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Strategies to Reduce Use of Antidepressants

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Abstract

Antidepressant prescribing has increased year on year since the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the 1980s. More than 10% of adults in England are now taking antidepressants for depression/anxiety, with a median length of treatment of more than two years, but antidepressants can cause side effects and withdrawal symptoms which increase with longer use. Surveys of antidepressant users suggest 30-50% have no evidence based indication to continue, but coming off antidepressants is often difficult due to fears of relapse, withdrawal symptoms, and a lack of psychological treatments to replace maintenance treatment and prevent relapse. GPs should not prescribe antidepressants routinely for mild depressive/anxiety symptoms. Patients starting antidepressants should be advised that they are to be taken for only a limited period, and that there is a risk of withdrawal problems on stopping them. Prescribers should actively review long-term antidepressant use and suggest coming off them slowly to patients who are well. The relationship between SSRI dose and serotonin transporter receptor occupancy suggests that hyperbolic tapering regimes may be helpful for patients with troubling withdrawal symptoms who cannot stop treatment within 4 to 8 weeks, and tapering strips can allow carefully titrated slower dose reduction over some months. Internet and telephone support to patients wanting to reduce their antidepressants is being trialled in the REDUCE programme. More research is needed to establish the incidence of withdrawal symptoms in representative samples of patients coming off antidepressants, and large randomised controlled trials are needed to test different tapering strategies.

(Word count 250)

Increasing antidepressant prescribing over three decades

Antidepressant prescriptions have been increasing steadily in England, as in other western countries, ever since the selective serotonin-reuptake inhibitors (SSRIs) were introduced at the end of the 1980s, with a doubling time of around 10 years [1, 2]. In England 71 million antidepressant items were dispensed in 2017-18 [1] (see Figure 1).

Most of the rise in antidepressant prescriptions in England is due to rising SSRI prescribing [1] (see Figure 2). Prescribing of tricyclic (TCA) and related antidepressants, has been increasing more slowly, with a trajectory not much greater than the rise in the population; they have tended to be used less and less for depression and anxiety since the advent of the better-tolerated SSRIs, but may still be used for insomnia especially in the elderly, to avoid using benzodiazepines (as may mirtazapine), and are increasingly being used for neuropathic pain (as may duloxetine) [3]. Most of the increased prescribing of antidepressants is however of SSRIs for depression and anxiety rather than other antidepressants for other indications, and nearly all these antidepressants are prescribed in the community by general practitioners (GPs) [3].

Why has antidepressant prescribing increased?

The determinants of increased antidepressant prescribing have been examined in several studies of databases of aggregated national prescribing cost data and GP medical record data.

Meijer *et al* analysed incident and prevalent prescribing of SSRIs in the Netherlands from 1992 to 2001 using the PHARMO database and found that both increased over the period, i.e. more patients were prescribed treatment with SSRIs each year, but the duration of treatment prescribed also increased over time. Almost 30% of patients became “long-term users” (prescribed SSRIs for more than 12 months) during the 10-year follow-up [4].

Moore *et al* examined prescribing for first-ever episodes of depression in the General Practice Research Database (GPRD) in England from 1993 to 2005. The incidence of new episodes declined slightly over the period, and the proportion of patients prescribed antidepressants remained around 80%. Despite this, antidepressant prescribing nearly doubled due to longer

treatment courses, and the large majority of prescriptions were given as long-term or intermittent treatment [5].

McCrea *et al* examined UK prescribing data in The Health Improvement Network (THIN) database. New SSRI prescribing doubled from 1995 to 2001, after which it remained relatively constant to 2012. However, again there was a steady increase in the duration of prescribing, by 50% overall [6].

Kendrick *et al* analysed data from England between 2003 and 2013, in the Clinical Practice Research Datalink (CPRD, formerly the GPRD). The incidence of new presentations of depression remained constant at around 10 per 1000 person-years. The prevalence of cases fell from around 60 to 50 per 1000 person-years between 2003 and 2007, but increased again after the economic recession, to 55 by 2013. Rates of treatment remained steady at around 75% of diagnosed cases, but prescriptions per patient increased over the 10 years, with a doubling in mean duration of prescribing [7].

Using Prescription Cost Analysis data (from 1998 to 2003) and Health and Social Care Information Centre data (from 2004 to 2012), Spence *et al* also found a small increase in the prevalence of depression from 2008 to 2012 in line with the financial recession, but again the main reason for increased antidepressant prescribing was a longer duration of courses dispensed. Detailed modelling showed wide variation in rates, and practices that prescribed more antidepressants tended to be in areas with generally worse health and worse housing, with a greater percentage of older, female and white patients. Higher antidepressant prescribing was associated with higher antibiotic prescribing, which was used as an indicator of overall prescribing behaviour [8].

In summary, studies using routinely available data have shown that the main reason antidepressant prescriptions have increased has been an increase in treatment duration, roughly doubling every 10 years. Relatively smaller increases in the incidence of depression, notably after the economic recession, have also contributed to increased prescribing, but to a lesser extent. Concerns that antidepressants are being increasingly overprescribed for mild depression [9, 10] are not borne out by these studies which show the proportion of patients

with recorded symptoms who are treated has remained the same, at around 70-80% [5, 7]. However prescribing rates vary widely between doctors.

The median duration of use among patients on antidepressants is now more than two years in the UK [11, 12] and more than five years in the USA [13, 14], which is ahead of us in this process of ever-increasing length of treatment. Public Health England's evidence review of prescribed medicines, using NHS Digital data [1], showed that antidepressants were prescribed for 4.8 million people in March 2018, over 10% of the 43.8 million adult population in England. Of those people, 4.4 million (43%) had at least one prescription in each of the three preceding years, and 1.1 million (23%) had received prescriptions continuously for three years [3].

