

Graylands Hospital Drug Bulletin

Antidepressant Switching Strategies

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Introduction

Suboptimal response of patients with depression to antidepressant medication is a common clinical scenario. It has been estimated that only 50% to 60% of patients respond to their initial antidepressant,¹ and less than a third of patients achieve full remission.¹

Clearly, in this context, switching antidepressant medication is likely to be a commonly occurring intervention. While there are a number of published studies examining outcomes following antidepressant switch,² it is perhaps surprising there is a lack of data to guide clinicians on the best method of switching from one antidepressant to another from a practical perspective.

In this edition of the Drug Bulletin we have evaluated the various switching strategies and recommended practical switching strategies for individual antidepressant drugs.

The following advice is based on a combination of published data (when available), theoretical concerns and good clinical practice. It is intended for general guidance only. Whichever strategy is used, patients should be closely monitored for any alterations in mood and adverse effects.

Antidepressant switching strategies

Given that there are over 20 different antidepressants available for use in Australia, from several distinct pharmacological classes, there are many switching permutations. However, in clinical practice the most commonly employed strategies include:

The direct switch, taper and then immediate switch, taper and then switch after a washout period and cross-titration.³

In some cases, the most appropriate switch method will clearly be dictated by the antidepressant being taken prior to the switch, or the antidepressant that is to be taken following the switch. For example, the combination of a non-selective, irreversible monoamine oxidase inhibitor (MAOI) (e.g. phenelzine or tranylcypromine) with

another antidepressant would expose the patient to a real risk of serotonin syndrome,⁴ so a substantial washout period between drugs is highly advisable.

The direct switch

When the direct switch is employed, the patient's current antidepressant is stopped abruptly and the new antidepressant is started the next day.

The advantage of this method is that it is quick and simple. However, discontinuation symptoms and drug interactions can be a concern.

This regimen may be suitable if the first antidepressant has been taken for less than six weeks, and is therefore unlikely to cause discontinuation symptoms or if severe side effects with the first antidepressant have occurred.

Abrupt cessation may also be acceptable when switching to a drug with a similar, but not identical, mode of action. An example of this would be switching from a selective serotonin reuptake inhibitor (SSRI) to duloxetine.³

Some guidelines suggest that it may be possible to switch one SSRI to another SSRI using the direct switch method.⁵ As it has been postulated that the effects of the individual SSRIs are so similar that administration of the second drug is likely to ameliorate withdrawal effects of the first.⁵ However, if switching from fluoxetine to another SSRI, then a gap of 4-7 days is recommended due to the long half-life of fluoxetine.³

This regimen is also suitable when switching from agomelatine,⁶ as abrupt withdrawal of agomelatine has not been associated with discontinuation symptoms. In addition, no significant problems have been reported when agomelatine is taken with other antidepressants⁶ (the exception being fluvoxamine).

Taper and then immediate switch

Gradually withdrawing (tapering) the first antidepressant and then starting the new antidepressant immediately after discontinuation.



This strategy is usually recommended when the first antidepressant has been taken for longer than six weeks (therefore likely to cause discontinuation symptoms if stopped abruptly). However there is an increased risk of drug interactions and this strategy is more time consuming than the direct switch.

This strategy is also recommended when switching from one SSRI to another SSRI, due to the combined risk of serotonin syndrome (it would be prudent to commence the new SSRI at a reduced dose).³ This strategy would also be suitable when switching from duloxetine to an SSRI or venlafaxine.³

Taper and then switch after a washout period

Gradually withdrawing the first antidepressant and then starting the new antidepressant after a washout period.

The washout period (time between stopping one drug and starting another) is dependent on the half-life of the first drug. As a general rule the majority of a drug is eliminated from the body within five half-lives.⁷ The benefit of this approach is safety, but the switch is slow and leaves the patient without treatment for some time.

This strategy should be used when switching to and from non-selective, irreversible MAOIs due to the risk of serotonin syndrome.³ The washout period required with non-selective, irreversible MAOIs varies depending on the drugs involved in the switch. For example, if a patient is taking an antidepressant that has a relatively short half-life, such as venlafaxine or paroxetine, a washout period of at least one week is needed. Whereas 5-6 weeks is recommended as the wash out period if switching from a drug with a long half life, such as fluoxetine to an MAOI.³

It is recommended to leave a gap of two weeks when switching from a non-selective, irreversible MAOI to another antidepressant (three weeks if switching to either imipramine or clomipramine). When switching from moclobemide, a reversible MAOI, to any other antidepressant, then a gap of 24 hours is sufficient.³

Cross-tapering

The dose of the first antidepressant is tapered down gradually, and the dose of the new medication is simultaneously built up.

The benefits of this strategy are that the patient does not have a break in treatment. However, potential dangers of simultaneously administering two antidepressants include pharmacodynamic

interactions (e.g. serotonin syndrome, hypotension, drowsiness) and pharmacokinetic interactions (e.g. elevation of tricyclic plasma levels by some SSRIs).⁷

The co-administration of some antidepressants, even when cross tapering, is absolutely contraindicated. In certain other cases, theoretical risks or lack of experience preclude recommending cross-tapering.

