How do you switch between monoamine oxidase inhibitors and SSRI, tricyclic or related antidepressants?

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Summary

- Care is required when switching between antidepressants.
- When switching between monoamine-oxidase inhibitor (MAOI) or moclobemide (a reversible inhibitor of monoamine-oxidase type A – RIMA) and other antidepressants, the first antidepressant agent should be withdrawn gradually and discontinued before starting the second antidepressant.
- For switches that involve a MAOI, a washout period is always advised.
- Patients should be assessed on an individual basis to determine how quickly the switch can be made by assessing history of discontinuation reactions, concurrent medication and severity of depression.
- The potential for medication errors 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, incoordination); 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 serotonergic 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 Most antidepressants should be withdrawn by reducing the dose gradually over a minimum of four weeks, using patients’ symptoms as a guide to the speed of withdrawal.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 six 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 serotonergic 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.
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**

Switches between selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCA) and serotonin-noradrenaline reuptake inhibitor (SNRI) antidepressants and either a monoamine-oxidase inhibitor (MAOI) or moclobemide (a reversible inhibitor of monoamine-oxidase type A – RIMA) require a washout period between stopping one agent and starting another to avoid the potential risk of serotonin syndrome. The first antidepressant should be gradually withdrawn over several weeks and the second antidepressant started after a suitable washout period.

The tables below provide guidance on switching between MAOI, RIMA and other antidepressant agents. Recommendations for switching from an MAOI or moclobemide to a SSRI, TCA or related antidepressant are in Table 1. Recommendations for switching from an SSRI or SSRI, TCA or related antidepressant are in Table 2.

**Table 1: Switching to an MAOI or moclobemide**

<table>
<thead>
<tr>
<th>1st agent ▼</th>
<th>MAOI (phenelzine or isocarboxazid or tranylcypromine)</th>
<th>Moclobemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Discontinue SSRI gradually and stop – start MAOI 7 days later [2,4,5,6].</td>
<td>Discontinue SSRI gradually and stop – start moclobemide 7 days later [2,4,6].</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Discontinue SSRI gradually and stop – start MAOI 7 to 14 days later [2,3,7].</td>
<td>Discontinue SSRI gradually and stop – start moclobemide 7 to 14 days later [2,3,7]. See note (a).</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Discontinue SSRI gradually and stop – start MAOI 7 to 14 days later [2,3,7].</td>
<td>Discontinue SSRI gradually and stop – start moclobemide 7 days later [2,10].</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Stop SSRI – start MAOI 5 to 6 weeks later [2,11].</td>
<td>Stop SSRI – start moclobemide 5 to 6 weeks later [2,11]. See note (a).</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Discontinue TCA gradually and stop – start MAOI 7 to 21 days later, depending on TCA being taken [2,3,9,12]. See note (b).</td>
<td>Discontinue TCA gradually and stop – start moclobemide 7 days later [2].</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Discontinue venlafaxine gradually and stop – start MAOI at least 7 days later [2,13].</td>
<td>Discontinue venlafaxine gradually and stop – start moclobemide at least 7 days later [2].</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Discontinue duloxetine gradually and stop – start MAOI at least 5 days later [3,14].</td>
<td>Discontinue duloxetine gradually and stop – start moclobemide at least 5 days later [2].</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Discontinue mirtazapine gradually and stop – start MAOI 14 days later [2,17].</td>
<td>Discontinue mirtazapine gradually and stop – start moclobemide 7 days later [2].</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Discontinue reboxetine gradually and stop – start MAOI at least 7 days later [2].</td>
<td>Discontinue reboxetine gradually and stop – start moclobemide at least 7 days later [2].</td>
</tr>
<tr>
<td>MAOI</td>
<td>Discontinue the first MAOI gradually and stop – start the second MAOI 14 days later [2,9].</td>
<td>Discontinue MAOI gradually and stop – start moclobemide 14 days later [2,8,9].</td>
</tr>
<tr>
<td>See note (c)</td>
<td>Discontinue moclobemide gradually and stop – start MAOI 24 hours later [2,3].</td>
<td>Discontinue MAOI gradually and stop – start moclobemide at least 7 days later [2].</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Discontinue moclobemide abruptly – start MAOI the next day [2].</td>
<td>Stop moclobemide abruptly – start MAOI the next day [2].</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>Stop agomelatine abruptly – start MAOI 14 to 21 days later [2,15].</td>
<td>Stop agomelatine abruptly – start MAOI 14 to 21 days later [2,15].</td>
</tr>
<tr>
<td>See note (d)</td>
<td>Stop vortioxetine abruptly – start MAOI 14 to 21 days later [2,15].</td>
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</tr>
<tr>
<td>Vortioxetine</td>
<td>Stop vortioxetine abruptly – start MAOI 7 days later [2].</td>
<td>Stop vortioxetine abruptly – start MAOI 7 days later [2].</td>
</tr>
</tbody>
</table>

§ Fluoxetine at doses greater than 20mg should be withdrawn gradually rather than stopping abruptly.

