Newer generation antidepressants and withdrawal effects: reconsidering the role of antidepressants and helping patients to stop

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Abstract

In England, the prescribing of antidepressants, primarily the newer generation antidepressant classes, has steadily increased over recent years. There is ongoing debate about how the efficacy of these drugs is viewed, their place in therapy and the harms associated with stopping them. Much of the evidence of their efficacy comes from short-term placebo-controlled trials which tend not to include outcomes that are of greatest relevance to patients, such as social functioning or quality of life, but rather restrict outcomes narrowly to symptom measures. On such measures these studies do not demonstrate clinically significant differences from placebo for depression. A range of adverse effects are also recognised, often greater in naturalistic studies of long-term antidepressants users than those measured in short-term efficacy studies, including emotional numbing, sexual difficulties, fatigue and weight gain. There is increasing recognition that withdrawal symptoms from antidepressants are common and that these symptoms can be severe and long-lasting in some patients. Recent guidance on how to stop antidepressants in a tolerable way has been presented by the Royal College of Psychiatrists. We believe that increasing awareness about the difficulty that some patients have in stopping antidepressants should lead to more cautious prescribing practice, with antidepressants given to fewer patients and for shorter periods of time. This article discusses the perceived benefits and harms of antidepressant use.

Key learning points

- There continues to be considerable uncertainty about the benefit of antidepressant use in the short- and long-term.
- There is increasing recognition of the possibility of severe and long-lasting withdrawal symptoms from antidepressants.
- In light of the uncertain balance of benefits and harms, we should revisit widespread—and growing—prescribing of antidepressants.
- New guidance on how to stop antidepressants in a tolerable way has been produced by the Royal College of Psychiatrists, though these methods require further research, especially regarding the optimal approach for a given individual.

Introduction

The prescribing of antidepressants, primarily the newer generation antidepressant classes—selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)—has steadily increased over recent years, and it is estimated that 7.8 million patients received at least one prescription for an antidepressant in 2019/20 in England.[1] This represents prescription of an antidepressant to one in six adults (with prescription rates 50% higher for women),[2] similar to that throughout the Western world.[3,4] The escalation in the prescription rate of antidepressants has led to much debate, especially in relation to the appropriateness of the increase, factors influencing the use of antidepressants, and how the efficacy of these drugs is viewed and their place in therapy.[5–8] More recently, there has also been a realisation that the harms associated with stopping antidepressant therapy are more serious than previously acknowledged.[9] Indeed, one reason for the increasingly long-term use of antidepressants is likely to be the difficulty that patients have in stopping these medications.[10] Here we consider some of the issues relating to the evidence of efficacy of antidepressants and discuss the problems associated with withdrawing from antidepressant treatment.

Questions relating to efficacy

Much of the evidence of the efficacy of antidepressants comes from placebo-controlled trials lasting 6–12 weeks.[11] Several meta-analyses of these studies, largely focusing on newer generation antidepressant classes (SSRIs and SNRIs), have found that the difference between antidepressant and placebo is about 2 points on the Hamilton Depression Rating Scale (HAM-D)[11–13]; this is a clinician-rated scale for the assessment of depression severity

in patients who have been diagnosed with a depressive disorder, and ranges from 0 to 52 points with higher scores representing greater depression severity. However, this difference between antidepressant and placebo does not meet the threshold for a clinically important difference. For example, the National Institute for Health and Care Excellence (NICE) had previously used a 3-point difference as its threshold for clinical importance in its 2004 guideline on the management of depression.[14] One analysis of 5000 patients has suggested that NICE's threshold was too liberal and that more than a 6-point change on the HAM-D was required for 'minimal improvement' to be detected by a clinician, whereas a change on the HAM-D of 3 points or less corresponded to 'no change'.[15 16] A comprehensive recent analysis has confirmed that a minimal clinically important difference on the HAM-D ranges between 3 and 5 points.[17]