Problems associated with long-term prescribing

Long-term use puts patients at increasing risk of side effects over time, some of which can be severe. The SSRIs frequently cause significant weight change, sleep disturbance, and sexual dysfunction [15]. Antidepressant side effects can worsen with age and their use in people aged over 65 is associated with serious adverse events and increased mortality. A retrospective cohort study of over 61,000 patients from 570 general practices found absolute risks over one year of exposure to SSRIs (adjusted for comorbidities and a range of potential confounding variables) of 5.7% for falls, 2.6% for stroke/TIA, 0.5% for upper gastrointestinal bleeding, 0.38% for seizures, and 0.44% for hyponatraemia [16]. Absolute risks over one year for all-cause mortality were 7.04% for patients not taking antidepressants, 8.12% for those taking TCAs, 10.61% for SSRIs, and 11.43% for other antidepressants [16]. This observational research is susceptible to confounding by indication, and residual confounding, so differences in characteristics between patients prescribed different antidepressants could account for some of the associations between them and the adverse outcomes [16].

In up to a half of patients long-term treatment may blunt their ability to feel emotions [17]. Treatment may also impair a person's autonomy and resilience, increasing their dependence on medical help, so no patients should be treated unnecessarily.

Increasing long-term use also means more and more people are at risk of having withdrawal problems when they stop using their antidepressant. Seventeen placebo-controlled trials (with 6,729 participants) have shown that withdrawal symptoms including sensory symptoms, insomnia, anxiety, depression, and even suicidal ideas follow cessation of antidepressants [3], and the incidence may be as high as 50% [18] although that estimate is based to a significant extent on Internet surveys which tend to over-represent the experience of people who have had significant withdrawal problems.

In theory, stopping antidepressants is straightforward, tapering them off over some weeks under supervision [19], but in practice patients are often anxious about stopping. Anxiety, mood swings and sleep disturbance may appear to be a recurrence of the original problem requiring treatment [20]. Restarting medication, before withdrawal symptoms can resolve spontaneously, quickly relieves the symptoms and reinforces this false perception of recurrence.

Unfortunately, the longer patients are taking antidepressants the less likely they are to be reviewed by their GP. Studies have found that at best 70% are reviewed once a year after three years of use [21, 22], reducing the opportunity to reassess the appropriateness of treatment and increasing the likelihood of continuing it unnecessarily. Patients are often put on repeat prescriptions of antidepressants by their GPs, and consequently may assume they are expected to continue treatment in the absence of any active discussion of need [23]. Many are prepared to continue indefinitely, due to fears of relapse and a perception that discontinuation would be a threat to their stability [24]. So patients need proactive review, and may need persuading to try withdrawing from treatment.

It has been suggested that increasing long-term prescribing is simply the result of correcting what was previously inadequate duration of treatment for depression [25], and it may be that long-term antidepressants are appropriate for some patients to reduce the risk of relapse [26, 27]. The National Institute for Health and Care Excellence (NICE) recommends treating people for two years in the first instance if there is a history of recurrent depression, or the risk of relapse is significant [28]. On the other hand, the evidence base for long-term treatment from placebo-controlled randomised controlled trials (RCTs) of maintenance antidepressants does

not extend much beyond two years [27]. There is also evidence that continuation of antidepressants for anxiety disorders prevents relapse, but little evidence that the protection extends beyond one year [29].

Notwithstanding the evidence that long-term treatment can prevent relapse, surveys of long-term antidepressant users in the UK, the Netherlands, and Australia have concluded that 30% to 50% of users have no evidence-based indications to continue them, and could try stopping treatment [30-33].

Furthermore, nearly all the placebo-controlled trials of maintenance antidepressants for preventing relapse have been done in secondary care, with populations of patients at relatively high risk of relapse [26, 27]. Relatively little research has been done on the need for maintenance antidepressants in the majority of patients seen only in primary care, who are at lower risk of relapse [28]. One trial in New Zealand found 23.3% relapsed on placebo versus 10.5% on maintenance antidepressants, which gives a number needed to treat to prevent relapse of 8. The trial showed that, if patients were carefully monitored, and antidepressant treatment was quickly restarted when they started to relapse, the outcome for depression in the two arms was similar at the end of the trial. This suggests that most patients can safely try stopping antidepressants in primary care as long as they are monitored for relapse, and treatment is restarted if necessary [34].

The conclusion of these studies of prescribing must be that, to have any impact on reducing high antidepressant prescribing rates, research studies and guidelines must address recurrent and long-term prescribing, as well as GPs' initial treatment decisions. Antidepressants constitute a substantial proportion of the National Health Service (NHS) drug budget (2.5% in 2010 [35]), and the costs of unnecessary treatment include appointments for GP or Nurse Practitioner (NP) reviews. The cost of general practice care for depression was estimated to be £200 m per year in 2006 [36], in addition to the cost of the antidepressant prescriptions of around £300 m per year [1], so substantial savings could also be made if significant numbers of long-term users of antidepressants were to come off them.

Strategies to reduce initial prescribing of antidepressants

GPs should not prescribe antidepressants routinely for mild depressive and anxiety symptoms. They should seek evidence of sufficient symptoms to fulfil criteria for major depressive disorder, or an anxiety disorder, and this may be helped by using a symptom questionnaire like the Patient Health Questionnaire (PHQ-9) for depression [37] and the Generalised Anxiety Disorder questionnaire (GAD-7) for anxiety [38]. Furthermore, the 2009 NICE Guideline states: When assessing a person who may have depression, conduct a comprehensive assessment that does not rely simply on a symptom count. Take into account both the degree of functional impairment and/or disability associated with the possible depression and the duration of the episode [28].

