40 - General guidelines

General guidelines

366 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Switching antidepressants General guidelines When changing from one antidepressant to another, abrupt withdrawal of the first drug should be avoided unless there has been a serious adverse event. Cross-tapering is usually preferred – the dose of the ineffective or poorly tolerated drug is slowly reduced while the new drug is slowly introduced. The time taken to withdraw from the first antidepressant is dependent on the drug, the dose, the duration of prior treatment and the drug to which the patient is being switched.1 Example Daily dose Week 1 Week 2 Week 3 Week 4 Withdrawing citalopram 40mg 20mg 10mg 5mg 2.5mg Introducing mirtazapine Nil 15mg 30mg 30mg 45mg (if required) ■ ■The speed of cross-tapering is best judged by patient tolerability. Extended periods of hyperbolic tapering may be necessary to mitigate withdrawal symptoms when they emerge.2 ■ ■Cross--tapering is not always possible. The co-administration of some antidepressants, even when cross--tapering, is absolutely contraindicated. In other cases, theoretical risks or lack of experience preclude recommending cross-tapering. ■ ■The switching strategy depends not only on the reason for switching – inadequate or non-response, poor tolerability or adverse effects – but also on the pharmacokinetic and pharmacodynamic properties of the antidepressants involved.3–5 ■ ■In some cases, cross-tapering may not be necessary. For example, people who have been treated with an antidepressant for less than 3–4 weeks can probably safely stop abruptly and the new antidepressant can be started the next day. Another example is when switching between SSRIs – their effects may be so similar that administration of the second drug is likely to ameliorate withdrawal effects of the first. The use of fluoxetine has been advocated as an abrupt switch treatment to mitigate SSRI discontinuation symptoms6 (but see below). Abrupt cessation may also, albeit rarely, be acceptable when switching to a drug with a similar, but not identical, mode of action.7 Thus, in some cases, abruptly stopping one antidepressant and starting another at the usual dose may not only be well tolerated but may also reduce the risk and severity of discontinuation symptoms. ■ ■It is usually advisable to reduce the first antidepressant to the minimum effective dose before directly switching to the minimum effective dose of the second (see section on recognised minimum effective doses of antidepressants in this chapter).

Depression and anxiety disorders CHAPTER 3 ■ ■Stop–start switching is not always successful, particularly when switching to fluoxetine. The probable reason for this is that plasma levels of fluoxetine and its active metabolite take time to build up to steady state – usually 1–2 weeks. So, even when switching from an apparently equivalent dose (say 20mg paroxetine to 20mg fluoxetine) the plasma levels after one 20mg dose8 of fluoxetine are only 20% of plasma concentration at steady state.9 Thus, this switch is effectively an 80% reduction in drug activity. Withdrawal reactions are almost inevitable. There is more discussion of this and other relevant

issues in the Maudsley Deprescribing Guidelines.10 ■ ■Potential dangers of simultaneously administering two antidepressants include pharmacodynamic interactions (serotonin syndrome, hypotension, drowsiness – depending on the drugs involved) and pharmacokinetic interactions (e.g. elevation of the co- administered antidepressant plasma levels by some SSRIs). In the absence of inhibitory pharmacokinetic interactions, it is best to keep the combined percentage maximum dose below 100% (e.g. 50% maximum dose of one drug + 50% maximum dose of another). ■ ■Agomelatine does not seem to be associated with a discontinuation syndrome,11 but slow withdrawal when switching is nonetheless recommended. Given agomelatine's mode of action (melatonin agonism; 5HT2C antagonism), it is not expected to mitigate discontinuation reactions of other antidepressants. There is no theoretical basis to suggest that pharmacodynamic interactions might occur between agomelatine and other co-administered antidepressants but, in the absence of useful data, caution is advised. Some pharmacokinetic interactions do occur, and agomelatine should not be administered with fluvoxamine or viloxazine. ■ ■Serotonin syndrome can occur with a single serotonergic drug at a therapeutic dose or more commonly in combination of serotonergic drugs or in overdose. Many severe cases of serotonin syndrome involve an MAOI (including moclobemide) plus an SSRI.12,13 Caution is advised when switching strategies call for the combining of serotonergic drugs. Serotonin syndrome – symptoms Increasing severity Severity Symptoms Mild Insomnia, anxiety, nausea, diarrhoea, hypertension, tachycardia, hyper-reflexia Moderate Agitation, myoclonus, tremor, mydriasis, flushing, diaphoresis, low fever (<38.5°C) Severe Severe hyperthermia, confusion, rigidity, respiratory failure, coma, death The advice given in Table 3.7 should be treated with caution and patients should be very carefully monitored when switching.

368 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 Table 3.7 Antidepressants – swapping and stopping.* To From Agomelatine Bupropion Clomipramine Fluoxetine Fluvoxamine MAOIs Phenelzine Tranylcypromine Selegiline Agomelatinea Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Stop agomelatine then start fluvoxamine Cross-taper cautiously Bupropionb Cross-taper cautiously Cross-taper cautiously with low-dose clomipramine Cross-taper cautiously Cross-taper cautiously Taper and stop then wait for 2 weeks then start MAOIs Clomipramine Cross-taper cautiously Cross-taper cautiously Taper and stop then start fluoxetine at 10mg/ day Taper and stop then start low-dose fluvoxamine Taper and stop then wait for 3 weeks then start MAOIs Fluoxetinec Cross-taper cautiously Stop fluoxetine then wait for 4–7 days then start bupropion Stop fluoxetine then wait for 2 weeks then start low-dose clomipramine Stop fluoxetine then wait for 4–7 days then start fluvoxamine Stop fluoxetine then wait for 5–6 weeks then start MAOIs Fluvoxamined Taper and stop then wait for 4 days Cross-taper cautiously Taper and stop then start low-dose clomipramine Direct switch possible^ Taper and stop then wait for 1 week then start MAOIs MAOIs Phenelzine Tranylcypromine Selegiline Cross-taper cautiously Taper and stop then wait for 2 weeks Taper and stop then wait for 3 weeks Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeks Moclobemide Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours then start MAOIs Mirtazapine Cross-taper cautiously Cross--taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Taper and stop then wait for 2 weeks Reboxetinee Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Taper and stop then wait for 1 week then start MAOIs

