events and sample sizes) or to split the control group equally (Deeks 2017).

Dealing with missing data

Where possible, we will carry out an intention-to-treat (ITT) analysis for all outcomes. We will contact investigators or trial sponsors in order to verify key trial characteristics and obtain missing numerical outcome data where possible (e.g. when a trial is identified as abstract only). We will document all correspondence with trial authors and report which trial authors responded in the full review. We will calculate the percentage lost to follow-up in each group and report this information. We will not make any assumptions about

loss to follow-up for dichotomous or continuous data. We will then conduct a complete-case analysis and include in the analysis only participants with a recorded outcome.

Assessment of heterogeneity

We will assess heterogeneity in two ways. First, we will explore the presence of heterogeneity at face value by comparing population groups, interventions or outcomes across trials. In the case of clear face value heterogeneity, we will not pool the results. We will only perform meta-analysis when trials are sufficiently homogeneous in terms of participants, interventions, and outcomes. If there is no obvious clinical heterogeneity we will use statistical tests such as the Chi² test and the I² statistic (Higgins 2003), to determine the presence and level of statistical heterogeneity for each outcome. We will interpret the I² statistic, accompanied by a statistically significant Chi² test as follows: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% considerable heterogeneity (Deeks 2017).

Assessment of reporting biases

To minimise risk of publication bias, we will perform a comprehensive search in multiple databases, including searching for unpublished trials. We will investigate potential publication bias by using a funnel plot if at least 10 trials meet the inclusion criteria of the review.

Data synthesis

We will pool data from different trials if we consider that the trials are sufficiently similar. If a Chi² test and I² statistic indicate there is no important heterogeneity, we will use a fixed-effect model for meta-analysis. If there is evidence of important heterogeneity between trials, we will either pool only homogeneous trials, or use a random-effects model (Deeks 2017). When a meta-analysis is not possible (e.g. owing to insufficient data or substantial heterogeneity), we will describe the results for individual trials separately. We will discuss the heterogeneity of the included trials and the external validity of the review in the section 'Overall completeness and applicability of evidence'. We will use hazard ratios to compare the outcome time to relapse between trials. We will also use a random-effects model to pool trial data reported as time-to-event rates. We will calculate the primary outcomes (i.e. successful and unsuccessful discontinuation rate, relapse rate, discontinuation symptoms and adverse events due to antidepressant use) as the proportion of all participants included in both intervention groups (ITT) and as the proportion of all participants with the intention to attempt discontinuation of unnecessary antidepressants (per-protocol analysis).

Subgroup analysis and investigation of heterogeneity

We will investigate heterogeneity by conducting prespecified subgroup analyses and compare subgroups using the formal test for subgroup differences for primary outcomes

- Age group: younger than 65 years versus 65 years and older. Harms of antidepressants and a higher risk for drug-drug interactions are more common in older people with often existing polypharmacy and co-morbidities due to changed pharmacokinetics and pharmacodynamics.

- Setting: primary care versus outpatient specialist clinics. Primary care can be primary care consultation and nursing home. The setting could influence the effect due to the severity of disease treated with antidepressants in outpatient specialist clinics.
- Indication of antidepressant drugs: anxiety versus depression. The original indication could influence the success of discontinuation due to the differences in clinical presentation and management of anxiety and depression.
- Type of antidepressants: TCA versus SSRI. Type of antidepressant could influence the effect due to the higher risk of adverse events with TCAs because of their anticholinergic properties. TCAs have a comparable effectiveness as SSRIs with a less favourable risk–benefit ratio (NICE 2016).
- Duration of antidepressant treatment: one year or longer versus less than one year. The recommended duration of continuation treatment after remission varies from four months to 12 months in depression guidelines. The duration of use could influence the success of discontinuation due to the dependence on medication (Kendrick 2015)

Sensitivity analysis

We will carry out sensitivity analysis to assess the impact on the effect estimate of trials with a high risk of bias. We will test the impact of including trials assessed as high risk of bias by removing trials with at least one high risk rating in the 'Risk of bias' assessment.