Nevertheless, some authors have argued that the small differences in rating scales scores produced by SSRI antidepressants constitute a worthwhile effect, postulating a sub-group with greater than average response.[8] However, recent analysis has found that there is not significant heterogeneity in antidepressant response and the published data are compatible with a 'near-constant treatment effect' across all patients, suggesting that a highly responsive sub-group is unlikely.[18] Indeed, although earlier analyses supported the idea that people with more severe depression show stronger responses to antidepressants,[19] more recent analyses find the effect is uniform across all baseline severity, with antidepressants having less than a 3-point difference on the HAM-D for mild, moderate and severe depression.[20–22]

These studies all involved adults, but it should be noted that the findings in adolescents and children are even less convincing.[23] A recent *Cochrane* review found no antidepressant had a clinically significant effect compared with placebo, leading the authors to question 'whether they should be used at all', especially considering some antidepressants increased suicide risk compared with placebo in this population.[24] Re-analysis of original clinical study reports from adolescent trials suggests that the published accounts of studies exaggerated benefits (for example, by switching reporting to outcomes not specified in the protocol) and under-reported risks (for example, by coding suicide attempts in the antidepressant group as 'emotional lability').[23 25] The number of 12- to 17-year-olds prescribed antidepressants more than doubled between 2005 and 2017.[26]

Regulatory issues

Since 2013, the European Medicines Agency's (EMA's) guideline on the assessment of the efficacy of drugs for treatment of major depressive disorder has required evidence from double-blind, randomised and parallel group trials against placebo and an active comparator ('generally accepted standard treatment').[27] Improvement is assessed on the difference between baseline and post-treatment depression scores with a 50% improvement on 'a usual rating scale' regarded as a clinically relevant response by the EMA, although this has not been demonstrated empirically.[12 17]

Sometimes small differences in treatment effect are exaggerated by dichotomisation of the data into the artificial categories of 'response' and 'non-response' (partly driven by the EMA's requirements), although these categories have little demonstrated clinical relevance.[12 17] Furthermore, dichotomising continuous data is recognised to increase the risk of false positives and create spuriously inflated effect sizes.[12 28] The effects of antidepressants in these studies are also probably inflated by unblinding of participants on antidepressants by noticeable adverse effects,[29] and the practice of taking patients abruptly off antidepressants to allocate them to placebo.[12] Lastly, most of these studies do not include outcomes that are of greatest relevance to patients, such as social functioning or quality of life, but rather restrict outcomes narrowly to symptom measures.[12]

Additionally, these studies of 6–12 weeks' duration are largely uninformative for the clinical treatment of depression, which often involves treatment with antidepressants for months or years.[12] Indeed, longer studies of antidepressants show poor outcomes; in the STAR-D trial only 108 (2.7%), out of 4041 participants who originally enrolled in the study, achieved remission and did not relapse or drop out at the endpoint of the study at 12 months.[30] There is a lack of data comparing outcomes for depression for people taking or not taking antidepressants over the long-term—one systematic review (24 studies, 3901 participants) found that outcomes (defined variously as recurrence, relapse, remission or recovery) did not vary between patients treated with antidepressants and untreated patients.[31] Further research of long-term outcomes is required and absence of evidence does not constitute evidence of absence. Despite these questions over the evidence for efficacy, NICE continues to recommend antidepressants as an option for people with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention.[32]

Harms of long-term use of antidepressants

Adverse effects of antidepressant use are also recognised, and are often greater in naturalistic studies of long-term antidepressant users than those measured in 6–12 week efficacy studies.[33 34] In a population of patients on antidepressants (average use about 1 year) recruited from primary care for a research study, 64% of people on an SSRI had at least one adverse effect, with 31% having three or more.[34] About a fifth of patients on SSRIs report sleepiness during the day, dry mouth, profuse sweating or weight gain.[34] A quarter of patients report sexual dysfunction, and about one in 10 report restlessness, muscle spasms or twitching, nausea, constipation, diarrhoea or dizziness.[34] In a survey of a self-selected population on long-term antidepressant use (62.5% for >3 years) adverse effect rates were even higher, with 71% reporting emotional numbness, 70% reporting feeling 'foggy or detached', 66% reporting sexual difficulties, and 63% reporting drowsiness.[33]