It is important to emphasise that antidepressant treatment is best avoided at the initial consultation for problems of depression and anxiety if possible, as a significant proportion of patients will improve without treatment over a few weeks of active monitoring, and their symptoms may then no longer fulfil criteria for major depressive disorder or an anxiety disorder [28, 39].

If symptoms persist, antidepressants should then only be prescribed if:

- the patient has persistent subthreshold depressive symptoms or mild to moderate depression and has not benefitted from a low-intensity psychosocial intervention (guided self-help, cognitive-behaviour therapy (CBT), behavioural activation or an exercise programme) or they are thought to be unsuitable, or
- the patient is at risk of developing more severe depression or anxiety in light of the trajectory of symptoms and previous course of depression (e.g. they have a past history of severe problems), or
- the patient has recurrent depression or anxiety and is asking for a new course of drug treatment previously prescribed (as long as the previous course of treatment seems to have been justified, which should be checked together with the response to previous treatment)

It should be emphasised however that, although psychological treatments are recommended before providing antidepressants, given the limited capacity of psychological therapy services, this may entail a wait of many months, and so prescribing may be the only alternative.

The rationale for taking SSRIs commonly presented in drug advertisements, and by GPs at initiation of treatment, is a deficiency of serotonin in the brain [40-42], but giving patients this justification is not supported by evidence from brain studies [40, 43] and should be avoided, as patients may conclude they must therefore remain on treatment for life, as they might for a thyroxine or insulin deficiency [41, 42].

Patients should be advised that treatment is to be for a limited period initially, continuing for six months after improvement to reduce the risk of relapse, i.e. usually nine to 12 months altogether in the first instance [28]. After that, prescribing should continue only if there have been two or more previous episodes of depression, or the patient is at significant risk of relapse due to ongoing symptoms, or ongoing significant life events and difficulties. Treatment should be actively reviewed again after two years of treatment, to consider whether to attempt coming off treatment [28].

When prescribing antidepressants, practitioners should also warn patients that they are commonly associated with withdrawal symptoms on stopping them, so that patients can make an informed decision about whether or not to take them in the first place. (Clearly this is not the only factor that patients need to consider when making an informed decision; they should obviously be advised of the risks of not adequately treating depression, so that they can weigh up the risks and benefits).

The effect of national guidance

There is evidence that national guidelines can influence levels of initiation of antidepressants for first episodes of depression, and for recurrent episodes, but in different directions. Kendrick *et al* used time trend analyses to explore the effects of guidance on initial prescribing of antidepressants in the CPRD database of GP medical records between 2003 and 2013 [44]. The first was the publication of the first NICE depression guideline in December 2004, which advised GPs not to prescribe for mild depression [45]. The second was the introduction of a quality indicator into the GP quality and outcomes framework (QOF) in April 2006, which

reinforced the message of the NICE guideline, by rewarding GPs financially for getting patients to fill out depression symptom questionnaires at diagnosis, and thereby demonstrating that they had actively tried to measure the severity of depression before prescribing [46].

Figure 3 below shows the proportion of patients with depressive symptoms who were prescribed antidepressants over the 10-year period in the CPRD sample. Prescribing for first ever presentations of depression (the lower blue line) declined by 4% after the NICE guideline was published in 2004, and by another 4% after the QOF incentive to measure patients' symptoms with questionnaires was introduced in 2006. These changes were statistically significant in time trend analyses. Overall, prescribing for first-ever episodes of depressive symptoms went down from over 70% to around 60% of episodes and stayed at that level for the rest of the period examined [44].

However, the 2004 NICE guideline also suggested that antidepressants should be prescribed for two years or more for patients with recurrent depression [45], and the CPRD data show that prescribing for recurrent episodes of depressive symptoms (the top orange line) increased after the guideline was introduced, from around 70% to 80% of cases over the 10 year period. Overall prescribing rates (the middle red line) stayed at around 70% of episodes as a result [44]. So the 2004 NICE guideline and 2006 QOF indicator may have changed prescribing behaviour but did not reduce antidepressant prescribing overall.

Database studies show only trends across patient populations over time, and do not usually have any data on severity of depression. However, studies of antidepressant prescribing at the individual patient level carried out following the introduction of the NICE guideline and QOF quality indicator showed that drug treatment was mostly appropriately related to greater severity of depression and anxiety at diagnosis [47], and was justified in most cases, against the 2004 NICE guidance [48].

Strategies to reduce long-term antidepressant use

Maud *et al* carried out a systematic review and meta-synthesis of qualitative research studies on patient and practitioner perspectives of barriers and facilitators to stopping long-term antidepressants [49]. The meta-synthesis yielded nine themes which were, in decreasing

order of the quantity of coded data contained within them: psychological and physical capabilities; perception of antidepressants; fears; intrinsic motivators and goals; the doctor 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

The most important barriers to discontinuation with relevance to the prescriber, as they may be amenable to intervention when considering how inappropriate long-term use can be addressed, are:

- patient fears of withdrawal symptoms and relapse of depression
- a lack of consistent guidance for practitioners on tapering off antidepressant doses and
- time constraints in follow-up appointments for depression treatment.

These factors tend to reduce greatly the likelihood of treatment review with a view to possible cessation of antidepressant treatment [23, 49].

Initiating discussion of antidepressant reduction and cessation

A key finding of the qualitative research is the commonly held belief on the part of patients that the prescriber is responsible for initiating discussions about stopping long-term treatment [23, 49]. Practitioners should not assume the patient will initiate a discussion about withdrawing treatment, and instead take the initiative themselves if they feel it is appropriate for the patient to consider it. In the absence of action by the GP or NP, the status quo will be the continuation of possibly unnecessary antidepressant treatment for many patients.