'Summary of findings' table

We will include a 'Summary of findings' table, prepared using GRADEpro GDT, for seven outcomes:

1. Successful discontinuation rate
2. Relapse rate
3. Discontinuation symptoms
4. Depressive and anxiety symptoms
5. Adverse events due to antidepressant use
6. Quality of life

7. Social and occupational functioning

Two review authors (EVL, KA) will use the GRADE approach independently to assess evidence certainty for all outcomes. We will assess evidence as high-, moderate-, low-, or very low-certainty, depending on the seriousness of concern about risk of bias, imprecision, inconsistency, indirectness, and publication bias. We will present the comparisons 'Tapering versus continued antidepressant use or usual care', 'Combined intervention (high-intensity psychological treatment) versus continued antidepressant use or usual care' and 'Combined intervention (low-intensity psychosocial treatment) versus continued antidepressant use or usual care' in the 'Summary of findings' table. For each outcome in the 'Summary of findings' table we will present a summary of the available data, the magnitude of the effect size, and the certainty of the evidence. We will justify all decisions to downgrade the certainty of evidence in the footnotes of the 'Summary of findings' table.

We will prioritise outcomes over the medium term (from four weeks to six months) and long term (follow-up 6 months or more).

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ADDITIONAL TABLES
Table 1. Different classes of antidepressants

Classes of antidepressants	Examples
A. Major classes of antidepressants	
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Duloxetine, venlafaxine, desvenlafaxine, milnacipran, levomilnacipran
Noradrenaline reuptake inhibitors (NARIs)	Reboxetine
Tricyclic antidepressants (TCAs) and related	Amitriptyline, clomipramine, dosulepine, doxepine, imipramine, nortriptyline, maprotiline
Noradrenaline-dopamine reuptake inhibitors (NDRIs)	Bupropion

Table 1. Different classes of antidepressants (Continued)

Monoamine oxidase inhibitors (MAOIs)	Fenelzine, moclobemide, tranylpromine
B. Other drugs used to treat depression	
Melatonergic antidepressants	Agomelatine
Noradrenergic and specific serotonergic antidepressant (NaSSA) and related drugs	Mirtazepine, mianserin
Serotonin antagonist and reuptake inhibitors (SARIs)	Trazodone
Multimodal serotonin reuptake inhibitor and receptor blocker	Vortioxetine, vilazodone
<i>Hypericum perforatum</i> (St John's Wort)	

APPENDICES

Appendix 1. Abbreviations

BAI	Beck Anxiety Scale
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CESD	Centre for Epidemiological Studies Depression Scale
CGI	Clinical Global Impression
IDS	Inventory of Depressive Symptomatology
DESS	Discontinuation-Emergent Signs and Symptoms Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
GAD-7	General Anxiety Disorder 7-item
GAFS	Global Assessment of Functioning Score
HAM-A	Hamilton Anxiety Scale
HDRS	Hamilton Depression Rating Scale
LSAS	Liebowitz Social Anxiety Scale
MADRS	Montgomery-Åsberg Depression Rating Scale
NNTB	Number needed to treat for an additional beneficial outcome
NNTH	Number needed to treat for an additional harmful outcome

(Continued)

OFS	Occupational Functioning Scale
PAS	Panic and Agoraphobia Scale
PHQ	Patient Health Questionnaire
QALY	Quality Adjusted Life Years
SF-12	Short Form 36 Items Health Survey
SF-36	Short Form 12 items Health Survey
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic agents

Appendix 2. OVID Medline: Cochrane Common Mental Disorders' core search strategy used to inform the specialised register

A weekly search alert based on condition + randomised controlled trial (RCT) filter only

The Cochrane Common Mental Disorders Controlled Trials Register (CCMD-CTR) is current to June 2016 only (when the editorial base moved from the University of Bristol to the University of York).

1. [MeSH Headings]:

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. [Title/ Author Keywords]:

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. [RCT filter]:

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or substitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders. Secondary reports of RCTs were also tagged to the appropriate study record.

Similar weekly search alerts were also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

A quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted c/o the Cochrane Register of Studies Online (CRSO).

Appendix 3. Other database searches

We will conduct a separate search of Ovid MEDLINE, tailored to this review.