Withdrawal effects

In relation to adverse effects, long-term use also puts people at risk of having withdrawal problems when they stop using their antidepressant. Withdrawal effects from SSRIs have been described in the literature for 30 years,[35] and a report by a Committee on the Safety of Medicines expert working group in 2004 concluded that all SSRIs may be associated with withdrawal reactions, including some that are severe and disabling to the individual.[36] It has been argued that a focus on the hypothesised notion that antidepressants correct an underlying serotonergic deficiency, propagated by their manufacturers, but now widely recognised to be unsupported by evidence, has obscured recognition of the actual effects of artificially elevating an endogenous neurotransmitter which would be expected to cause adaptation, dependence and withdrawal effects.[37]

A recent review published by Public Health England noted that 17 placebo-controlled trials (6729 participants) looked at withdrawal symptoms, such as insomnia, depression, suicidal ideation and physical symptoms, that might follow when patients stop taking medication, though the evidence was mostly very low to moderate quality.[2] A systematic review (n=24 studies, 8737 participants) of the research literature on the incidence, duration and severity of antidepressant withdrawal reactions found that about half of patients who stopped taking different classes of antidepressants, either abruptly or tapered, experienced withdrawal symptoms.[9]

The proportion of patients affected differed only slightly between randomised controlled trials (54%), observational cohorts (53%) and surveys of patients (57%).[9] The review also found that some patients reported withdrawal effects that last several months and even years. Severity was not often measured in these studies, but in those surveys which asked about this, 46% of patients reported that effects were severe.[9] It may be possible that these surveys captured a self-selected group of patients with more severe withdrawal effects than average, but it is striking that in these studies a relationship between duration of exposure to the antidepressant and severity of withdrawal effect was reported.[9] There is also a group of patients for whom withdrawal from antidepressants causes debilitating symptoms, leading to job loss, disability, relationship breakdown,[2 38] and suicide.[39]

The recognition that withdrawal effects from antidepressants are more common, more long-lasting and more severe than previously recognised prompted the Royal College of Psychiatrists to issue a position paper,[40] alerting prescribers to this issue, including the recommendation that patients be informed of this risk when discussing initiation of an antidepressant. In 2019, NICE also updated its guidance on antidepressants to reflect these risks with the recommendation that people are advised that 'while the withdrawal symptoms which arise when stopping or reducing antidepressants can be mild and self-limiting, there is substantial variation in people's experience, with symptoms lasting much longer (sometimes months or more) and being more severe for some patients'.[32 41]

Relapse or withdrawal effects?

This recognition of withdrawal effects should also modify our perspective on those antidepressant trials which are purported to show relapse prevention properties.[42 43] These studies are discontinuation studies in which a group of patients already established on antidepressants (and showing a good response) are randomised to either continue or stop their antidepressant.[42] An increase in scores on a depression scale indicates relapse. One authoritative systematic review of these studies found that 41% of patients randomised to stop their antidepressants relapsed, while only 18% of those who continue their antidepressant relapsed.[42] This review formed the basis of the current NICE guidance for use of antidepressants to prevent relapse.[32]

However, withdrawal effects, which include anxiety, insomnia, depression, and appetite changes, all register on depression scales, and so these withdrawal effects in the discontinued group are likely to inflate the apparent relapse rate in this group.[43 44] As the average period taken to stop the antidepressants in the studies included in the meta-analysis that provided these data was 5 days (in patients who had been on antidepressants for months and years), withdrawal effects may account for the majority of 'relapses' recorded in these studies.[43] One study, in patients who had been on maintenance treatment for a mean of 11 months, found that withdrawal effects produced by abruptly stopping sertraline or paroxetine for 5–8 days were severe enough for 19–27% of patients to experience an increase of 10 HAM-D points, sufficient for many to meet criteria for relapse (which resolved on restarting the antidepressant).[45] Consequently, discontinuation studies that are thought to demonstrate the relapse prevention properties of antidepressants are at high risk of bias because of confounding withdrawal effects for relapse, rendering these studies 'uninterpretable', leading to considerable uncertainty regarding the extent of relapse prevention properties attributed to antidepressants.[43]