This suggests that prompting GPs to review patients on long-term antidepressant treatment actively, with a view to reducing treatment where it is inappropriate, might enable more patients to stop antidepressants. However, an uncontrolled trial of pharmacist-prompted GP review of long-term users in Scotland resulted in only 7% of patients stopping their antidepressants, although an additional 13% did reduce the dose [12]. Similarly, prompting GPs to review patients eligible for withdrawal was tested in an RCT in the Netherlands and found to be ineffective, with only 6% of patients discontinuing antidepressants in the intervention group compared to 8% in the control group [31, 32].

Prompting the prescriber to review treatment seems therefore to be insufficient by itself to enable a significant proportion of patients to discontinue antidepressants. Prescribers need more guidance on tapering off treatment, and patients need more psychological support to manage without the drug treatment.

Antidepressant drug tapering regimes

A systematic review of interventions to support discontinuation of antidepressants found that the risk of withdrawal symptoms is higher with abrupt termination of antidepressants [50]. Until recently, NICE and other guidelines recommended relatively rapid tapering, over 2 to 4 weeks, halving doses and perhaps halving again before complete cessation [28], but such rapid tapering is not much better than abruptly stopping treatment, and is often not tolerated by patients [50]. Withdrawal symptoms are also more likely when coming off drugs with shorter half-lives, particularly the SSRI paroxetine and the serotonin and nor-adrenaline reuptake inhibitor (SNRI) venlafaxine [50]. Withdrawal symptoms are probably reduced by slower tapering, but this can be a challenge given a lack of suitable formulations of antidepressant tablets and capsules [50]. One study found that most patients could discontinue paroxetine with a taper of 5 mg every 2 to 4 weeks, but patients had to break their tablets in half [51]. Switching to fluoxetine or citalopram, with their longer half-lives and availability in liquid form, may enable successful slower tapering [52], but this strategy does not appear to have been tested in a trial [50].

'Hyperbolic' antidepressant tapering regimes have been recommended recently. Horowitz and Taylor reviewed positron emission tomography imaging data of SSRI inhibition of the SERT monoamine transporter (<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=928>) and noted it is a hyperbolic relationship, dropping slowly as doses are halved and quartered, but then more sharply down through the range of doses lower than the minimum therapeutic dose [53]. They therefore suggested that SSRIs should be tapered hyperbolically: initially quickly but then more and more slowly to very small doses before complete cessation, in line with tapering for other medications associated with withdrawal symptoms like the benzodiazepines. This may take months and involve reducing to doses much lower than

minimum therapeutic doses, but may lead ultimately to greater success in reducing and stopping medication with minimal withdrawal symptoms [53].

Horowitz and Taylor recommend using 'mini-tapering' rather than 'micro-tapering' [53]. Micro-tapering starts with very small decreases in medication, of less than 10% of the starting dose, and relatively short intervals of a few days or a week between each decrease. Mini-tapering involves initially larger decreases, with intervals of weeks in between, allowing time for withdrawal symptoms to resolve, and only then reducing the dose again. They recommend this rather than micro-tapering as they suggest the latter might lead to cumulative withdrawal effects from each dose reduction becoming superimposed on each other, leading to a more prolonged period of withdrawal symptoms without relief in between reductions. Micro-tapering might also make it difficult to recognise the level of reduction responsible for triggering withdrawal symptoms in an individual patient [53].

Ruhe and colleagues recently described a collaboration between the Dutch College of General Practitioners, Royal Dutch Pharmacists Association, Dutch Association for Psychiatry, and the patient organisation MIND, to develop multidisciplinary recommendations for stopping SSRIs and SNRIs in the Netherlands [54]. Independent of Horowitz and Taylor [53] but with identical reasoning, they proposed reducing doses hyperbolically, and also advocated mini-tapering [54].

Ruhe *et al* suggest three risk-factors indicate an increased risk of withdrawal symptoms: "(1) dosing above the minimal effective dose to reach efficacy, (2) antidepressant withdrawal symptoms when a dose was missed or during strategic treatment interruption, and (3) earlier failed attempts to discontinue the SSRI or SNRI". They suggested these three factors might indicate a need to apply hyperbolic dose decreases instead of halving the minimal effective dose and stopping immediately thereafter [54]. They have published a table of suggested steps in dosing to discontinue SSRIs and SNRIs in case of the presence of one or more of these risk factors for acute withdrawal syndrome [54]. Unlike Horowitz and Taylor though, Ruhe and colleagues recommended initial reductions at weekly intervals with observation of withdrawal symptoms in between, rather than several weeks between each which is more time-consuming. As there is a lack of evidence to guide tapering regimes, they strongly

advocate *shared decision making* with patients and careful, repeated evaluation of the dosing steps [54].

Tapering strips

Also in the Netherlands, a not-for-profit organisation Cinderella Therapeutics has since 2013 overseen the development of personal tapering strips for very gradual reduction of antidepressant medication in those suffering withdrawal or deemed to be at particular risk [55]. A tapering strip consists of medication packaged in a roll or strip of small pouches of slowly decreasing doses for 28 consecutive days each strip. Dose and day information printed on each pouch allow patients to precisely monitor their reduction [55].

A survey of 1750 users of tapering strips was carried out, of whom 1194 (68%) responded, including 895 (51%) who wished to discontinue their antidepressant medication [56]. The most common medications were paroxetine (in 47%) and venlafaxine (43%). In these 895, the median length of antidepressant use was 2–5 years, with an interquartile range (IQR) from 1–2 years to more than 10 years, and nearly two-thirds had unsuccessfully attempted withdrawal before (median two attempts). Almost all had experienced some degree of withdrawal, with half experiencing severe withdrawal. Of the 895 wishing to discontinue, 71% succeeded in tapering off their antidepressant medication completely, using a median of two tapering strips (IQR one to three) over a median of 56 days (IQR 28 to 84). Tapering strips therefore seem to offer a simple and effective method of achieving a gradual dosage reduction, particularly in those people with a history of previous withdrawal problems on drugs with shorter half-lives including paroxetine and venlafaxine [56].