We will translate the MEDLINE search across to the other bibliographic databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 onwards>

Search Strategy (compiled April 16, 2019):

1 ((deprescrib* or de prescrib* or deprescrip* or de prescrip* or cease or cessation* or discontinu* or dropout or drop out or interrupt or interruption* or interrupting or taper* or reduce or drug holiday or (stop* adj (taking or using)) or stopping or withdraw* or withhold* or terminat*) adj4 (antidepress* or anti-depress* or ADM or mADM or psychotropic* or SSRI* or SNRI* or MAOI* or TCA* or tricyclic* or NARI or NARIs or NDIR* or SARI or SARIs or NaSSA* or ((serotonin or monoamine oxidase or MAO) adj2 inhibitor*))).ti,ab,kf. (1904)

2 deprescriptions/ (204)

3 Inappropriate Prescribing/ (2571)

4 Withholding Treatment/ (11101)

5 (deprescrib* or de prescrib* or deprescrip* or de prescrip*).ti,ab,kf. (558)

6 (stop using or stop taking or stopping treatment).ti,ab,kf. (1946)

7 (cease or cessation* or discontinu* or dropout or drop out or interrupt or interruption* or interrupting or taper* or reduce or drug holiday or stop or stopping or withdraw* or withhold* or terminat*).ti,kf,hw. (158349)

8 ((long term or longterm) adj3 (cease or cessation* or discontinu* or dropout or drop out or interrupt or interruption* or interrupting or taper* or reduce or drug holiday or stop or stopping or withdraw* or withhold* or terminat*)).ab. (3275)

9 2 or 3 or 4 or 5 or 6 or 7 or 8 (165117)

10 exp Antidepressive Agents/ (144038)

11 exp Neurotransmitter Uptake Inhibitors/ (142539)

12 exp Monoamine Oxidase Inhibitors/ (21319)

13 (psychotropic* or antidepress* or anti depress* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) adj3 (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or MAOI* or ((serotonin or monoamine oxidase or MAO) adj2 inhibit*) or TCA* or tricyclic* or NARI or NARIs or NDIR* or SARI or SARIs or NaSSA*).ti,kf,hw. (119809)

14 (Agomelatine 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 Chlropoxiten 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 Dimetacrin* or Dosulepin* or Dothiepin or Doxepin* or Duloxetine or DVS 233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fenelzine or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine).ti,kf,hw. (40793)

15 (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. (72558)

16 (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 Vortioxetine or Zalospiroone or Zimeldine).ti,kf,hw. (75794)

17 or/10-16 (326547)

18 9 and 17 (6834)

19 1 or 18 (8100)

20 controlled clinical trial.pt. (93029)

21 randomized controlled trial.pt. (480058)

22 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf. (579180)

23 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).ti,ab,kf. (488976)

24 placebo*.ab,ti,kf. (204145)
25 trial.ab,ti,kf. (544160)
26 groups.ab. (1901185)
27 (control* and (trial or study or group*) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw. (186303)
28 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf. (163907)
29 double-blind method/ or random allocation/ or single-blind method/ (264679)
30 or/20-29 (2820037)
31 exp animals/ not humans.sh. (4569557)
32 30 not 31 (2381687)
33 19 and 32 (1996)
34 *Depression/ (65673)
35 *Depressive Disorder/ (51970)
36 *Depressive Disorder, Major/ (22776)
37 drug therapy.fs. (2099633)
38 34 or 35 or 36 (133590)
39 37 and 38 (32923)
40 9 and 32 and 39 (217)
41 33 or 40 (2041)
42 (smoking or tobacco or nicotine or alcohol or substance).ti. or smoking cessation.ab,kf,hw. (238392)
43 41 not 42 (1298)

CONTRIBUTIONS OF AUTHORS

EVL: is the lead author of the protocol, wrote the protocol and developed the selection criteria and the methodology.

MVD: developed the selection criteria, the methodology, contributed to the background and carried out text editing.

ADS: contributed to the background of the protocol.

KA: contributed to the background of the protocol.

LR: commented on the methodology of the protocol.

TC: developed the selection criteria, the methodology and contributed to the background.

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