This confounding of relapse by withdrawal effects is perpetuated in a recent discontinuation study.[46] In this discontinuation study, which attracted considerable media coverage, patients were randomised to either continue maintenance treatment with antidepressants or to discontinue them over 8 weeks (halving the dose for 4 weeks, then having half the dose every second day for 4 weeks, before stopping the drugs). The maintenance group showed a 39% relapse rate in the following 12 months, with 56% of the discontinuation group relapsing. Withdrawal effects, measured on a scale of 15 withdrawal symptoms (the modified Discontinuation Emergent Signs and Symptoms [DESS]), were considerable in the discontinuation group—almost triple that in the maintenance group at 12 weeks, and still present even 12 months after stopping. As described further below, this pronounced withdrawal effect is not surprising for such a rapid tapering phase, which is inconsistent with current guidance on slow tapering over months for people on long-term treatment (the patients in the study had been on the drugs for >2 years).[47]

However, the possibility that withdrawal effects would register on the scale used to detect relapse (the rCIS-R), and thereby artificially elevate the levels of detected relapse in the discontinuation group, was neglected by the authors. This is an obvious concern as the rCIS-R measures the domains of depressed mood, anhedonia, depressive thoughts, fatigue, loss of concentration, and sleep disturbance; all of these are recognised withdrawal effects from antidepressants, and indeed the withdrawal scale used in the study measured 'confusion or trouble concentrating', 'brain fog, forgetfulness or problems with memory', 'trouble sleeping, insomnia', 'fatigue, tiredness', while other authoritative sources identify anhedonia, depressive thoughts and mood as cardinal symptoms of withdrawal.[45 48 49] The notion that relapse was confounded by withdrawal effects is strengthened by the strong correlation between withdrawal effects (as scored on the modified DESS), with mood and anxiety symptoms throughout the study, as well as the fact that relapses in the discontinuation group occurred almost exclusively within 12 weeks of stopping medication, the time during which withdrawal effects were most pronounced.

It is important to acknowledge the uncertainties over the effectiveness of antidepressants and the impact that withdrawal effects can have on patients. Although antidepressants might have a role for some people with severe depression, widespread long-term use of antidepressants is probably inappropriate. Hence, it is important that in relation to antidepressants there should be shared decision-making between the healthcare professional and the patient, with appropriate discussion of short- and long-term harms and benefits.

Stopping antidepressants

The process of stopping antidepressants can be difficult for some people as the withdrawal symptoms can interfere with professional and social roles. However, it should be noted that most difficulties occur in patients who come off these drugs quickly, and patients who come off more gradually (see below) generally have a more tolerable experience.[48 50] Therefore, patients should be informed of the risk of withdrawal effects on stopping and in particular the problems associated with rapid withdrawal. It should be noted that for some people it may not be possible to stop their antidepressants, even with gradual tapering, either because the withdrawal effects are too aversive, or their professional or social duties preclude the disruption caused by the process; patients considering antidepressant treatment should be made aware of this possibility. Withdrawal from antidepressant therapy should not be imposed on patients, but those who are prepared to undergo this process should be supported to do so.[51]

Patient factors

Patients may be motivated to stop by the likelihood of reducing adverse effects such as sexual dysfunction, emotional numbing,

drowsiness, insomnia, weight gain and agitation, among many others.[33 34] Although many of these adverse effects can improve on stopping, there is evidence that some adverse effects can persist after cessation,[52] including sexual dysfunction, now recognised as 'post-SSRI sexual dysfunction' by the EMA.[53] Patients who are considering stopping should be made aware of this possibility; equally so, patients considering starting should be aware that there is a small risk of permanent effects.

Other patients may need further support in developing non-pharmacological coping strategies or wait for a moment in their lives conducive to tapering. A recent meta-analysis (four randomised controlled trials, 714 participants) found that a psychological intervention (including mindfulness-based or preventative cognitive therapy) along with tapering of antidepressants was no different in terms of outcome than continuing antidepressants.[54] As there is widespread variation between individuals in their response to stopping medication, some may not find it difficult—these differences may only be evident after a test reduction.

How to discontinue

How should we help patients reduce and stop their antidepressants? We must first acknowledge that there is a paucity of evidence to answer this question: in a recent *Cochrane* review only 33 randomised controlled trials examining antidepressant discontinuation were identified.[44] The majority of these were uninformative because they mostly stopped antidepressants abruptly or in less than 4 weeks, only one measured withdrawal symptoms, and most were at high risk of bias because detection of relapse was confounded by withdrawal symptoms.[44] There are observational trials that have found that tapering antidepressants over months and to doses much lower than those used in clinical practice generally have better outcomes than tapering over weeks to 25% or 50% of the dose of currently available tablet formulations.[55] In particular, one observational study found that reducing doses over months down to as low as 0.5% of clinically used doses (eg, 0.1 mg of paroxetine and 1 mg of venlafaxine) allowed the majority (71%) of a group of patients to cease their antidepressant.[50] Notably, two thirds of this group had been unable to stop antidepressants with conventional methods.[50] The practical issues relating to reducing to these doses are discussed below.

The Royal College of Psychiatrists has recently published updated guidance on how to stop antidepressants, endorsed by the Royal Pharmaceutical Society, the Royal College of General Practitioners and NICE.[47] This guideline was derived from existing studies, pharmacological principles relevant to tapering antidepressants,[55] and expert consensus including from experts by experience.[48] There is a clear need for further studies to clarify these principles, including establishing how to determine the ideal taper method for a given individual. It is worth bearing in mind that the current NICE guidance suggesting tapering antidepressants over 4 weeks was based on a single trial demonstrating that stopping antidepressants abruptly caused significant withdrawal effects[45]; it was the consensus of the panel that 4 weeks was a reasonable period of time for tapering.[56]

The main principles espoused by guidance from the Royal College of Psychiatrists, supported by patient accounts[48 57] and a review of observational trials,[55] is that tapering antidepressants by small amounts over a long enough period can minimise withdrawal symptoms to tolerable levels. Patients should be informed about the process so that they expect withdrawal symptoms and are not alarmed by them,[47] and that slow and cautious tapering can prevent these symptoms from being severe or debilitating, and often no more than mild.

According to the Royal College of Psychiatrists' guidance, patients should be advised to start with a test reduction—as small as 5% of their current dose of antidepressant if they have had difficulty in the past, or as large as 25–50% if they are in a low risk category for withdrawal.[47] Their withdrawal symptoms can be monitored for the following 2–4 weeks by using, for example, a withdrawal symptom checklist such as the DESS,[45] and subsequent reductions made based on the tolerability of this process.

As outlined in a recent paper, the relationship between dose of antidepressant and its effect on the serotonin transporter is hyperbolic.[55] That is, consistent with the law of mass action, the increase in effect on target receptors rises steeply for small total dosages of antidepressant, and then flattens out at clinically employed doses. In fact, this relationship between dose of antidepressant and myriad cellular and clinical effects observe this hyperbolic relationship.[58 59] This relationship suggests that reductions should be made according to a hyperbolic pattern, whereby reductions need to be made in smaller and smaller decrements as the total dosage gets lower in order to produce even reductions in effect on target receptors (and other biological processes).[55] This process can be roughly approximated by exponential reductions—for example, 10% of the most recent dose—so that the reductions become smaller and smaller. The final dose before completely stopping antidepressants should be very small to prevent the reduction in effect at receptors from being larger than the reductions previously tolerated, an idea supported both by an increased understanding of receptor occupancy and an observational trial described above.[50] This requires that most antidepressants need to be tapered down to a fraction of a milligram for that sub-set of patients who experience significant withdrawal effects in the course of stopping.[47 55]