Psychological support for patients to manage without drug treatment

The systematic review of interventions to support discontinuation of antidepressants [50] identified six reports of RCTs of psychological or psychiatric treatment plus drug tapering which led to relatively high antidepressant cessation rates of between 40% and 95% of patients [57-62]. Meta-analysis of two studies by Fava *et al* showed significantly lower risks of recurrence with CBT and tapering versus clinical management and tapering after two years (15% versus 35% and 25% versus 80% respectively) [50, 57, 58], and after six years (40% versus 75% and 50% versus 90% respectively) [50, 59, 60]. Meta-analysis of two studies by Kuyken

et al of mindfulness-based cognitive therapy (MBCT) with antidepressant tapering versus maintenance antidepressants showed similar rates of relapse in each arm at 15 months or more (47% versus 60% and 46% versus 49% respectively) [61,62]. The recurrence rate at 15 months was similar (54%) in another study providing MBCT with tapering support in one arm [63]. Since the systematic review, Bockting *et al* have reported that preventive cognitive therapy (PCT) and tapering of antidepressants is also equal to maintenance antidepressants in terms of relapse prevention, although adding PCT to antidepressants was more effective than either continuing antidepressant alone, or combining PCT with antidepressant withdrawal [64].

Psychological therapies may work by providing support to patients to manage fears of withdrawal, relapse, and lack of self-efficacy, which are possible barriers to discontinuation [65]. Alternatively, having an effective therapy for the depression or anxiety for which the medication was initially given removes the need for the antidepressant, without increasing the risk of relapse [50]. One in six patients referred or self-referred for psychological therapy through the Improving Access to Psychological Therapies (IAPT) programme in England is able to come off their psychotropic medication [66].

However, while psychological therapies can significantly improve the chances of patients discontinuing maintenance antidepressants without relapsing, they are very resource intensive, and access to face-to-face therapy is quite limited in most countries. Even in England, where there has been a huge increase in the availability of psychological therapies through the IAPT programme since 2008, the estimated proportion of people with depression and anxiety referred or self-referred to the IAPT services was only 15% by 2016 [67]. The Mental Health Taskforce indicated an aim to increase the offer of treatment up to 25% of people with depression and anxiety by 2021, entailing the training of many thousands more therapists, but even if this is achieved it will still be a minority of patients who might benefit from psychological treatment. The relatively low proportion (from a primary care perspective) of patients with depression or anxiety who receive psychological therapy may explain why no relationship has been found between increasing provision through IAPT and subsequent rates of antidepressant prescribing by general practices [8, 67].

More scalable interventions incorporating psychological support are therefore needed to address what may be unnecessary long-term antidepressant treatment in millions of people nationally. This situation warrants exploration of psychologically informed digital (on-line) support for discontinuation to complement primary care clinician management.

In England the REDUCE programme, funded by the National Institute for Health Research (NIHR; grant reference no. RP-PG-1214-20004), has identified barriers and facilitators to stopping antidepressants through qualitative research with patients and practitioners [49,68] and used this to inform the design of Internet patient and practitioner support packages aimed at helping patients discontinue antidepressants [69]. The intervention consists of GP or NP and patient access to Internet programmes designed to support antidepressant withdrawal, plus three patient telephone calls from a psychological wellbeing practitioner. Control patients receive usual care without Internet or telephone support, but patients are also prompted to seek a review of their antidepressant treatment and may also decide to try to taper it off in discussion with their GP or NP.

The patient intervention (called 'ADvisor' as it provides advice on antidepressants) has been developed by psychologists Geraghty and Bowers, drawing on theory, evidence and in-depth systematic qualitative research with patients [49,70]. The aim is to increase patients' self-efficacy for stopping antidepressants in a way that is safe and suited to their preferences. It focuses on increasing patients' reflective motivation for stopping, and supporting their psychological and physical capability to do so through modules that include: *Reducing and stopping (introduction to website); How to reduce antidepressants; Thinking about antidepressants (their effects and why lifelong treatment may not be necessary); Dealing with withdrawal symptoms; I am worried about stopping; Keeping well; thinking about what you value in life; and Moving forward*. Exercises based on CBT, MBCT and acceptance and commitment therapy (ACT) are included in the patient support package. Figure 4 shows the front page of the ADvisor patient Internet intervention.

The practitioner intervention (called 'ADvisor for Health Professionals') has drawn on new in-depth qualitative research with health professionals [68] and includes Internet modules on: *Why reduce; Broaching the subject; When to start tapering; Reduction schedules for individual antidepressants; Dealing with withdrawal symptoms; and Dealing with relapse*. It also

includes a summary of the ADvisor intervention for patients; and printable pages on antidepressant reduction regimes and sections of ADvisor for patients that are recommended for the patients to consult. The intervention broadly targets increasing the self-efficacy of GPs and NPs to safely discontinue patients from antidepressants where appropriate [70]. Figure 5 shows the front page of the ADvisor for Health Professionals intervention.

Detailed reduction schedules for all antidepressants are included in the ADvisor for Health Professionals intervention, grouped under four plans. Plan A is for patients on the majority of antidepressants with fewer associated withdrawal problems, who have no history of distressing withdrawal, and no particular fear of undergoing withdrawal over 4-6 weeks (or longer if necessary). Plan B is for antidepressants associated with more withdrawal symptoms due to particularly short half-lives (paroxetine, venlafaxine and duloxetine). Plan C is for patients who have a history of difficult or distressing withdrawal, or have a particular fear of withdrawing over six weeks or less, and includes suggestions for hyperbolic dose reduction when necessary. Plan D is for patients on tricyclic and related drugs, in particular older patients at risk of cholinergic rebound.

Practitioners are advised that for each tapering plan, reductions in dose can be slowed down if distressing withdrawal symptoms occur. If symptoms are severe, they are advised to return to the previous dose until symptoms subside then change to a slower taper for future steps. If symptoms are tolerable, the patient should be advised to continue taking the current dose until the symptoms subside, and then consider changing to a slower taper. All schedules in the ADvisor for Health Professionals intervention can be achieved without a need for pill cutters or liquids. If a slower taper is needed however, in exceptional cases practitioners may wish to suggest the patient uses pill cutters or liquid formulations of fluoxetine or citalopram, after discussion with the pharmacist, who would usually need to take steps to obtain liquid formulations.

The need for more research

The ongoing REDUCE RCT will provide evidence on whether scalable, Internet and telephone psychological support to patients, and guidance on antidepressant tapering to practitioners, leads to more patients successfully coming off their antidepressants without becoming

depressed. It is powered as a non-inferiority trial and the primary outcome is depressive symptoms on the PHQ-9 questionnaire at six months [69].

In Australia another primary care RCT called STOPS (STructured Online intervention to Promote and Support antidepressant de-prescribing in primary care), is going to provide on-line guidance (called *WiserAd*) and practice nurse support to patients (personal communication Jane Gunn, University of Melbourne) <https://medicine.unimelb.edu.au/research-groups/general-practice-research/mental-health-program/stops-a-randomised-trial-of-a-structured-online-intervention-to-promote-and-support-antidepressant-de-prescribing-in-primary-care>.

More research is also needed to establish:

- the incidence of antidepressant withdrawal symptoms in representative samples of patients tapering off antidepressants,
- risk factors which predict more withdrawal symptoms in prospective studies to avoid recall bias, and
- the relative advantages of different dose reduction regimes, including comparing mini-tapering and micro-tapering, the use of tapering strips, and the impact on withdrawal symptoms of a range of different intervals between dose reductions [53-55]

The first two issues are being addressed in the ongoing OPERA project, the Netherlands Study of Optimal, PERSONAL Antidepressant use, a collaboration between departments of primary care and psychiatry of five University medical centres in the Netherlands which started in 2019 and will continue until 2025 [54]. The third issue will require large trials of different dose reduction regimes, in large numbers of patients, allowing sub-group analyses to test the different recommended approaches.

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Nomenclature of Targets and Ligands

The key protein target SERT in this article is hyperlinked to the corresponding entry in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [SLC6A4], and permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [SLC6A4]

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Conflict of interest statement

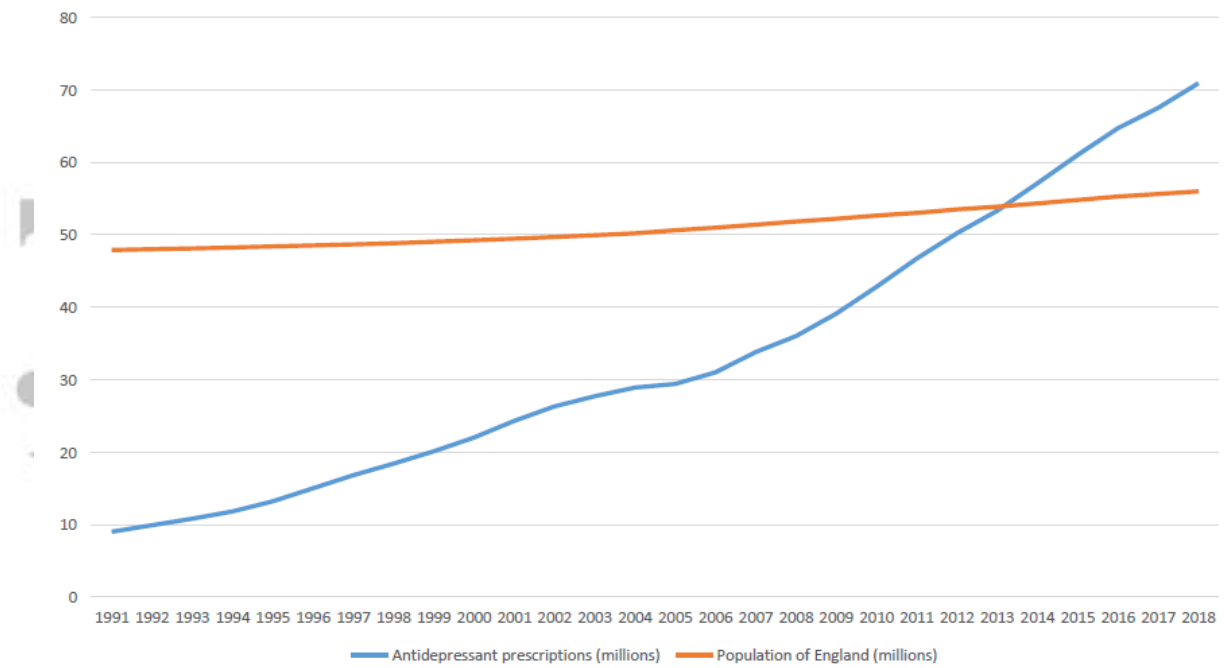
Tony Kendrick receives funding from the NIHR as Chief Investigator of the REDUCE programme testing Internet and telephone support for antidepressant reduction. He chaired the GP contract quality and outcomes framework (QOF) expert committee which recommended that the use of depression symptom questionnaires be financially incentivised in 2006 [46]. He received an educational grant from Lilly, Lundbeck, Servier, and Wyeth pharmaceuticals for the 2009 study of GP management of depression following the introduction of the QOF indicator [47]. He has received no other funding from pharmaceutical companies since 2009. He is a member of the NICE Depression Guideline Development Group for the 2020 update.

