

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

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Date prepared: October 2019

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.

This medicines Q&A considers how to switch between tricyclic, SSRI and related antidepressants.

Answer

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 Most antidepressants should be withdrawn by reducing the dose gradually over a minimum of four weeks, using patients' symptoms as a guide to the speed of withdrawal.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.

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- the current dose of the first antidepressant and how easily this can be withdrawn.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 pharmacodynamic and pharmacokinetic profiles of the antidepressants involved.
- 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.

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.

An advantage of this method is the minimal risk of precipitating drug interactions [3]. However, it is not always possible to use this method, e.g. 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.

2. Cross-tapering

Gradually reducing the dose of the first antidepressant, while starting the second antidepressant at a low dose and then gradually increasing this dose as the first drug is withdrawn.

Cross-tapering is an option when switching between some antidepressants, and is usually preferred to abruptly stopping the first antidepressant [2]. It is unnecessary if switching from fluoxetine because of the long half-life of the drug (see direct 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 (CYP1A2) which is largely responsible for metabolism of amitriptyline, clomipramine and imipramine [2,3,4], concomitant use can result in increased TCA levels [3]. Paroxetine and fluoxetine are inhibitors of cytochrome P450 2D6 isoenzyme (CYP2D6) and concomitant use with clomipramine or nortriptyline may result in increased plasma levels of these TCAs [3,5,6]. Be aware that because of its long half-life, interactions with fluoxetine may potentially occur up to five weeks after stopping [2,6].

When cross-tapering from a TCA to a SSRI, gradually reduce the TCA dose to 25-50mg daily and start the SSRI at the normal starting dose. Gradually discontinue the TCA over five to seven days [3].

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].

Switch	Week 1	Week 2	Week 3	Week 4
From citalopram 40mg daily	20mg daily	10mg daily	Nil	Nil
To mirtazapine	15mg daily	30mg daily	30mg daily	45mg daily (if required)

3. Direct switch

Stopping the standard starting dose of the first antidepressant (e.g. citalopram 20mg) abruptly, and starting treatment with the usual starting dose of a second antidepressant (e.g. duloxetine 60mg) the next day [2]. If the prescribed dose of the first antidepressant is greater than the usual starting dose, this should be reduced gradually to the usual starting dose before making the switch, 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.

This method is also suggested for switching from SSRIs to venlafaxine [2,8,9] and from SSRIs to duloxetine [2,3,10]. Some caution is advised when switching from fluvoxamine (a potent inhibitor of CYP1A2), paroxetine or fluoxetine (inhibitors of CYP2D6) as duloxetine is metabolised principally by CYP1A2, but also by CYP2D6 and venlafaxine is metabolised, in part, by CYP2D6 [1,3]. Interactions with fluoxetine may potentially occur up to 5 weeks after stopping, because of its long half-life [2,6].

Discontinuation syndromes can occur with all classes of antidepressants therefore a direct 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 CYP1A2 thus increasing agomelatine levels [3,14]. It is recommended that when switching from fluvoxamine to agomelatine, fluvoxamine is withdrawn gradually and a four day washout period is allowed before starting agomelatine [2,15].

Vortioxetine switching

Vortioxetine is a relatively 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.

Summary

- Care is required when switching between antidepressants.
- When switching between selective serotonin reuptake inhibitors, tricyclic and related antidepressants, individual patient circumstances should be considered (see answer section).
- It is considered safer, in order to avoid 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.

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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Date Prepared

October 2019

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October 2019

Search strategy

Search updated 02/10/19

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 *ANTIDEPRESSANT AGENT AND [DRUG SWITCH OR WITHDRAWAL SYNDROME, DRUG]. 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]. 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.

Table 1: Switching antidepressants.

Important: Use this table in conjunction with the previous notes

1st agent ▼	Citalopram, escitalopram, paroxetine or sertraline	Fluvoxamine	Fluoxetine	TCA (except clomipramine)	Clomipramine [†]	Venlafaxine	Duloxetine	Mirtazapine	Reboxetine [‡]	Agomelatine	Vortioxetine
2nd agent ▶											
Citalopram, escitalopram, paroxetine or sertraline	Direct switch* possible [2,8,9,15]	Direct switch* possible [2]	Direct switch* possible [2]	Cross-taper cautiously with low dose of TCA [2]	Discontinue SSRI gradually and stop - start clomipramine at low dose the following day [2]	Direct switch* possible [2] (caution if paroxetine used) [8,9]	Direct switch* possible (caution if paroxetine used) [2,3,10]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Direct switch* possible (caution if paroxetine used) [2]
Fluvoxamine*	Direct switch* possible [2]		Direct switch* possible [2]	Cross-taper cautiously with low dose of TCA [2]	Discontinue fluvoxamine gradually and stop - start clomipramine at low dose the following day [2]	Direct switch* possible (caution advised) [2,3]	Direct switch* possible (caution advised) [2,3]	Cross-taper cautiously. Start mirtazapine at 15mg daily [2]	Cross-taper cautiously [2]	Discontinue fluvoxamine gradually and stop – start agomelatine 4 days later [2]	Direct switch* possible [2]
Fluoxetine 20mg daily[#]	Stop fluoxetine – start second SSRI at a low dose 4 to 7 days later [2]	Stop fluoxetine – start low dose fluvoxamine 4 to 7 days later [2]		Stop fluoxetine – start TCA at low dose 4 to 7 days later and increase dose very slowly [2,3,9]	Stop fluoxetine – start low dose clomipramine 2 weeks later [2]	Stop fluoxetine – start venlafaxine 4 to 7 days later (caution advised) [2,3]	Stop fluoxetine – start duloxetine 4 to 7 days later (caution advised) [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Stop fluoxetine – start vortioxetine at low dose 4 to 7 days later (caution advised) [2]
TCA (except clomipramine)	Gradually reduce the dose of TCA to 25-50mg daily - start SSRI then slowly withdraw TCA over next 5 to 7 days [3]	Cross-taper cautiously [2]	Halve dose of TCA, add fluoxetine and then slowly withdraw TCA [2]	Direct switch* possible [2]	Direct switch* possible [2]	Cross-taper cautiously, starting with low dose venlafaxine [2]	Cross-taper cautiously starting with low dose duloxetine [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Halve dose of TCA, start vortioxetine and then slowly withdraw TCA [2]