Practical considerations

The gradual reductions in dose and the very small final doses required for pharmacologically-informed tapering will necessitate the use of formulations of medication other than the commonly available tablet forms.[55 57] Some possibilities for useful formulations include liquid versions (available for commonly used SSRIs, and for SNRIs, except duloxetine, in the UK, some as 'Specials'). 'Tapering strips' (tablets manufactured in smaller doses) are available from Holland, although their cost is not currently covered by the National Health Service (NHS).[57] Given the barriers to accessing some of these solutions, many patients are currently forced to resort to opening capsules and counting individual beads, or using nail files to remove parts of tablets and jeweller's scales to measure weight or crushing tablets to make suspensions of medication.[48 60] With greater support provided for these patients—for example, by prescribers providing appropriate formulations, with advice from pharmacists—the need for such kitchen pharmacology could be avoided. As this process may be challenging for some patients, specialist services dedicated to helping patients withdraw from antidepressants will be needed.

Supporting patients

During this process of tapering antidepressants, many affective and physical symptoms can arise and patients may benefit from increased psychosocial support, including mindfulness,[54 61] acceptance,[62] peer group support,[48 63] and individual support[64] as outlined in guidance that was facilitated by the All-Party Parliamentary Group for Prescribed Drug Dependence.[64] The recent Public Health England report on prescribed drugs of dependence, including antidepressants, identified a need for more services for people who wish to stop their antidepressants and signalled a plan by NHS England to create tiered services to enable this.[2] This will involve training of primary and secondary care staff to assist with

de-prescribing antidepressants. There are currently no dedicated NHS services to support antidepressant de-prescribing, while there are third sector de-prescribing support services in England, and one long-running service provided by the NHS in North Wales. These services will need to be emulated and expanded throughout the NHS, with pilot services being set up in some parts of the country.

It should also be noted that it is not certain whether gradually tapering off antidepressants will prevent all the consequences of withdrawal or the persisting adverse effects of long-term use of these drugs. From clinical experience and pharmacological principles, such tapering is thought to reduce the morbidity caused by antidepressant withdrawal; however, there is no guarantee that patients will avoid consequences such as long-lasting sexual side effects or persistent withdrawal symptoms even with a cautious taper.[52] Nevertheless, gradual tapering remains the central principle of harm reduction when approaching withdrawal from these drugs.

Conclusion

There continues to be considerable uncertainty about the benefits of antidepressant use in the short- and long-term, particularly in regard to the lack of a clinically significant difference between antidepressant and placebo treatment. There is increasing recognition of the possibility of severe and long-lasting withdrawal symptoms from antidepressants. This recognition casts doubt on the relapse prevention properties of antidepressants as these properties have been demonstrated in discontinuation trials in which withdrawal effects may have inflated relapse rates. Antidepressants can have significant adverse effects, which appear to be greater in longer-term use compared with short-term efficacy trials. In light of this uncertain balance of benefits and harms, we should re-visit the widespread—and growing—prescription of antidepressants.

New guidance on how to stop antidepressants in a tolerable way has been presented by the Royal College of Psychiatrists, drawing on relevant pharmacological principles, observational trials and clinical experience (including that of experts by experience). These methods require further research, especially regarding the optimal approach for a given individual. This approach to tapering also presents practical challenges to the health system in terms of the small doses suggested, necessitating the use of formulations other than readily available tablets. Pharmacists will have an important role to play in assisting patients to implement this new guidance. Current practice should be guided by the knowledge available; the uncertainty in guidance can be managed by shared decision making. Given the considerable challenges involved for some patients in coming off their antidepressants, it should be recognised that for some, perhaps especially long-term users, the harms of stopping medication may be greater than the risks of continuing. Increasing knowledge about the difficulty that some patients have in stopping antidepressants should lead to more cautious prescribing practice—with antidepressants given to fewer patients, for shorter periods of time.

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