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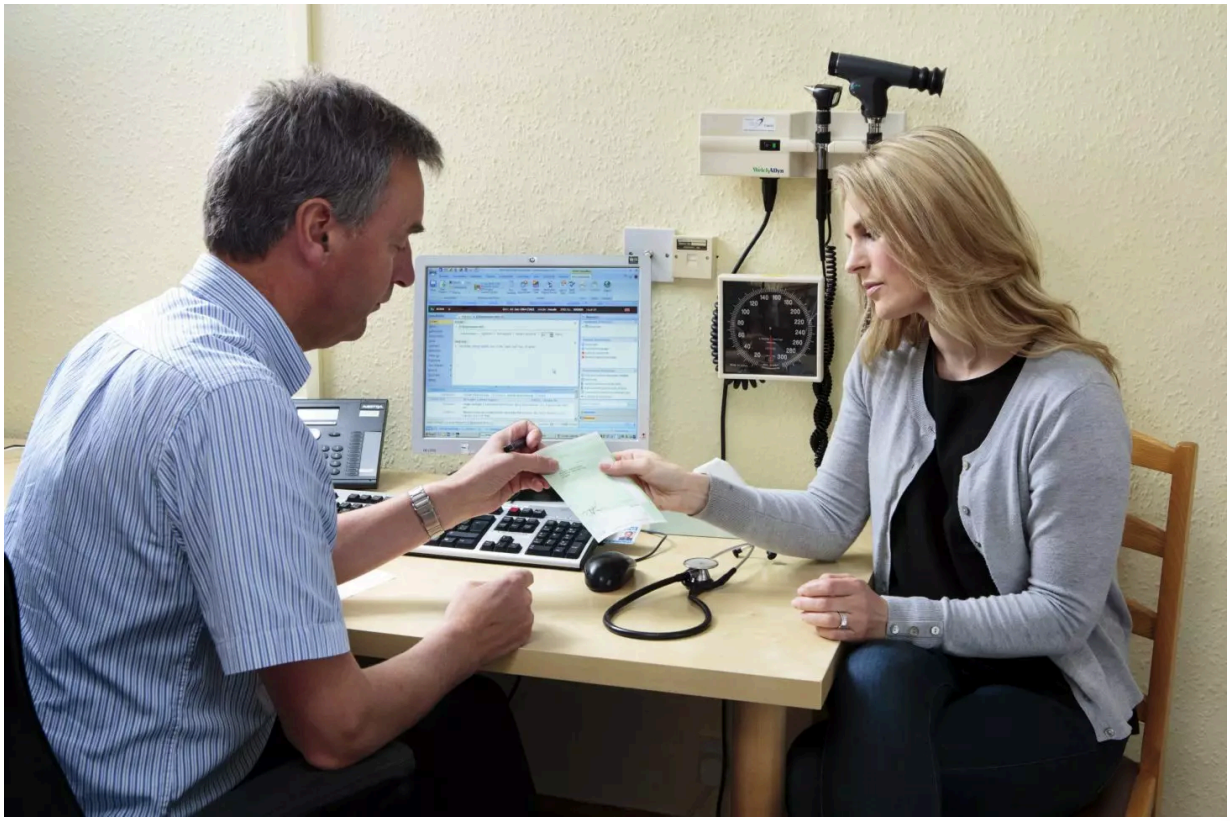
Switching antidepressants: advice and practicalities

In the right circumstances, changing to a different antidepressant can improve the chances of successfully treating depression. This article outlines when switching medicines may be appropriate and how to select a strategy that reduces risk to the patient.

Drug switching

13 January 2023.By **Dimple Oza (https://pharmaceutical-journal.com/author/dimple-oza)** .



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After reading this learning article, you should be able to:

- Understand (#h-why) when switching antidepressants may be necessary for patients;
- Determine when it is appropriate to switch (#h-assess) antidepressants and how to safely switch between antidepressants;
- Recognise and manage (#h-management) discontinuation and withdrawal symptoms;
- Effectively counsel patients when discussing/implementing antidepressant switches.