1st agent ▼	Citalopram, escitalopram, paroxetine or sertraline	Fluvoxamine	Fluoxetine	TCA (except clomipramine)	Clomipramine [†]	Venlafaxine	Duloxetine	Mirtazapine	Reboxetine [‡]	Agomelatine	Vortioxetine
2nd agent ▶											
Clomipramine[†]	Discontinue clomipramine gradually then stop – start SSRI at low dose the following day [2]	Discontinue clomipramine gradually then stop – start fluvoxamine at low dose the following day [2]	Discontinue clomipramine gradually then stop – start fluoxetine 10mg daily the following day [2]	Cross-taper cautiously [2]		Discontinue clomipramine gradually and stop - start venlafaxine at low dose the following day [2]	Discontinue clomipramine gradually and stop - start duloxetine at low dose the following day [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Discontinue clomipramine gradually and stop – start vortioxetine at low dose the following day [2]
Venlafaxine	Direct switch* possible [2] (caution advised if paroxetine used) [8]	Direct switch* possible [2]	Direct switch* possible [2] (caution advised) [8]	Cross-taper cautiously with low dose of TCA [2]	Discontinue venlafaxine gradually and stop – start clomipramine at low dose the following day [2]		Direct switch* possible starting with duloxetine 60mg daily [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Direct switch* possible [2]
Duloxetine	Direct switch* possible [2]	Direct switch* possible [2]	Direct switch* possible [2]	Cross-taper cautiously with low dose of TCA [2]	Discontinue duloxetine gradually and stop – start clomipramine at low dose the following day [2]	Stop duloxetine – start venlafaxine at low dose the following day [2]		Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Direct switch* possible [2]
Mirtazapine	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]		Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]
Reboxetine	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]		Cross-taper cautiously [2]	Cross-taper cautiously [2]

1st agent ▼	Citalopram, escitalopram, paroxetine or sertraline	Fluvoxamine	Fluoxetine	TCA (except clomipramine)	Clomipramine [†]	Venlafaxine	Duloxetine	Mirtazapine	Reboxetine [‡]	Agomelatine	Vortioxetine
2nd agent ▶											
Agomelatine	Stop agomelatine – start SSRI the following day [2,14,15]	Stop agomelatine – start fluvoxamine the following day [2]	Stop agomelatine – start fluoxetine the following day [2]	Stop agomelatine – start TCA the following day [2]	Stop agomelatine – start clomipramine the following day [2]	Stop agomelatine – start venlafaxine the following day [2]	Stop agomelatine – start duloxetine the following day [2]	Stop agomelatine – start mirtazapine the following day [2]	Stop agomelatine – start reboxetine the following day [2]		Stop agomelatine – start vortioxetine the following day [2]
Vortioxetine^a	Direct switch ^{**a} possible (caution if paroxetine used) [2]	Direct switch ^{**a} possible [2]	Direct switch ^{**a} possible (caution advised) [2]	Cross-taper cautiously with low-dose TCA [2]	Discontinue vortioxetine ^a gradually and stop – start clomipramine at low dose the following day [2]	Direct switch ^{**a} possible [2]	Direct switch ^{**a} possible [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	

* See notes regarding direct switch. Stopping the standard starting dose of the first antidepressant (e.g. citalopram 20mg), and starting treatment with the usual starting dose of a second antidepressant (e.g. duloxetine 60mg) [2].

† 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].

§ Extra caution is required when switching from fluvoxamine (a potent inhibitor of CYP1A2, and to a lesser extent of CYP2C and CYP3A4), as there is a high potential for interactions [2].

|| Fluoxetine at doses greater than 20mg may need to be withdrawn gradually, over 2 weeks, rather than stopping abruptly [2].

Be aware that interactions with fluoxetine may potentially occur up to 5 weeks after stopping, because of its long half-life [2,6].

^a See notes on vortioxetine. Vortioxetine at doses greater than 10mg should be reduced to 10mg over 1 week before stopping [2].