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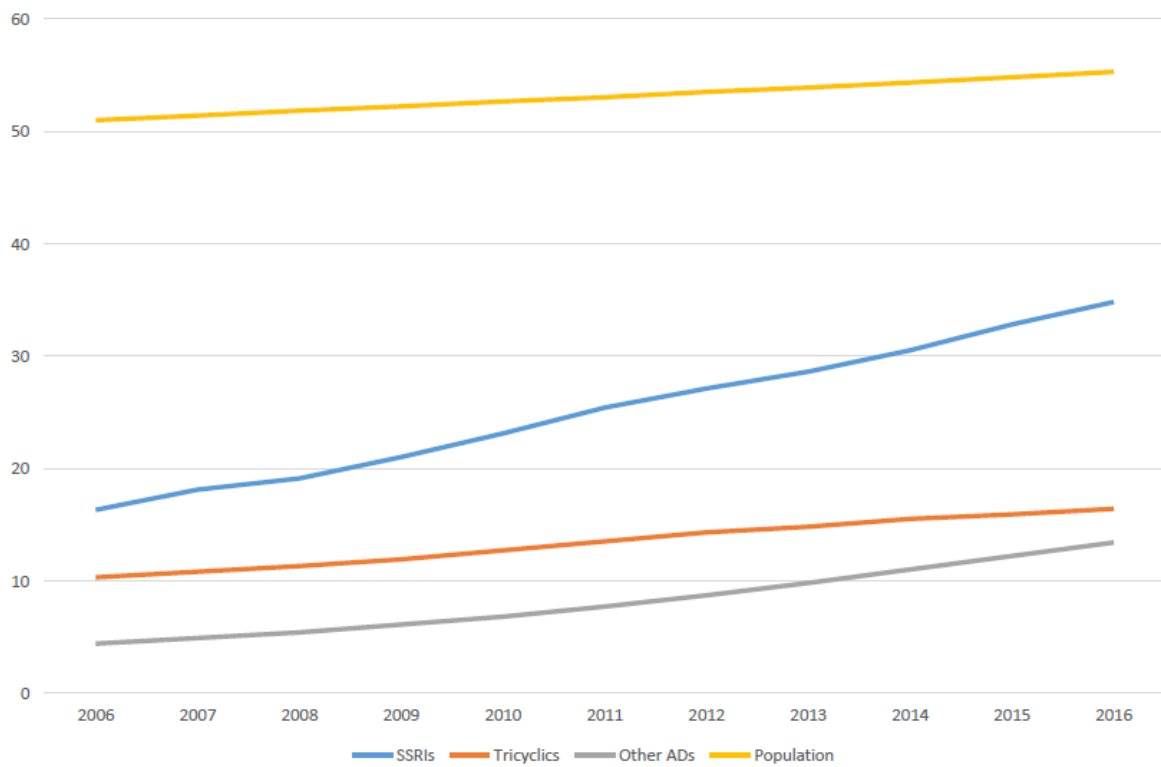
Accepted Article



Data for prescriptions dispensed from NHS Digital (millions of prescriptions per year)
 Data for population of England from ONS (millions of people mid-year)

Figure 1 Increasing antidepressant prescribing in England 1991-2018

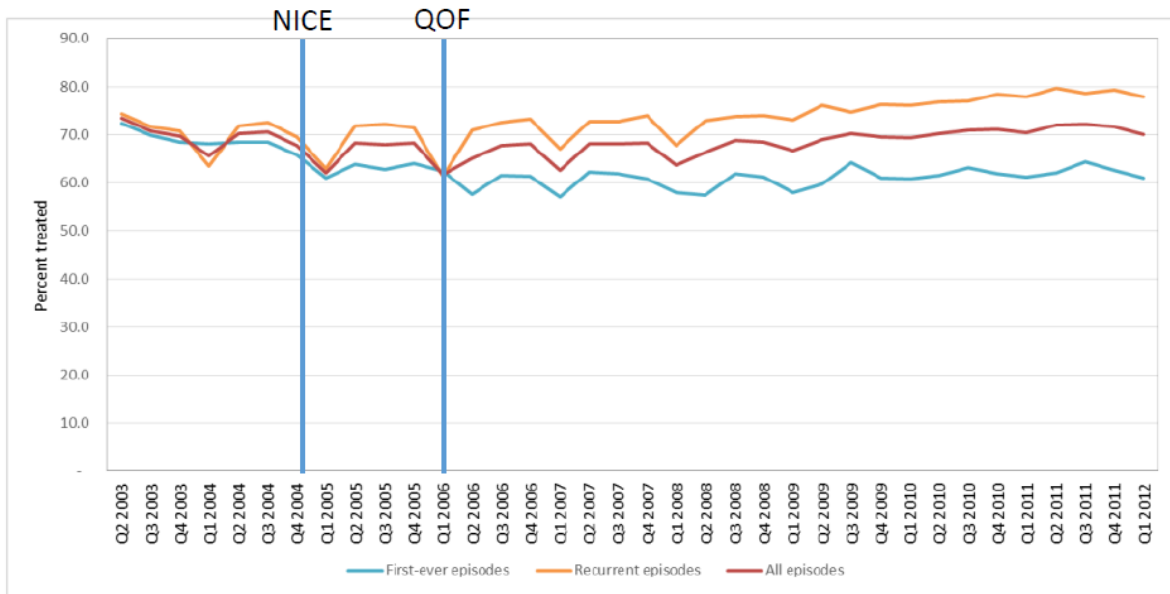
Accepted



Data for prescriptions dispensed from NHS Digital (millions of prescriptions per year)
Data for population of England from ONS (millions of people mid-year)