Clomipramine should not be co-administered with SSRIs, venlafaxine or duloxetine - except under specialist use - and therefore cross-tapering is not recommended. Clomipramine should be withdrawn before starting an SSRI, venlafaxine or duloxetine, and vice versa if switching to clomipramine.³

Due to the potential for serious drug interactions, cross tapering between tricyclic antidepressants (TCAs) and SSRIs should be done very cautiously. Particularly when switching to fluvoxamine, paroxetine or fluoxetine.

Fluvoxamine is a potent inhibitor of the cytochrome P4501A2 isoenzyme that is largely responsible for the metabolism of amitriptyline, clomipramine and imipramine; concomitant use can result in increased (up to 4-fold) levels⁸ and possible signs of toxicity. Paroxetine and fluoxetine are inhibitors of the cytochrome P4502D6 isoenzyme and concomitant use with clomipramine or nortriptyline may result in increased plasma levels of these TCAs.⁸

When cross-tapering from a TCA to an SSRI, gradually reduce the dose of the TCA by up to 50% and start the SSRI at the normal starting dose.³ Gradually discontinue the TCA over the next few weeks.

If cross-tapering from venlafaxine to an SSRI, reduce the dose of venlafaxine then start the SSRI at half the normal starting dose³ (e.g. citalopram 10mg daily or fluoxetine 10mg daily).

Switching antidepressants and serotonin syndrome

SSRIs have gained wide acceptance in the treatment of depressive disorders because of the perception that they do not cause major adverse reactions either in therapeutic doses or overdose. Since the introduction of these agents, the risk of severe cardiotoxicity (as seen with TCAs) seems to have decreased, but there have been increasing reports of other side effects, such as serotonin syndrome.⁴

Serotonin syndrome is characterised by alterations in mental status, autonomic stability and neuromuscular activity.⁴ It was first described in 1955 in a patient who experienced a drug interaction between pethidine and iproniazid. Sternbach⁴ published a review of serotonin syndrome in 1991, and since then,

the number of reports has increased steadily as clinicians have become more aware of its existence.

Table 1: Symptoms of serotonin syndrome used by Sternbach⁴

Altered mental status	Autonomic dysfunction	Neuromuscular abnormalities
agitation confusion mania	diaphoresis diarrhoea fever shivering	hyper-reflexia incoordination myoclonus tremor

Serotonin syndrome can be a life-threatening condition and occurs acutely due to markedly increased serotonin levels in the brain, often following co-prescription or overdose of serotonergic drugs.⁹

These drugs can increase serotonin levels by inhibiting metabolism (such as MAOIs), increasing formation (such as L-tryptophan), inhibiting reuptake (such as SSRIs, SNRIs and TCAs), increase release (such as amphetamines) or increasing postsynaptic receptor sensitivity (such as lithium).

The combination of non-selective irreversible MAOIs and SSRIs appears to be particularly toxic.⁴ This is probably a result of simultaneous blockade of serotonin reuptake by SSRIs and the inhibition of serotonin degradation by MAOIs, leaving no mechanism to control serotonin concentration in the synapse.⁴

The exact role of the various serotonin receptors is not completely clear, but there is good evidence that the severe life-threatening clinical effects such as rigidity and hyperthermia are mediated by the 5-HT_{2a} receptors.¹⁰

Discontinuation symptoms

If taken continuously for six weeks or longer abrupt withdrawal of antidepressant medication should be avoided, except in the case of a serious adverse event, due to the risk of discontinuation symptom.¹¹

Discontinuation symptoms are experienced by at least a third of patients and are seen to some extent with all antidepressants. They may be hard to distinguish from some of the original symptoms of the underlying illness.¹¹

Discontinuation symptoms can be broadly divided into five groups; affective (e.g. irritability), gastrointestinal (e.g. diarrhoea), vasomotor (e.g. sweating), neurosensory (e.g. paraesthesia) and other neurological (e.g. dreaming).¹¹

Symptoms can vary in form and intensity and occur in any combination. They are usually mild and self-limiting, but can be severe and prolonged, particularly if withdrawal is abrupt.³

Table 2: FINISH - Remembering the discontinuation syndrome

F	Flu-like symptoms
I	Insomnia
N	Nausea
I	Imbalance
S	Sensory disturbances
H	Hyperarousal (agitation/anxiety)

Some symptoms are more likely with individual drugs, for example dizziness and electric shock-like sensations with SSRIs, and sweating and headache with TCAs.¹¹ Of the commonly used antidepressants, the risk of discontinuation symptoms seems to be greatest with paroxetine, venlafaxine and amitriptyline.¹¹ The onset is usually within a few days of stopping treatment, or occasionally during taper or after missed doses. This is influenced by a number of factors, which predominantly includes a drug's half-life.¹⁰ At 20mg/day abrupt withdrawal of fluoxetine is generally safe because fluoxetine has a long half-life and is therefore not usually associated with discontinuation symptoms.⁹ At higher doses, fluoxetine should be withdrawn over two weeks.