Depression and anxiety disorders CHAPTER 3 Moclobemide Mirtazapine Reboxetine Trazodone Other SSRIsf Vortioxetine SNRIs Duloxetine Venlafaxine Desvenla- faxine TCAs (except clomipramine) Viloxazine Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Stop agomelatine then start viloxazine Taper and stop then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross--taper cautiously with low-dose TCA Cross-taper cautiously Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Taper and stop then start low dose Taper and stop then start low-dose SNRI Cross-taper cautiously Cross-taper cautiously Stop fluoxetine then wait for 5–6 weeks then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Stop fluoxetine then wait for 4–7 days then start low dose Stop fluoxetine then wait for 4–7 days then start SNRI Stop fluoxetine then wait for 4–7 days then start low-dose TCA Cross-taper cautiously Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously then start mirtazapine at 15mg Cross-taper cautiously Cross-taper cautiously Direct switch possible Direct switch possible Cross-taper cautiously with low-dose TCA Cross-taper cautiously Taper and stop then wait for 2 weeks then start moclobemide Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeks Taper and stop then wait for 2 weeksj Taper and stop then wait for 2 weeks Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 24 hours Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously (Continued)

370 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 To From Agomelatine Bupropion Clomipramine Fluoxetine Fluvoxamine MAOIs Phenelzine Tranylcypromine Selegiline Trazodone Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously with low-dose clomipramine Cross-taper cautiously Cross-taper cautiously Taper and stop then wait for 1 week Other SSRIsf Vortioxetineg Cross-taper cautiously Cross-taper cautiously Taper and stop then start low-dose clomipramine Direct switch possible^ Direct switch possible Taper and stop then wait for 1 weekh SNRI Duloxetinei Venlafaxine Desvenlafaxine Cross-taper cautiously Cross-taper cautiously Taper and stop then start low-dose clomipramine Direct switch possible^ Direct switch possible Taper and stop then wait for 1 week Tricyclics Cross-taper cautiously Halve dose and add bupropion and then slow withdrawal Direct switch possible Halve dose and add fluoxetine and then slow withdrawal Cross-taper cautiously Taper and stop then wait for 2 weeksj Viloxazinek Taper and stop then wait for 48 hours Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Taper and stop then wait for 2 weeks Table 3.7 (Continued)

Depression and anxiety disorders CHAPTER 3 Moclobemide Mirtazapine Reboxetine Trazodone Other SSRIsf Vortioxetine SNRIs Duloxetine Venlafaxine Desvenla- faxine TCAs (except clomipramine) Viloxazine Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously with low-dose TCA Cross-taper cautiously Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Direct switch

possible Direct switch possible Cross-taper cautiously with low-dose TCA Cross-taper cautiously Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Direct switch possible Direct switch possible Cross-taper cautiously with low-dose TCA Cross-taper cautiouslyk Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Halve dose and add trazodone and then slow withdrawal Halve dose and add SSRI and then slow withdrawal Cross-taper cautiously starting with low-dose SNRI Direct switch possible Cross-taper cautiously Taper and stop then wait for 1 week then start moclobemide Cross-taper cautiously Cross-taper cautiously Cross--taper cautiously Cross-taper cautiously Cross-taper cautiously Cross-taper cautiously Notes: * Advice given in this table is partly derived from manufacturers' information and available published data and partly theoretical. There are several factors that affect individual drug handling and caution is required in every instance. Cross taper cautiously – usually over 2–4 weeks as per example. a Agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors. The potential for interactions between agomelatine and other antidepressants is low and it is not expected to mitigate discontinuation reactions of other antidepressants. Some crossover with other antidepressants might be cautiously attempted when switching from agomelatine, as indicated in the table. b Bupropion is licensed for smoking cessation but unlicensed for the treatment of depression in the UK. It is a CYP2D6 inhibitor and particular caution is required when cross-tapering with drugs metabolised by this enzyme. c Beware: interactions with fluoxetine may still occur for 5 weeks after stopping fluoxetine because of its metabolite's long half-life. d Fluvoxamine is a potent inhibitor of CYP1A2, and to a lesser extent of CYP2C and CYP3A4, and has a high potential for interactions hence extra caution is required. e Switching to reboxetine as antidepressant monotherapy is no longer recommended. f Citalopram, escitalopram, paroxetine and sertraline. g Limited experience with vortioxetine and extra caution is required. Take particular care when switching to or from bupropion and other CYP2D6 inhibitors such as fluoxetine and paroxetine.14 h Wait 3 weeks in the case of vortioxetine.15 i Abrupt switch from SSRIs and venlafaxine to duloxetine is possible, starting at 60mg/day.7 j Wait 3 weeks in the case of imipramine. k Viloxazine is a selective noradrenaline reuptake inhibitor. Now licensed for the treatment of ADHD in the US. Increases in heart rate and diastolic blood pressure have been reported, so caution with SNRIs. ^ Caution when directly switching to fluoxetine. Some overlap (a few days) may be advisable to allow fluoxetine plasma concentration to build up before stopping the first antidepressant. Switching from vortioxetine is a probable exception to this, given its long half-life.

Revision #1
Created 2026-01-04 20:15:27 UTC by Omar Ayman
Updated 2026-01-04 20:15:28 UTC by Omar Ayman