An estimated 3.8% of the world's population is affected by depression, including 5.0% of adults and 5.7% of adults aged 60 years or older[1]. Symptoms of depression include low mood and/or a loss of pleasure or interest in activities for most of the day, nearly every day, for at least one month[2]. Depression can cause significant distress and poor function at work, school and in the family and, at its most severe, can lead to suicide (/article/ld/suicide-how-to-recognise-the-warning-signs-and-deal-with-disclosure) [1] . People who experience depression are often incorrectly diagnosed, while others who do not have depression are too often misdiagnosed and prescribed antidepressants[1]. In England, the number of antidepressants prescribed each year has increased steadily, rising from 61.9 million to 83.4 million (2015/2016 to 2021/2022)[3].

Antidepressants are recommended as first-line treatment for moderate and severe depression, depression that has persisted for two years or more (irrespective of severity), or mild depression that has persisted for longer than three months[2,4]. Treatment is usually as monotherapy or in combination with psychological therapy, dependent on the duration, severity and impact of depressive symptoms on the individual. Antidepressants are also used to treat other conditions, including anxiety disorders (/article/ld/case-based-learning-anxiety-disorders) , obsessive compulsive disorder and neuropathic pain (/article/research/treatments-for-neuropathic-pain) (peripheral neuropathy)[5].

Antidepressants have been shown to be equally effective in treating a first episode of depression and up to 60% of patients show a response within the first two weeks of treatment[6]. However, it is not uncommon for people to trial multiple antidepressants during depressive episodes and pharmacists have an active role in supporting patients if a change in their prescribed antidepressant is required.

Why antidepressant switching may be required

Antidepressant switching happens for two main reasons: if there is inadequate response from the antidepressant prescribed; and/or the patient experiences intolerable side effects, such as weight gain, increased anxiety and insomnia (/article/ld/insomnia-disorder-management-strategies) [2]. Although most side effects are transient and can be managed through counselling, dose reduction (where appropriate) and simple strategies – such as taking the antidepressant with or after food to minimise gastrointestinal side effects – there are instances where the severity of side effects outweigh the therapeutic benefits resulting in the decision to switch to an alternative antidepressant[4]. For these patients, switching to an antidepressant with a lower tendency to cause the same problematic side effects should be considered[4].

If adverse effects are intolerable, Maudsley Prescribing Guidelines recommend considering switching antidepressants as early as after one to two weeks from commencement[7,8].

Non-response to antidepressant treatment is also common in UK primary care, with 55% of patients not responding to medication despite adequate dose and duration of treatment (see 'Depression in adults: recognition and management' (/article/ld/depression-in-adults-recognition-and-management) for more information on dose and duration)[3]. Depression is a heterogenous disorder, meaning there is no single reason to explain why an individual may not respond to antidepressant treatment[9]. Factors such as age, sex, quality of life, financial burden, a lack of support network and other comorbid conditions – such as substance misuse, chronic pain and hypothyroidism (/article/ld/hypothyroidism-causes-diagnosis-and-treatment) – can contribute to limited/no response to an antidepressant[9]. Genetic predisposition, such as being fast or slow metabolisers of certain antidepressants, can also contribute to lack of response[9].

All antidepressants show a pattern of response where the rate of improvement is highest during week one to two and lowest during weeks four to six[7]. In clinical practice, using simple observations and rating scales (see below) an antidepressant effect in an individual is usually seen within two weeks[7]. In individuals where no antidepressant effect is evident after three to four weeks of treatment, a change in dose or drug should be considered[7].

Switching to another antidepressant can improve remission rates; for example, in the 'Sequenced Treatment Alternatives to Relieve Depression' (STAR*D) trial, around one in four patients who did not respond/were intolerant to an initial selective serotonin reuptake inhibitor (SSRI) treatment, achieved remission after switching antidepressants[10–12].

Assessing antidepressant response

The British Association for Psychopharmacology (BAP) guidelines state to "continue adequately dosed antidepressants for at least four weeks, before changing treatment for lack of effect"[6]. It is important to understand what constitutes 'lack of effect' and that this will vary between individuals. Different patterns of response to antidepressants have been identified and in some individuals, response is slow[10]. Those responsive to treatment will have likely begun to show at least minor improvement at four weeks and for these patients it is then advisable to continue with the same antidepressant for another two to four weeks [6]. For those showing only small improvements at four weeks (i.e. <50% reduction in their depression rating score – see Box 1 (#box-1)), they may well go on to respond fully if the treatment period is extended[11].

Box 1: Criteria for defining antidepressant response

Antidepressant response and non-response is assessed through comparison of baseline scores using depression rating scales. There are several formal rating scales that can be used to assess symptom severity to produce scores to assess response, such as the Hamilton Depression Rating Scale (https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf) and the Patient Health Questionnaire (https://www.phqscreeners.com/) (PHQ-9)[13,14]:

- Non-response is defined as ≤25% decrease in symptom severity compared with baseline;
- A partial response is defined as a 26–49% decrease in symptom severity compared with baseline;
- A response is defined as a ≥50% reduction in symptom severity cores compared with baseline[15].

Patients showing no improvement will likely not respond to the prescribed drug at that dose; however, if a patient has trialled several antidepressant treatments with minimal effect, it is advisable to consider longer trials of treatment before considering further switching[6,7].

Selecting an alternative antidepressant

When an antidepressant has been deemed as unsuitable or ineffective for a patient, there are two options:

1. Change within the same drug class (i.e. from one SSRI to another), or;

2. Change to another drug class (i.e. from SSRI to serotonin–norepinephrine reuptake inhibitor [SNRI])[2].

As a rule, switching within a class is appropriate if the initial antidepressant caused intolerable side effects. However, if the side effect is common to an entire class of antidepressants (e.g. sexual dysfunction induced by SSRIs), switching to another class of drugs that does not have the same incidence of this side effect would be more appropriate [2,6,8,12,15–17].

For cases of non-response, SNRIs tend to be adopted as second line treatment where SSRIs have failed to be effective but there are limited data as to whether switching to an alternative drug class is effective. A study by Rush *et al.* of adult outpatients with a non-psychotic major depressive disorder (n=727) who experienced failure of treatment with an initial SSRI, found that switching to a SNRI (such as venlafaxine-XL or sertraline, if not trialled already) had no difference in efficacy and tolerability[10]. However, Baldomero *et al.* found that those who received prolonged release of venlafaxine (n=967) demonstrated a significantly higher rate of remission than those who were prescribed conventional antidepressants, such as SSRIs, and mirtazapine (n=7,540) may be more effective for those people who have not responded to SSRIs[18].

Current BAP guidelines state that after initial antidepressant failure, it is advisable to switch within the same class[6]. If there is more than one failure with an SSRI, venlafaxine or antidepressants where there is evidence of marginally higher efficacy than others owing to dose response such as: clomipramine, venlafaxine (doses equivalent to or higher than 150mg daily), escitalopram 20mg, sertraline, amitriptyline, or mirtazapine should be considered[6].

Managing an antidepressant switch

Abrupt discontinuation of an antidepressant should be avoided to minimise withdrawal effects[2,6,7,19,20]. Examples of withdrawal effects include: dizziness, anxiety, insomnia, mood fluctuations, electric shock-like feelings in the body and generally feeling unwell [21,22]. Given that depression and response to treatment is heterogeneous, there is limited information about how to conduct individual switches and variability to approaches should be expected. However, there are general principles and strategies that have been developed for common switches (see Figure 1), with cross-tapering being the most widely preferred strategy[7,20,23]. Cross-tapering is where the initial antidepressant is gradually reduced, whilst the second antidepressant is introduced at a lower dose and gradually increased[23].

Antidepressant switching strategies
Click on the arrows to see the four switching strategies.

If withdrawal symptoms are intolerable during the cross-tapering period, tapering should occur at a slower pace that is more manageable for the patient. Alternatively, the patient can return to the previous dose tolerated for stability before attempting a slower reduction (either by lengthening duration or reducing the dose in smaller increments)[7].

Although cross tapering is common, other switching strategies can be considered, see Figure 1[2,7]. Selecting an appropriate strategy will be based on the pharmacological profile of the drug originally prescribed as well as the assessed level of risk for the patient. Similarly, the pace of tapering requires clinical judgement although the Royal College of Psychiatrists guidance recommends that if an individual has been taking an antidepressant for only a few weeks, the initial dose should be reduced over four weeks by 25–50%, allowing two to four weeks to adjust to the new dose before considering another reduction. If an individual has been taking antidepressants for many months or years, it is best to taper more slowly over a period of months[21].