How long should the taper be when switching antidepressants?

Two of the antidepressant switch strategies described above involve tapering the first antidepressant, before introducing the new one. It is presumed that tapering is an effective strategy to minimise discontinuation symptoms but there is a lack of evidence about this or the optimal rate of taper. A study randomising patients on SSRIs/venlafaxine to a 3-day or 14 day taper found a discontinuation syndrome in 46% of patients with no difference according to rate of taper.¹²

In clinical practice, the taper period when switching antidepressants in non-responders will depend upon a number of factors. For example, in a severely depressed patient a long taper prior to starting the new antidepressant would delay treatment significantly. Conversely, in an elderly or medically ill patient it may be reasonable to use a longer taper. Clearly the clinician needs to be prudent in balancing the length of taper - and subsequent risk of discontinuation symptoms - with any delay in treatment. When stopping an antidepressant altogether (not switching to another drug) then most guidelines suggest that antidepressants should be discontinued over about four weeks.⁴

Table 3: Switching antidepressants - adapted from Maudsley Prescribing Guidelines 11th edition⁴

To / From	Non-selective, irreversible MAOI	Tricyclics	SSRIs (except fluoxetine)	Fluoxetine	Moclobemide	Reboxetine	SNRIs - duloxetine, venlafaxine, desvenlafaxine	Mirtazapine
Non-selective, irreversible MAOI		Taper & stop then wait for 2 weeks	Taper & stop then wait for 2 weeks	Taper & stop then wait for 2 weeks	Taper & stop then wait for 2 weeks	Taper & stop then wait for 2 weeks	Taper & stop then wait for 2 weeks	Taper & stop then wait for 2 weeks
Tricyclics	Taper & stop then wait for 2 weeks	Cross-taper cautiously	Halve dose & add SSRI then slow withdrawal	Halve dose & add fluoxetine then slow withdrawal	Taper & stop then wait for 1 week	Cross-taper cautiously	Cross-taper cautiously, start with low dose SNRI	Cross-taper cautiously
SSRIs (except fluoxetine)	Taper & stop then wait for 1 week	Cross-taper cautiously	Taper & stop then start new SSRI at a low dose	Taper & stop then start fluoxetine 10mg/day	Taper & stop then wait for 1 week	Cross-taper cautiously	Cross-taper cautiously, start with low dose SNRI & increase v slowly	Cross-taper cautiously
Fluoxetine	Taper & stop then wait 5-6 weeks	Taper & stop then wait 4-7 days. Start TCA at very low dose & increase slowly	Taper & stop then wait 4-7 days. Start fluoxetine at low dose & increase slowly		Taper & stop then wait at least 5 weeks	Cross-taper cautiously	Taper & stop. Start with low dose SNRI & increase very slowly	Cross-taper cautiously start mirtazapine 15mg/day
Moclobemide	Taper & stop then wait 24h	Taper & stop then wait 24h	Taper & stop then wait 24h	Taper & stop then wait 24h		Taper & stop then wait 24h	Taper & stop then wait 24h	Taper & stop then wait 24h
SNRIs - duloxetine, venlafaxine, desvenlafaxine	Taper & stop then wait at least 1 week	Cross-taper cautiously with low dose of TCA	Cross-taper cautiously with low dose of SSRI	Cross-taper cautiously with low dose of fluoxetine	Taper & stop then wait for 1 week	Cross-taper cautiously	Taper & stop then start new SNRI	Cross-taper cautiously
Mirtazapine	Taper & stop then wait for 2 weeks	Cross-taper cautiously with low dose of TCA	Cross-taper cautiously	Cross-taper cautiously	Taper & stop then wait for 1 week	Cross-taper cautiously	Cross-taper cautiously	

Exercise particular caution when switching in the following circumstances

- From fluoxetine to other antidepressants, due to long half-life of fluoxetine.
- If switching from fluoxetine to another SSRI, then a gap of 4-7 days is recommended.
- If switching from fluoxetine to a non-selective irreversible MAOI, then a gap of 5-6 weeks is recommended.
- From SSRIs to TCAs and from TCAs to SSRIs because certain SSRIs (mostly fluvoxamine, fluoxetine and paroxetine) will inhibit the metabolism of TCAs.
- To a new serotonergic antidepressant or MAOI, because of the risk of serotonin syndrome.
- From a non-selective irreversible MAOI: a 2-week washout period is required. 3 weeks in the case of imipramine and clomipramine.
- Do not administer clomipramine and SSRIs, venlafaxine or duloxetine. Due to a high risk of serotonin syndrome.
- Do not co-administer agomelatine and fluvoxamine.
- Switching to reboxetine is no longer recommended in some guidelines.

The above table has been adapted from the Maudsley Prescribing guidelines 11th edition. See guidelines for full table. Other helpful antidepressant switching tables can be found in the Psychotropic Drug Directory (Bazire 2012) and the Therapeutic Guidelines (Psychotropic) version 6 2008.

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References available on request.

For all Psychiatric Drug Information enquiries, please contact the Statewide Psychiatric Drug Information Service on (08) 9347 6400.

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