

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

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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 [1,2,3]. 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 Most antidepressants should be withdrawn by reducing the dose gradually over a minimum of four weeks, using patient's symptoms as a guide to the speed of withdrawal.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).

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- the current dose of the first antidepressant and how easily this can be withdrawn.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 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 to an MAOI or moclobemide are in Table 1.

Recommendations for switching from an MAOI or moclobemide to a SSRI, TCA or related antidepressant are in Table 2.

Table 1: Switching to an MAOI or moclobemide

1st agent ▼	MAOI (phenelzine or isocarboxazid or tranylcypromine)	Moclobemide
2nd agent ▶		
Citalopram Escitalopram Fluvoxamine	Discontinue SSRI gradually and stop – start MAOI 7 (phenelzine or isocarboxazid) to 14 (tranylcypromine) days later [2,3,4,5,6,7,8].	Discontinue SSRI gradually and stop – start moclobemide 7 days later [2,3,4,6].
Sertraline	Discontinue sertraline gradually and stop – start MAOI 7 to 14 days later [2,3,7,8,9,10].	Discontinue sertraline gradually and stop – start moclobemide 7 to 14 days later [2,3,9]. See note (a).
Paroxetine	Discontinue paroxetine gradually and stop – start MAOI 7 to 14 days later [2,7,8,10,11].	Discontinue paroxetine gradually and stop – start moclobemide 7 days later [2,11].
Fluoxetine[§]	Stop fluoxetine – start MAOI 5 to 6 weeks later [2,7,8,10,12].	Stop fluoxetine – start moclobemide 5 to 6 weeks later [2,3]. See note (a).
TCA	Discontinue TCA gradually and stop – start MAOI 7 to 21 days later, depending on TCA being taken [2,3,8,10,13]. See note (b).	Discontinue TCA gradually and stop – start moclobemide 7 days later [2].
Venlafaxine	Discontinue venlafaxine gradually and stop – start MAOI at least 7 days later [2,14].	Discontinue venlafaxine gradually and stop – start moclobemide at least 7 days later [2,14].
Duloxetine	Discontinue duloxetine gradually and stop – start MAOI at least 5 days later [3,15].	Discontinue duloxetine gradually and stop – start moclobemide at least 5 days later [3,15].
Mirtazapine	Discontinue mirtazapine gradually and stop – start MAOI 14 days later [2,18].	Discontinue mirtazapine gradually and stop – start moclobemide 7 days later [2].
Reboxetine	Discontinue reboxetine gradually and stop – start MAOI at least 7 days later [2].	Discontinue reboxetine gradually and stop – start moclobemide at least 7 days later [2].
MAOI See note (c)	Discontinue the first MAOI gradually and stop – start the second MAOI 14 days later [2,3,10].	Discontinue MAOI gradually and stop – start moclobemide 14 days later [2,10,19].
Moclobemide	Discontinue moclobemide gradually and stop – start MAOI 24 hours later [2,3].	
Agomelatine See note (d)	Stop agomelatine abruptly – start MAOI the next day [2].	Stop agomelatine abruptly – start moclobemide the next day [2].

1st agent ▼	MAOI (phenelzine or isocarboxazid or tranylcypromine)	Moclobemide
2nd agent ▶		
Vortioxetine^{§§} See note (e)	Stop vortioxetine abruptly – start MAOI 14 to 21 days later [2,16].	Stop vortioxetine abruptly – start moclobemide 7 days later [2].

§ Fluoxetine at doses greater than 20mg should be withdrawn gradually rather than stopping abruptly [2].

§§ Vortioxetine at doses greater than 10mg should be reduced to 10mg over one week before stopping [2].

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

1st agent ▼	SSRI	TCA	SNRI (venlafaxine, duloxetine) and mirtazapine	Reboxetine	Agomelatine See note (d)	Vortioxetine See note (e)
2nd agent ▶						
MAOI See note (c)	Discontinue MAOI gradually and stop – start SSRI 14 days later [2,3,4,5,6,8,11,12].	Discontinue MAOI gradually and stop – start TCA 14 days later. Increase this interval to 21 days with clomipramine or imipramine [2,13,17,20].	Discontinue MAOI gradually and stop – start SNRI or mirtazapine 14 days later [2,3,14,15,18].	Discontinue MAOI gradually and stop – start reboxetine 14 days later [2,3].	Cross-taper cautiously [2].	Discontinue MAOI gradually and stop – start vortioxetine 14 days later [2,3,16].
Moclobemide	Discontinue moclobemide gradually and stop – start SSRI 24 hours later [2,6,11].	Discontinue moclobemide gradually and stop – start TCA 24 hours later [2,17,19].	Discontinue moclobemide gradually and stop – start SNRI or mirtazapine 24 hours later [2].	Discontinue moclobemide gradually and stop – start reboxetine 24 hours later [2].	Discontinue moclobemide gradually and stop – start agomelatine 24 hours later [2].	Discontinue moclobemide gradually and stop – start vortioxetine 24 hours later [2].

Prescribing notes

a. SSRI to moclobemide

When switching from an SSRI to moclobemide, the Summary of Product Characteristics (SmPC) for citalopram, fluvoxamine, sertraline and paroxetine recommend a washout period of seven days before starting moclobemide [4,6,9,11]. 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].

b. TCA to MAOI

When switching from a TCA to a MAOI, general advice is to allow at least 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 [1,8,10]. The BNF suggests a

seven to 14 day washout period, extended to 21 days if clomipramine or imipramine have been taken [13].

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 (6 months in patients who have been on long-term maintenance treatment) [13]. 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, 10].

d. Agomelatine

Agomelatine is an antidepressant agent with selective agonist action at melatonin receptors and selective antagonist action at serotonin 5HT-2C receptors [2]. It does not affect uptake of serotonin, noradrenaline or dopamine [3,21]. Abrupt withdrawal of agomelatine has not been associated with discontinuation symptoms. This means that no dose tapering is necessary when stopping treatment [22]. 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 a MAOI to agomelatine, agomelatine can be started whilst gradually withdrawing the first antidepressant.

e. Vortioxetine

Vortioxetine is a relatively new antidepressant and there is limited experience when switching, therefore extra caution is required [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]. When switching from vortioxetine to a MAOI, the manufacturer recommends a 14 day interval [16]. Another source suggests a gap of 21 days [2].

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.

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.

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Quality Assurance

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Search strategy

1. EMBASE: [exp SEROTONIN UPTAKE INHIBITOR OR exp TRICYCLIC ANTIDEPRESSANT AGENT OR exp SEROTONIN NORADRENALIN REUPTAKE INHIBITOR OR exp TETRACYCLIC ANTIDEPRESSANT AGENT OR REBOXETINE OR AGOMELATINE OR MONOAMINE OXIDASE INHIBITOR OR *ANTIDEPRESSANT AGENT AND [DRUG SWITCH OR WITHDRAWAL SYNDROME, DRUG] [DT 2015-2019]. Search limited to 'human', 'english' and 'adults'.
2. MEDLINE: [exp ANTIDEPRESSIVE AGENTS OR exp ANTIDEPRESSIVE AGENTS, SECOND-GENERATION OR exp ANTIDEPRESSIVE AGENTS, TRICYCLIC OR exp SEROTONIN UPTAKE INHIBITORS OR exp SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS OR exp MONOAMINE OXIDASE INHIBITORS] AND [SUBSTANCE WITHDRAWAL SYNDROME OR (SWITCH*).ti,ab] [DT 2015-2019]. Search limited to 'human', 'english' and 'adults'.
3. In-house database/ resources
4. electronic Medicines Compendium (eMC) www.medicines.org.uk
5. Expert comments - contacted in 2009 when developing the first issue of this Medicines Q&A :
 - Agatha Munyika. Medicines Information Pharmacist. Mossley Hill Hospital Liverpool. August 2009.
 - Anne Connolly. Medicines Information Pharmacist. Maudsley Hospital, London. July 2009.