Management of withdrawal and discontinuation symptoms

Withdrawal effects can happen both when reducing an antidepressant or stopping completely[21,22]. For this article, withdrawal symptoms are discussed in relation to switching from one antidepressant to another. Withdrawal symptoms can be differentiated by their rapid onset (occurring within days, rather than weeks); rapid response to the re-introduction of antidepressant or previous tolerated dose (usually within hours rather than days); and the presence of somatic and psychological symptoms, which are different to the original depressive symptoms (e.g brain zaps, dizziness and nausea, see Table 1)[7]. Patients should be informed that there is a risk of withdrawal symptoms when switching antidepressants and dose reductions, as well as how to recognise withdrawal symptoms so that they can differentiate them from re-emerging depressive symptoms and do not wrongly attribute to them to the new antidepressant they are being switched to, or deem it ineffective[7,20,22].

Table 1: Examples of antidepressant withdrawal symptoms

Antidepressant	Withdrawal symptoms (list not exhaustive)
Selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors	Irritability, anxiety, insomnia, 'brain zaps', headache, fatigue, dizziness, nausea, panic attacks
Mirtazapine	Panic, anxiety, restless, irritability, hypomania, insomnia
Trazadone	Hypomania, anxiety, restless sleep, headache
Tricyclic antidepressants	Sleep disturbance, akathisia, hypomania/mania, vivid dreams
Agomelatine	Associated with very low risk of

Withdrawal symptom risk factors

It is difficult to predict who will experience withdrawal symptoms; however, the risk appears to be greater for patients' taking antidepressants at a higher dose for a long period of time[7]. Nevertheless, patients who have taken antidepressants for a short period (i.e. a month only) can also experience effects[7,21]. Antidepressants with a short half-life, such as paroxetine or venlafaxine, can produce withdrawal symptoms within one to two days[7,24]. In comparison, fluoxetine has a longer half-life and symptoms can be delayed by up to six weeks[7,25]. Most symptoms tend to be mild and self-limiting; however, there is variation between individuals with some patients experiencing severe effects. This should be explained to the patient prior to commencing a switch. Cross-tapering or stopping antidepressants should be individualised in line with the patient's tolerability and specific circumstances and risk factors and patients should be monitored closely throughout the switch[7].

Managing risk during a switch

Different switching strategies can also be selected to minimise the potential risk or severity of withdrawal effects (see Figure 1). Abrupt discontinuation or a severe decrease in dosing is the highest contributor to a patient developing withdrawal symptoms[2,7,20–22]. Evidence on the best methodology for reducing antidepressant dosage is limited: a recent Cochrane review found relatively few studies focused on different approaches to discontinuation of long-term antidepressants; therefore, pharmacists and other prescribers will need to consider several factors and apply clinical judgement (/article/ld/how-to-use-clinical-reasoning-in-pharmacy) when tapering or stopping an antidepressant[26]. These include:

- The pharmacokinetic profile of the medication being switched (those with shorter half-lives may require longer cross-tapering/slower reductions over a longer period);
- Slowly reducing the dose (by 50%) of previous dose;
- Consider reducing by smaller doses when doses become lower (reduction by 25%);
- Consider smaller dose reductions for liquid formulations;
- Ensuring the speed and duration of switching antidepressants is led by the patient and any withdrawal symptoms are resolved/tolerable before the next dose-reduction is made. Remember, everyone is different;
- Recognising that appearance of withdrawal symptoms can sometimes take weeks or months (more so when not cross-tapering);
- Recognise that there may be situations where a non-cautious approach may be required when switching antidepressants. For example, if the patient is at risk of relapse or withdrawal symptoms are intolerable during a cautious approach. In situations such as these, pharmacists and other prescribers should ensure this is done under close supervision with an expert specialist/prescriber and plan for more regular follow-ups;
- Consider assessing withdrawal symptoms using the 'Discontinuation-Emergent Signs and Symptoms' (DESS) scale[7].

The case study below illustrates how these principles can be applied in practice.

Patient case study

A 32-year-old Indian female – 'Patient A' – was diagnosed with moderate depression four months ago. She is being reviewed in a pharmacist-led mental health clinic because she feels her medication is no longer effective. She has been on her current medication (citalopram 40mg once daily) since her diagnosis and this is the first one she has trialled. She has been with her partner for two years, has no children and lives alone with her cat. She works as a finance analyst but is currently off sick from work because of her depressive symptoms.

Past medical history

Irritable bowel syndrome, for which she uses over-the-counter Buscopan (hyoscine butylbromide; Sanofi) and occasional sleep difficulties related to her high pressured job.

Family history

Patient A's mother has a history of postnatal depression, which was treated with antidepressants and a mood stabiliser at the time.

Social history

Patient A smokes and drinks at social occasions, which is often once per week.

Biomedical results

All blood test results are normal including vitamin D, thyroid function test, iron levels and vitamin B12.

Current medication

- Citalopram 40mg once daily;

- Zopiclone 3.75mg – 1–2 tablets daily as required for insomnia.

During the 15-minute consultation, the pharmacist checks medicines adherence (/article/ld/how-pharmacists-can-encourage-patient-adherence-to-medicines) and gathers information to assess symptoms, response to treatment, current circumstances and risk. Patient A reports that she does experience fleeting suicidal thoughts (/article/ld/suicide-how-to-recognise-the-warning-signs-and-deal-with-disclosure) but has no plan or intent to act on this. When she has bad days (which is often), she says she feels like "what is the point in living?" and "it would be easier if I wasn't here", but is able to identify that she does want to get better and just live her life. She has no previous suicide attempts and no thoughts to, or currently self-harms.

Patient A says she does not use zopiclone often, mainly when she has a big meeting the next day and feels anxious, which prevents her from falling asleep. She has a supportive network around her but continues to feel persistently low and is constantly tearful, with a lack of motivation and no interest in what she used to do, such as going to the gym and socialising with friends.

Consultation outcome

As the patient is on the maximum dose of citalopram and no longer finding it effective, it was agreed with the pharmacist to switch to another antidepressant.

Considering that the risk of suicide and self-harming is low, as identified by the risk assessment, and the patient is not utilising zopiclone as often, it was decided to trial another SSRI. Sleep is not a major issue here, meaning that an antidepressant with sedating properties is not required.

All things considered, it was decided to trial sertraline owing to evidence that supports dose response, and also because when switching from one SSRI to another antidepressant, sertraline should be considered[6]. In this case, a direct switch method is possible because it is a switch from one SSRI to another and also because the patient is not presenting as imminent risk to self (see Table 2[27]). As a result, a slower approach can be considered to change antidepressant without additional antidepressant coverage required.

Table 2: Method of switching — direct switch

	Starting dose	Week 1	Week 2	Review with pharmacist	Week 3	Week 4	W
Withdrawing citalopram	40mg once daily	Reduce to 30mg once daily	Reduce to 20mg once daily	Review with pharmacist	10mg once daily	Nil	R w pl
Sertraline	-	Nil	Nil	Review with pharmacist	Nil	50mg once daily but can be titrated upwards (weekly) according to patient's symptoms and tolerability	R w pl

The pharmacist explains the risks around potential withdrawal symptoms, such as irritability, anxiety and brain zaps. The pharmacist checks the patients understanding of these symptoms and describes brain zaps as an electrical shock sensation felt in the brain. The pharmacist agreed to speak with the patient every two weeks during the reduction period (Table 2) to check in on her and see how Patient A is managing.

Discussion

Had the patient responded differently to the question about suicide ideation, the pharmacist would have taken a different approach. Had there been active suicide ideation, the pharmacist would have needed to consider the strength of the patient's support network and most likely would have selected a cautious cross tapering strategy with regular weekly review during the reduction period.

In all instances, the pharmacist would need to hold an effective consultation that carefully considers the specific circumstances affecting the patient and create an appropriate structure for safely monitoring the change in medication.

Summary

Antidepressant switches primary occur owing to intolerable side effects or an inadequate response. Pharmacists have an important role to play to ensure that antidepressant switches are managed appropriately and safely, taking into consideration the underlying pharmacokinetics and pharmacology to minimise adverse reactions. Specific risk factors influencing switching strategy need to be carefully considered and appropriate management of withdrawal and discontinuation symptoms should be provided. Adequate support, follow up, patient education and counselling should be made readily available for patients when switching.

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