§§ Vortioxetine at doses greater than 10mg should be reduced to 10mg over 1 week before stopping.

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Table 2: Switching from an MAOI or moclobemide to SSRI, TCA or related antidepressants

<table>
<thead>
<tr>
<th>1st Agent ▼</th>
<th>SSRI</th>
<th>TCA</th>
<th>SNRI (venlafaxine, duloxetine) and mirtazapine</th>
<th>Reboxetine</th>
<th>Agomelatine See note (d)</th>
<th>Vortioxetine See note (e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOI</td>
<td>Discontinue MAOI gradually and stop – start SSRI 14 days later [2,3,4,5,6,7,10,11].</td>
<td>Discontinue MAOI gradually and stop – start TCA 14 days later. Increase this interval to 21 days with clomipramine or imipramine [2,3,16].</td>
<td>Discontinue MAOI gradually and stop – start SNRI 14 days later [2,3,13,14,17].</td>
<td>Discontinue MAOI gradually and stop – start reboxetine 14 days later [2].</td>
<td>Cross-taper cautiously [2]</td>
<td>Discontinue MAOI gradually and stop – start vortioxetine 14 days later [2,15].</td>
</tr>
</tbody>
</table>

Prescribing notes

a. SSRI to moclobemide

When switching from an SSRI to moclobemide, the Summary of Product Characteristics (SmPC) for citalopram, escitalopram, fluvoxamine, sertraline and paroxetine recommend a washout period of seven days before starting moclobemide [4,5,6,7,10]. Another source suggests a longer washout period of 13 days for sertraline due to its half-life [3]. As fluoxetine has a longer half-life than the other SSRIs, a washout period of five to six weeks is recommended before initiating moclobemide [2,11].

b. TCA to MAOI

When switching from a TCA to a MAOI, general advice is to allow a seven day washout period before starting treatment with low-dose MAOI [3]. However, the SmPC for phenelzine tablets (Nardil®) advises a 14 day washout period after stopping a TCA. This should be extended to 21 days if the TCA is clomipramine or imipramine as these are more potent inhibitors of serotonin reuptake and the risk of serotonin syndrome will consequently be increased [9]. The BNF suggests a seven to 14 day washout period, extended to 21 days if clomipramine or imipramine have been taken [12]. Switches involving tranylcypromine, phenelzine, clomipramine or imipramine, are at greater risk of adverse reactions due to their potent effects on serotonin reuptake. Switching between any of these agents should be done with extreme caution [1].

c. MAOI withdrawal

Withdrawal of an MAOI should be over four weeks or longer if symptoms of withdrawal emerge [12]. Features of MAOI withdrawal include nausea, vomiting, malaise, nightmares, agitation, irritability, movement disorders, insomnia, slowed speech and convulsions. Symptoms usually respond to initiation of low-dose MAOI therapy followed by cautious downward titration and discontinuation [2,9].

d. Agomelatine

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 [2]. Abrupt withdrawal of agomelatine has not been associated with discontinuation symptoms. This means that no dose tapering is necessary when stopping treatment [18]. 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 [3,18]. It is recommended that when switching from fluvoxamine to agomelatine, fluvoxamine is withdrawn gradually and a three day washout period is allowed before starting agomelatine [19].

**e. Vortioxetine**

Vortioxetine is a new antidepressant and there is limited experience when switching, therefore extra caution is required [2]. The manufacturer advises that when stopping vortioxetine without switching to an alternative antidepressant, patients can abruptly stop it without gradual dose reduction [15]. 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]. When switching from vortioxetine to a MAOI, the manufacturer recommends a 14 day interval [15]. Another source suggests a gap of 21 days [2].

**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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Search strategy
- In-house databases/resources.
- Medline:
  1. Antidepressive-agents AND Substance-withdrawal-syndrome
  3. Vortioxetine and Switch.
     Search limited to ‘human’, ‘english’ and ‘adults’.
- 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.
     Search limited to ‘human’, ‘english’ and ‘adults’.
- electronic Medicines Compendium (eMC) www.medicines.org.uk
- Expert comments: