Interventions to help patients withdraw from antidepressants

Protocol for a Cochrane review

Anders K Sørensen, Marie S Bohlbro, Peter C Gøtzsche

Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark

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Background

Many patients on antidepressant drugs have tried to come off them but have failed because the withdrawal process was too difficult for them to go through; especially for people who have been taking the drugs for a long time, stopping can be a difficult process due to withdrawal symptoms (Breggin 2012; Kessing 2005). In Denmark, there is a helpline (www.benzo.dk) for such patients, and in the UK, the Council for Evidence-based Psychiatry works with the All Party Parliamentary Group for Prescribed Drug Dependence with setting up a 24 hour helpline to support people trying to withdraw from prescribed drugs, including benzodiazepines and antidepressants. The very fact that this population of patients are organizing themselves in survivor groups and various withdrawal-related initiatives around the world is a clear sign that such help is needed.

Withdrawing from psychiatric drugs can have beneficial effects for some patients because the patients may then avoid drug-induced harms, which all psychiatric drugs are capable of causing (Breggin 2012). Furthermore, studies of psychiatric drug treatment consistently show better recovery rates in the non-medicated group or the group that managed to come off after long follow up. In one randomised trial, withdrawal of such drugs in people aged 65 years and older reduced the number of falls (Campbell 1999), which would be expected to increase survival because of fewer hip fractures (Coupland 2011). Another trial, of patients with schizophrenia treated with antipsychotics and currently in the early stages of remitted first episode psychosis, showed that more patients (twice as many) had recovered in the dose reduction/withdrawal group than in the maintenance group at seven years of follow-up (Wunderink 2013). In an earlier follow-up of the same study (Wunderink 2007), the dose reduction/withdrawal group deteriorated initially before improving, suggesting the transition from medicated to drug-free is a difficult process for patients to go through. The patients in this study did not receive much psychological support or other help during withdrawal, which might be the reason for the temporary deterioration. How to help patients so they do not deteriorate but go straight to improving is the aim of our review.

Prevalence and type of withdrawal symptoms

A major reason for having difficulties coming off antidepressants is that these patients experience withdrawal symptoms upon dose reduction (Fava 2015; Nielsen 2011). A recent systematic review and meta-analysis on the prevalence of withdrawal symptoms (Davies 2018) found that 56% of patients who tried to stop or reduce antidepressant dosage experienced withdrawal symptoms, 46% of whom rated these symptoms as severe. Contradicting current guidelines, the duration of these symptoms was usually more than a few weeks, and could last months or even longer. In one of the studies reviewed, the symptoms lasted for at least 6 weeks in no less than 40% of the patients, and

in another study, they lasted 3 months for 25% of the patients (Davies 2018). A 2017 survey about the experiences, strategies and types of support during psychiatric drug withdrawal found that 54% of the patients who attempted succeeded; 54% rated the withdrawal symptoms as severe (Ostrow 2017).

We found in a systematic review that withdrawal symptoms were described with similar terms for benzodiazepines and selective serotonin reuptake inhibitors (SSRIs); 37 of 42 identified symptoms were virtually the same (Nielsen 2011). These data are in close agreement with patient reports, as around half the patients agree that their body can "become addicted to antidepressants" (Kessing 2005) or say that they have experienced withdrawal effects (Read 2014).

There is a clear overlap between the withdrawal symptoms and the diagnostic criteria for many of the diagnoses treated with antidepressants, for example depression, anxiety, panic, suicidal ideation, bouts of crying, mood swings, sleep disturbance, decreased concentration, agitation, irritability, and aggression (Fava 2015; Nielsen 2011). Because of this overlap, both clinicians and patients may confuse the two, thus resuming full dose of the drug when patients actually may be in withdrawal rather than true relapse, resulting in misguided treatment. Thus, if a dose reduction elicits the symptoms used to diagnose depression, it doesn't necessarily mean that the disease has come back. Two hallmarks of withdrawal depressions are that they usually come rather quickly and disappear within hours when the full dose is resumed (Breggin 2012).

A trial of 242 patients with remitted depression illustrates these diagnostic difficulties (Rosenbaum 1998). The patients had received open maintenance therapy with fluoxetine, sertraline, or paroxetine for 4 to 24 months after they had become well. They then suddenly had their therapy changed to a double-blind placebo for 5-8 days at a time unknown to the patients and clinicians. The investigators had developed a 43-item list based on withdrawal symptoms reported in the literature, and after the placebo period patients were asked if they had experienced any of these. The three most common withdrawal symptoms were worsened mood, irritability and agitation, which in these cases are not signs of a relapse of the depression, and one-third of the patients on sertraline or paroxetine, which have short half-lives, had an increase in their Hamilton depression score of at least eight, which is a clinically relevant increase (Leucht 2013). This study shows why doctors and patients may get it wrong when they think the disease has come back.