Figure 2 Increasing antidepressant prescribing in England by class of antidepressant

Accepted



Percentage treated by quarter year within the Clinical Practice Research Datalink (CPRD) sample of 293,596 patients from 142 practices. NICE = introduction of NICE Depression guideline. QOF = introduction of Quality and Outcomes Framework depression quality indicator

Figure 3 Percentage of first-ever and recurrent episodes of depression treated with antidepressants within 12 months of diagnosis (Clinical Practice Research Datalink data 2003-2013)

Accepted

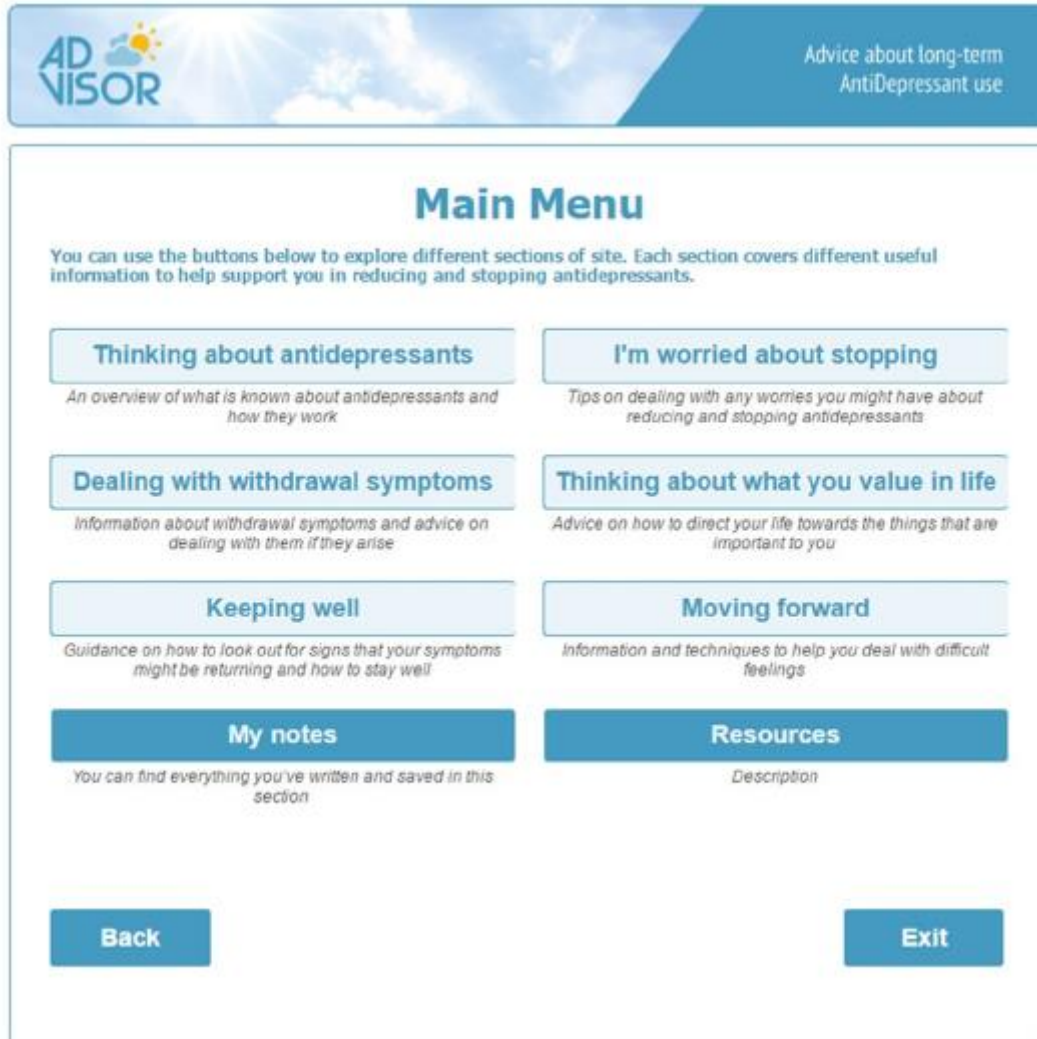


Figure 4 Front page of ADvisor Internet support package for patients wanting to withdraw from their antidepressants

Accepted Article

The screenshot shows the front page of the ADvisor for Health Professionals Internet support package. At the top left is the logo for ADvisor Health Professional, featuring a sun and clouds. At the top right, the text reads "Advice about long-term AntiDepressant use". Below this is a "Main menu" section with a list of topics, each with a corresponding button and a brief description. The topics are: "Why reduce", "Broaching the subject", "When to start tapering", "Reduction schedules", "Dealing with withdrawal symptoms", "Dealing with relapse", "ADvisor for patients", "Printable pages", and "Resources". At the bottom right of the menu area is a blue "Exit" button.

Topic	Description
Why reduce	An introduction to why reducing and stopping antidepressants might be preferred for some patients
Broaching the subject	Advice for approaching the initial conversation about withdrawal with patients
When to start tapering	Information about which patients might be in the best position to start tapering
Reduction schedules	Suggested tapering schedules for reducing particular antidepressants in different circumstances
Dealing with withdrawal symptoms	Information and guidance on dealing with mild, moderate and severe withdrawal symptoms
Dealing with relapse	Guidance on when to restart antidepressants in the face of relapse
ADvisor for patients	Brief descriptions of what patients see when they log into ADvisor
Printable pages	Printable handouts to give to patients
Resources	Links to relevant papers and guidelines

[Exit](#)

Figure 5 Front page of the ADvisor for Health Professionals Internet support package on supervising antidepressant reduction and cessation