How do you switch between tricyclic, SSRI and related antidepressants?

Summary
- Care is required when switching between antidepressants.
- When switching between selective serotonin reuptake inhibitors, tricyclic and related antidepressants, it is considered safer, in order to avoid inducing a drug discontinuation syndrome or precipitating drug interactions, to incrementally reduce the dose of the first antidepressant and discontinue it before starting the second antidepressant. This is not always possible. In severely depressed patients who have failed to respond to one antidepressant, or in cases of severe adverse reaction, it may be necessary to shorten the process of substitution.
- Cross-tapering is an option for some switches but should always be done cautiously.
- Patients should be assessed on an individual basis to determine how quickly the switch can be done.
- The potential for medication errors with complicated switching regimens should be considered.

Background
The main reasons for switching antidepressants are an inadequate response to initial therapy despite being used at the right dose for an appropriate duration of time, or the presence of intolerable side effects. When switching between antidepressants there is the potential for interaction between the two agents and/or for the patient to experience drug discontinuation symptoms from withdrawal of the first drug.

Most commonly used antidepressants affect serotonin transmission. Concomitant or sequential use can increase the risk of serotonin syndrome. The characteristic symptoms of this syndrome include altered mental state (agitation, confusion), autonomic dysfunction (fever, sweating) and neuromuscular abnormalities (tremor, in-coordination); convulsions and fatalities have been reported [1,2]. Although serotonin syndrome can occur exceptionally after taking only one drug, it is more likely to develop when two or more drugs with serotoninergic activity are taken together [1].

Symptoms of antidepressant discontinuation syndrome are likely when a drug is stopped abruptly after regular administration for six weeks or more [2]. Most antidepressants should be withdrawn by reducing the dose gradually over a minimum of four weeks, using patients’ symptoms as a guide to the speed of withdrawal. Fluoxetine and vortioxetine are the exceptions. Because of their long half-lives, vortioxetine can be stopped abruptly as can fluoxetine at a dose of 20mg daily; at higher doses, incremental withdrawal is required with fluoxetine [2].

When switching antidepressants, individual patient circumstances should be assessed, taking into account the following factors:
- the urgency of the switch. In severely depressed patients who have failed to respond to one antidepressant, or in cases of severe adverse reaction, it may be necessary to shorten the process of substitution. With less urgency a more cautious approach can be used.
- the patient’s physical condition. Caution is required in older patients and those with co-morbidities.
- the current dose of the first antidepressant and how easily this can be withdrawn.
- the duration of antidepressant treatment. If this has been less than 6 weeks then it may be possible to shorten the withdrawal period or stop the drug abruptly.
- the risk of serotonin syndrome. Serotonin syndrome is more likely to occur if the patient is on other drug therapy with serotoninergic activity, for example opioids, tramadol, selegiline, lithium, linezolid and dextromethorphan [1,3].
- any history of discontinuation reactions.
- the risk that the switching regimen will confuse the patient and result in medication error.

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Few studies have specifically examined the best strategy for switching between antidepressants. The following advice is based on available information, theoretical concerns and clinical experience. It is intended for general guidance only. For patients with complex medical or drug histories, specialist advice should be sought. Whichever strategy is used, patients should be closely monitored for adverse effects.

**Answer**

In practice, switches between selective serotonin reuptake inhibitors (SSRIs), tricyclic (TCA) and related antidepressants can be carried out in one of three ways:

1. **Gradual withdrawal and then switch**
   Gradually withdrawing the first antidepressant over several weeks and starting the second antidepressant, at a low dose, either
   ♦ immediately after discontinuation, or
   ♦ 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.

2. **Cross-tapering**
   Gradually reducing the dose of the first antidepressant while starting the second antidepressant at a low dose and then increasing this dose as the first drug is withdrawn.

   Cross-tapering is an option when switching between some antidepressants. It is unnecessary if switching from fluoxetine because of the long half-life of the drug (see immediate switch). Clomipramine is a potent inhibitor of serotonin reuptake and serotonin syndrome is more likely to occur if it is co-administered with SSRIs, venlafaxine or duloxetine, therefore cross-tapering is not recommended, except under specialist use [2,3]. Clomipramine should be withdrawn before starting an SSRI, venlafaxine or duloxetine, and vice versa if switching to clomipramine [2].

   Due to the potential for serious drug interactions, cross-tapering with TCAs is inadvisable with paroxetine and fluvoxamine, although it can be done very cautiously if necessary. As fluvoxamine is a potent inhibitor of the cytochrome P450 1A2 isoenzyme which is largely responsible for metabolism of amitriptyline, clomipramine and imipramine [3,4], concomitant use can result in increased TCA levels [3]. Paroxetine and fluoxetine are inhibitors of cytochrome P450 2D6 isoenzyme and concomitant use with clomipramine or nortriptyline may result in increased plasma levels of these TCAs [3,5,6].

   When cross-tapering from a TCA to an SSRI, gradually reduce the dose of TCA to 25-50mg daily and start the SSRI at the normal starting dose. Gradually discontinue the TCA over the next 5 to 7 days [3]. If cross-tapering from venlafaxine to an SSRI, reduce the dose of venlafaxine then start the SSRI at half the normal starting dose e.g. citalopram 10mg daily or fluoxetine 10mg daily [2].

   Cross-tapering should always be carried out cautiously. An example of cross-tapering between citalopram and mirtazapine is given below. The example uses a weekly schedule; however, some patients may not tolerate this, and for these patients a two week schedule or longer may be more appropriate [7]. The speed of cross-tapering is best judged by monitoring patient tolerability [2].

<table>
<thead>
<tr>
<th>Switch</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>From citalopram 40mg daily</td>
<td>20mg daily</td>
<td>10mg daily</td>
<td>5mg daily</td>
<td>Nil</td>
</tr>
<tr>
<td>To mirtazapine</td>
<td>15mg daily</td>
<td>30mg daily</td>
<td>30mg daily</td>
<td>45mg daily (if required)</td>
</tr>
</tbody>
</table>

3. **Immediate switch**
   Stopping the first antidepressant abruptly, and starting the second antidepressant at a low dose, either
   ♦ immediately after stopping, or
   ♦ following a washout period.

   In theory, because the half-lives of SSRIs are similar, it should be possible to immediately switch from one to another, with administration of the second SSRI ameliorating the withdrawal effects of the first [2]. The
exception is fluoxetine which has a long half-life and a washout period is required. This regimen may be an option if the first antidepressant has been taken for less than six weeks or if severe side effects with the first antidepressant have occurred. If this regimen is chosen, a low starting dose of the second SSRI should be used and titrated up. This method has also been suggested for switching from SSRIs to venlafaxine [8,9] and from SSRIs to duloxetine [10]. Discontinuation syndromes can occur with all classes of antidepressants therefore an immediate switch may put the patient at risk of discontinuation symptoms (especially with paroxetine and venlafaxine [2,11], particularly if the switch is to an agent of a different class [12].

Agomelatine switching
Agomelatine is an antidepressant agent with selective agonist action at melatonin receptors and selective antagonist action at serotonin 5HT-2C receptors. It does not affect uptake of serotonin, noradrenaline or dopamine [13]. Abrupt withdrawal of agomelatine has not been associated with discontinuation symptoms. This means that no dose tapering is necessary when stopping treatment [14,15]. No significant problems have been reported when agomelatine is taken with most other antidepressants so patients can be switched to and from this with negligible risk [3]. When switching from another antidepressant to agomelatine, agomelatine can be started whilst gradually withdrawing the first antidepressant. The exception is fluvoxamine which affects the metabolism of agomelatine by inhibiting cytochrome P450 1A2 (CYP1A2) thus increasing agomelatine levels [3,14]. It is recommended that when switching from fluvoxamine to agomelatine, fluvoxamine is withdrawn gradually and a three to seven day washout period is allowed before starting agomelatine [2,15].

Vortioxetine switching
Vortioxetine is a new antidepressant and there is limited experience when switching, therefore extra caution is required, particularly when switching to or from inhibitors of CYP2D6, such as fluoxetine and paroxetine [2]. The manufacturer advises that vortioxetine can be stopped without gradual dose reduction [16]. However when switching to another antidepressant, doses above 10mg should be reduced to 10mg over a period of 7 days before stopping and starting the new antidepressant [2]. In studies in which patients were abruptly switched from an SSRI or a serotonin and noradrenaline reuptake inhibitor (SNRI) to vortioxetine, about 25% experienced nausea [17,18]. However, in a study in which patients were gradually switched from an SSRI or SNRI by cross tapering doses, rate of nausea was 16% with vortioxetine [19].

Suggested guidelines for switching between individual antidepressants are included in Table 1, at the end of the document.

Limitations
Few studies have investigated the best strategy for, and outcomes of, switching antidepressants. The literature search was limited to adults only, therefore guidance may differ for children and young adults.

References

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19. Montgomery SA, Nielson RZ, Poulsen LH, Haggstrom L. A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. Hum Psychopharmacol 2014; 29: 470-82.

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Search strategy
- In-house databases/resources.
- Medline:
  1. Antidepressive-agents AND Substance-withdrawal-syndrome
  3. Vortioxetine and Switch$.
- Embase:
  1. Antidepressant-agent AND Drug-withdrawal
  2. Antidepressant-agent OR Tricyclic-Antidepressant-Agent OR Serotonin-Uptake-Inhibitor OR Monoamine-Oxidase-Inhibitor AND Switch$.
  3. Vortioxetine and Switch$.
- electronic Medicines Compendium (eMC) www.medicines.org.uk
- Expert comments:
### Table 1: Switching antidepressants: Use this table in conjunction with the previous notes

<table>
<thead>
<tr>
<th>1st agent</th>
<th>Citalopram, escitalopram, paroxetine, or sertraline</th>
<th>Fluvoxamine</th>
<th>Fluoxetine</th>
<th>TCA (except clomipramine)</th>
<th>Clomipramine*</th>
<th>Venlafaxine</th>
<th>Duloxetine</th>
<th>Mirtazapine</th>
<th>Reboxetine**</th>
<th>Agomelatine</th>
<th>Vortioxetine*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2nd agent</strong></td>
<td>Discontinue first SSRI gradually and stop - start second SSRI at low dose the following day [2] or Immediate switch [8,9,15]</td>
<td>Discontinue SSRI gradually and stop - start fluvoxamine at low dose the following day [2]</td>
<td>Cross-taper cautiously with low dose of TCA [2]</td>
<td>Discontinue SSRI gradually and stop - start fluoxetine 10mg the following day [2]</td>
<td>Cross-taper cautiously, starting with low dose venlafaxine e.g. 37.5mg daily and increase very slowly [2] or Immediate switch (caution if fluoxetine or paroxetine used) [8,9]</td>
<td>Immediate switch starting with duloxetine 60mg daily has been well tolerated [2,3,10]</td>
<td>Cross-taper cautiously [2]</td>
<td>Cross-taper cautiously [2]</td>
<td>Cross-taper cautiously starting with low-dose vortioxetine [2]</td>
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</tbody>
</table>

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<th>Duloxetine</th>
<th>Mirtazapine</th>
<th>Reboxetine**</th>
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<td>Agomelatine</td>
<td>Vortioxetine#</td>
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<tr>
<td><strong>Duloxetine</strong></td>
<td><strong>Cross-taper cautiously with low dose SSRI [2]</strong></td>
<td><strong>Discontinue gradually then stop – start fluvoxamine at low dose the following day [2]</strong></td>
<td><strong>Discontinue gradually then stop – start fluoxetine 10mg daily the following day [2]</strong></td>
<td><strong>Cross-taper cautiously using a very low starting dose of TCA e.g. amitriptyline 25mg daily [2]</strong></td>
<td><strong>Discontinue gradually then stop – start clomipramine at low dose the following day [2]</strong></td>
<td><strong>Cross-taper cautiously with low dose venlafaxine e.g. 37.5mg [2]</strong></td>
<td><strong>Cross-taper cautiously [2]</strong></td>
<td><strong>Cross-taper cautiously [2]</strong></td>
<td><strong>Cross-taper cautiously [2]</strong></td>
<td><strong>Cross-taper cautiously with low-dose vortioxetine [2]</strong></td>
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<td><strong>Mirtazapine</strong></td>
<td><strong>Cross-taper cautiously [2]</strong></td>
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<td><strong>Reboxetine</strong></td>
<td><strong>Cross-taper cautiously [2]</strong></td>
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<td><strong>Cross-taper cautiously [2]</strong></td>
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<tr>
<td><strong>Agomelatine</strong></td>
<td><strong>Stop agomelatine abruptly – start SSRI the following day [2,14,15]</strong></td>
<td><strong>Stop agomelatine abruptly – start fluoxetine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start fluoxetine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start TCA the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start clomipramine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start venlafaxine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start duloxetine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start mirtazapine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start reboxetine the following day [2]</strong></td>
<td><strong>Stop agomelatine abruptly – start vortioxetine the following day [2]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Vortioxetine#</strong></td>
<td><strong>Cross-taper cautiously starting with low-dose SSRI [2]</strong></td>
<td><strong>Stop vortioxetine# abruptly – start fluoxetine at low dose the following day [2]</strong></td>
<td><strong>Stop vortioxetine# abruptly – start fluoxetine 10mg the following day [2]</strong></td>
<td><strong>Cross-taper cautiously with low-dose TCA [2]</strong></td>
<td><strong>Stop vortioxetine# abruptly – start clomipramine at low dose the following day [2]</strong></td>
<td><strong>Cross-taper cautiously with low-dose venlafaxine e.g. 37.5mg [2]</strong></td>
<td><strong>Cross-taper cautiously with low-dose duloxetine [2]</strong></td>
<td><strong>Cross-taper cautiously [2]</strong></td>
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</tbody>
</table>

* See notes regarding cross-tapering. Cross-tapering clomipramine with venlafaxine, duloxetine or a SSRI is not recommended.
** Switching to reboxetine as antidepressant monotherapy is no longer recommended [2].
§ Fluoxetine at doses greater than 20mg may need to be withdrawn gradually, over 2 weeks, rather than stopping abruptly [2].
# See notes on vortioxetine. Vortioxetine at doses greater than 10mg should be reduced to 10mg over 1 week before stopping [2].