Some people get severe withdrawal symptoms when they try to stop, both symptoms that resemble the disease and many other symptoms including some they have never experienced before and which can frighten them, e.g. electric shock sensations in the head (Breggin 2012; Fava 2015; Nielsen 2011). The full list of identified withdrawal symptoms - as replicated and crosschecked from Nielsen 2011 and Fava 2015 - is as follows:

Flu-like symptoms, fatigue, weakness, tiredness, sleep disturbance, insomnia, vivid dreams, somnolence, headache, tachycardia, dyspnea, gait instability/unsteady gait, ataxia, dizziness, light-headedness, vertigo, sensory paresthesia, tingling, shaking, imbalance, parkinsonism, feeling tense, electric-shock sensations, myalgias, neuralgias, tinnitus, rushing noise in head, altered taste/taste perversion, pruritus, Visual changes/disturbances, blurred vision, sore eyes, tremor, myoclonus/myoclonic jerks, muscle rigidity, jerkiness, restless legs, muscle aches, convulsion, arthralgias, facial numbness, sweating, flushing, chills, nightmares, hypersomnia, lethargy, nausea, vomiting, appetite disturbance, diarrhea, anorexia, abdominal pain, nervousness, anxiety, agitation, tension, panic/sudden panic, depression, intensification of suicidal ideation, irritability,

impulsiveness, aggression, anger, bouts of crying, low mood, emotional lability, mood swings, derealization and depersonalization, visual and auditory hallucinations, detachment, confusion, decreased concentration, slowed thinking, memory problems, amnesia, delirium, catatonia, genital hypersensitivity, premature ejaculation.

Difficulties with withdrawing antidepressants

Coming off psychiatric drugs can also be difficult for psychological and emotional reasons, especially during the part of the transition from medicated to drug-free where the thoughts and emotions "come alive" again, depending on which effect the drugs have had on the person's emotions and thoughts. Anxiety, uncertainty, worry of relapse, poor emotion regulation skills and need of social support may be crucial during this phase (Bosman 2016; Leydon 2007; Lucassen 2014; Verbeek-Heida 2006). Valuable information on the experienced difficulties and barriers to psychiatric drug withdrawal can be found in patient reports (Breggin 1999; Breggin 2012; Lehmann 1998, Gøtzsche 2015, Whitaker 2010, Glenmullen 2005 and Glenmullen 2000). In addition to the medical aspects (i.e. withdrawal symptoms), many of these stories point to psychological, emotional and existential aspects of the transition from medicated to medicine-free. These have not much to do with dose reductions and tapering schemes per se but are just as relevant and legitimate obstacles to coming off, and therefore relevant for our review. Some patients refer to the discredited hypothesis about a chemical imbalance in their brain being the cause of their disorder and therefore also the reason for not daring to stop (Lucassen 2014).

There is a lack of knowledge about how to cope with the withdrawal effects in the best and safest way, and official guidelines provide little help. They often recommend cutting the dosage in half as the first step and then tapering off over a few weeks (NICE 2016; RADS 2015). Cutting the dosage in half as the first step is often possible because most patients are overdosed. But it is far too quickly after this initial step, and rarely leads to successful withdrawal (Eveleigh 2014; Breggin 2012; Glenmullen 2000; Kessing 2005). In one withdrawal study using these official guidelines, only 4 of 70 patients randomized to withdraw antidepressant drugs succeeded (Eveleigh 2014). Since millions of patients can be expected to have become dependent on antidepressant drugs worldwide (Davies 2018), there is a pressing need to do research on interventions aimed at helping patients withdraw from antidepressant drugs and to review it.

Description of the condition

The patients' condition is best described as drug dependence, not because we, and the patients themselves, see them as addicts, but because the absence of withdrawal symptoms is obtained by continuous drug intake. The main challenge is therefore to taper the drugs in a way that minimizes the withdrawal symptoms and to support the patient during the process to increase the chance of a succesful outcome During withdrawal some of the original mental health problems can surface, because the drugs have only provided symptomatic relief. Hence, psychotherapy during withdrawal can be helpful for some patients. Since the drugs can cause emotional blunting, it can be challenging for the patients to deal with the naturally fluctuating emotional life that has been suppressed for so long, which means that psychotherapy involving emotion regulation, or other social support can be helpful.

People taking antidepressant drugs who wish to come off is a very heterogeneous population. The patients have many different reasons for wanting to come off and the obstacles for succeeding are

also different. It can also be the clinician who takes the initiative to safely and comfortably withdraw the medication.

Description of the intervention

The interventions of interest are broadly defined, and we include anything that can facilitate and ease the withdrawal process. These can be different speeds, different dose reduction schemes, tapering guidelines, tapering support, medical advice, psychotherapy, mindfulness, peer support, addition of other drugs, and whether the patient or the health care professional manages the process.

The most obvious and obligatory intervention is to reduce the dose slowly and gradually so that the nervous system has enough time to readapt, which will reduce the intensity and incidence of withdrawal symptoms. To our knowledge, there is no standard procedure about how to do this and not much science that can guide us.

How the intervention might work

Many patients who have managed to come off antidepressants report that it has resulted in a better life overall, especially because they no longer suffer from drug harms. Different interventions have different mechanisms of action that cannot be described as one particular way of working, except easening the withdrawal period.

Why it is important to do this review

About half of the hundreds of millions of people who take antidepressants have become dependent on them (Davies 2018; Gøtzsche 2015; Kessing 2005; Read 2014) in the sense that reducing the current dose will elicit withdrawal symptoms, which may lead to unsuccessfull attempts at coming off. It is evident that it would be beneficial for many patients' health to come off the drugs, particularly considering their long-term harms, which might involve long-lasting brain damage (Breggin 2012; Gøtzsche 2015) including permanent sexual dysfunction (Healy 2018; Hogan 2014; Simonsen 2016).

Objectives

To assess the effects of different interventions aimed at helping patients come off antidepressant drugs safely.

We seek to describe and review the efficacy of any intervention aiming at stopping treatment with an antidepressant drug.

Methods

Criteria for considering studies for this review

Types of studies

Studies of interest are those aimed at helping patients, through various interventions, come off any antidepressant drug completely. We will include randomised trials, also cluster randomised trials. All other types of studies on the subject will be excluded from the main analysis but might be described narratively in the Discussion section, if appropriate.

Types of participants

People taking antidepressant drugs who wish to come off them. We are interested in withdrawal irrespective of age, sex, setting, diagnosis of depression, types of antidepressants, or the reason for wanting to come off.

Types of interventions

Any type of intervention aimed at helping patients withdraw from antidepressant drugs will be included. These may vary in terms of duration, speed, dose reductions, use of psychotherapy or other drugs, tapering support, medical assistance and degree of health care professional involvement. No types of interventions will be excluded, as long as the study measures antidepressant drug withdrawal.

Types of outcome measures

The primary outcome is complete cessation of antidepressant drug use. Studies that meet the inclusion criteria will be included regardless of whether they report on the following outcomes.

Primary outcomes

Successful withdrawal – whether or not the patient succeeds stopping treatment with an antidepressant drug.

The primary outcome is complete cessation of antidepressant drug use.

Secondary outcomes

Incidence of withdrawal symptoms, e.g. as measured by the Discontinuation-Emergent Signs and Symptoms scale (DESS), such as anxiety, irritability, mood swings, shaking, fatigue, dizziness, fever, increased dreaming (Fava 2015: Nielsen 2011), all of which are characterized by being temporary and related to recent dose reduction.

Severity of withdrawal symptoms – also measured for example by the DESS and by patient reports of their experiences, especially if and to what extent they interfere with normal life and function.

Quality of life (as measured by various questionnaires, e.g. the World Health Organization Quality of Life (WHOQOL) or The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-les-Q).

Patient views on their drug-free state (preferably measured by qualitative interviews).

Search methods for identification of studies

Electronic searches

PubMed search on: (antidepressants[MeSH Terms]) AND (withdraw* or taper* or discontinu* or stop* or coming off* or cessat*).

Searching other resources

We will scan reference lists of relevant articles and will contact authors to obtain additional information if needed and to ask about ongoing research. We will use the "related articles" feature in PubMed to identify additional studies.

Data collection and analysis

Selection of studies

We will include randomised trials. Screening of titles and abstracts will be performed by one observer. When in doubt, the second observer will be consulted. All relevant articles will be read in full by both observers independently.

Data extraction and management

Two observers will independently extract relevant information from studies meeting the inclusion criteria. Any disagreements will be resolved by discussion. We will use standard Cochrane methods and software. For the searching and screening part of the process, and for data extraction, we will use Excel. Review Manager will be used for meta-analyses. Studies in languages we cannot read will be translated. We will contact authors regarding missing data.

We will use endpoint scores if possible. If we need to combine change scores with endpoint scores, we will use the inverse variance method.

Data will be extracted using a standardised and piloted extraction form with the following types of data:

- Number of patients in the study.

- Number of patients stopping the antidepressant drug.

- Patient views of the drug-free state (see ”secondary outcomes” above).

- Tapering scheme (how the dose reductions were performed).

- Interventions used.

- Diagnosis.

- Duration of drug treatment.

- Starting dose.

- Type of antidepressant (e.g. SSRI (serotonin-norepinephrine reuptake inhibitor), SNRI (serotonin-norepinephrine reuptake inhibitor), TCA (tricyclic antidepressant), MAOI, (monoamine oxidase inhibitor).

- Authors' own conclusion, especially regarding the ability of coming off the drugs considering the limitations of the study.

- Authors' own considerations and discussion regarding withdrawal symptoms and relapse.

If feasible, these different variables will be object for subgroup and sensitivity analyses.

Skewed data will be handled according to the Cochrane Handbook for systematic reviews, section 9.4.5.3.

Assessment of risk of bias in included studies

We will assess the risk of bias independently according to the Cochrane Handbook, and external validity using the GRADE tool (chapter 11 in Handbook). We will use the 5 bias domains (selection bias, performance bias, detection bias, attrition bias and reporting bias) and judge whether there is a high, low or unclear risk of bias. The two review authors will do this independently and any disagreements will be resolved by discussion.

Measures of treatment effect

Dichotomous data

Whether the patient comes off or not will be reported as a risk ratio with 95% confidence intervals.

Continuous data

Continuous data will be analysed using the mean difference and standardised mean difference (SMD) as appropriate.

Unit of analysis issues

If the available data allow this, cluster randomised trials will be included using statistical methods that allow analysis at the level of the individual while accounting for the clustering in the data. The specific method used will depend on the design of the study and may include multilevel models, variance components analysis or Generalized Estimating Equations.

For cluster randomised trials, see the Cochrane Handbook, section 16.3.

For multiple treatment arms, we will combine groups to create a single pair-wise comparison, see the Cochrane Handbook, section 16.5.4.

Dealing with missing data

We will contact the original investigators to request missing data; if these data remain unavailable to us, we will try to perform intention to treat (ITT) analysis, in which it will be assumed that patients who dropped out did not come off the drug.

Assessment of heterogeneity

Clinical and methodological differences between trials will be assessed before it is decided whether any meta-analysis would be feasible. Meta-analysis will only be performed when studies are sufficiently homogeneous in terms of outcomes, interventions and participants. Heterogeneity between the trials will be assessed using I^2 statistics, which describe the variation between trials in relation to the total variation.

Assessment of reporting biases

In order to reduce the risk of publication bias, we will ask the authors for further data if the study design implied that data on outcomes other than the ones reported exist. We will also search for unpublished studies. The existence of publication bias will be explored by means of funnel plot analysis if at least 10 trials are available.

Data synthesis

Data synthesis will be done in Review Manager 5.3. If studies are considered clinically and methodologically suitable to be combined, a meta-analysis will be conducted using a random effects model. If studies of variable quality are pooled in the same meta-analysis, this will be noted. The studies not suitable for meta-analysis will be described narratively.

Other relevant studies will only be mentioned narratively, in our Discussion section.

We will prepare a summary of findings table in accordance with the Cochrane Handbook and GRADE for the primary outcome.

Subgroup analysis and investigation of heterogeneity

If the data permit this, we will do two subgroup analyses, dividing the studies into two groups of about equal size, those with drugs with a short and a long half-life, respectively. Active metabolites will count for this division.

Sensitivity analysis

We will do a sensitivity analysis where only those studies are included where the patients took the initiative to getting their drug withdrawn. Such patients might be more motivated to endure any withdrawal symptoms, which might result in greater success rates.

Results

Discussion

Authors' conclusions

Acknowledgements

Contributions of authors

AS and PCG contributed about equally to writing the protocol; MB will be second observer.

Declarations of interest

We have no conflicts of interest.

Differences between protocol and review

Published notes

Characteristics of studies

Summary of findings tables

Additional tables

Add Table

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References to studies

Other references

Additional references

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- Nordic Cochrane Centre, Other

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External sources

- No sources of support provided

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Appendices

1 OVID Medline: CCMD's core search strategy used to inform the specialised register

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