

Antidepressants – how to switch or stop

Antidepressants are used to treat a variety of conditions such as depression, bipolar disorder, obsessive-compulsive disorder, anxiety, panic disorder, eating disorders and ejaculation disorder. This bulletin discusses antidepressant classes, mechanisms of action, switching and stopping common antidepressants, and recent availability issues.

Mechanism of action

Most antidepressants act by increasing concentrations of centrally-acting amines, mainly noradrenaline (NA) and serotonin (5-HT), in the synaptic cleft. This results in homeostatic adjustment of receptors to the increased concentrations.

- **Tricyclic Antidepressants (TCAs)** e.g. amitriptyline
TCAs inhibit the reuptake of NA and 5-HT, as well as antagonising cholinergic, histaminic and alpha (α)-1 receptors. TCAs contain a tricyclic ring and activity to some extent depends on the remaining structure.

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
e.g. citalopram, fluoxetine, paroxetine
SSRIs increase 5-HT concentrations in the synaptic cleft by inhibiting reuptake. They are less anticholinergic, sedating and cardiotoxic than TCAs.

- **Serotonin–Noradrenaline Reuptake Inhibitors (SNRIs)** e.g. venlafaxine
SNRIs inhibit the reuptake of both 5-HT and NA in the synaptic cleft. They have minimal sedative or anticholinergic activity.

- **Monoamine Oxidase Inhibitors (MAOIs)**
e.g. moclobemide (reversible inhibitor); phenelzine, tranylcypromine (irreversible inhibitors)
MAOIs increase intracellular NA concentrations by inhibiting MAO, the enzyme responsible for degradation of NA.

- **Others** e.g. mirtazapine
Mirtazapine increases NA and 5-HT release in the synaptic cleft by blocking pre-synaptic receptors responsible for feedback inhibition.

Stopping antidepressants

All antidepressants have the potential to cause withdrawal symptoms. When taken for > 6 weeks, doses should generally be tapered, unless a serious adverse reaction has occurred. A reduction of 25% per week may be used as a general guide, although drugs with long half-lives (e.g. fluoxetine) can often be withdrawn more quickly. Withdrawal symptoms may include flu-like symptoms (chills, myalgia, sweating, headache, nausea), insomnia, excessive dreaming and irritability. Alleviation of withdrawal symptoms can be achieved by returning to the previous dose, or by re-instituting the drug at the previous or lower dose, and withdrawing more slowly.

Switching antidepressants (see table below)

Cross-tapering is generally preferred, where the dose of the existing drug is slowly reduced while the new drug is introduced cautiously at a low dose. However, this may not always be necessary, or recommended. Abrupt withdrawal should usually be avoided. Potential dangers of co-administering two antidepressants include pharmacodynamic (e.g. serotonin syndrome, hypotension, sedation) and pharmacokinetic interactions (e.g. enzyme inhibition by SSRIs) and these should be taken into consideration.

Availability of Clomipramine and Trimipramine

Recently clomipramine and trimipramine were discontinued; however, clomipramine is again available. For patients who have been taking trimipramine, it would seem logical to prescribe an alternative tertiary TCA such as doxepin or amitriptyline, which are also markedly sedating and are dose equivalent. Alternatively, this may be a good opportunity to consider an antidepressant from another class.

A Guide to Switching Common Antidepressants^(a)

Switching: From \ To	TCA	SSRI	SNRI or mirtazapine	MAOI (reversible)	MAOI (irreversible)
TCA	No washout	Ideally washout 5 half-lives of TCA or tetracyclic	No washout – taper ^b	Washout 5 half-lives of TCA or tetracyclic	Washout 5 half-lives of TCA or tetracyclic
SSRI	Ideally washout 5 half-lives of SSRI. (Caution: fluoxetine ^b)	No washout – taper over 2-5 days (longer if high-dose fluoxetine) then start new SSRI ^c	No washout – taper ^c (Caution: fluoxetine has long half-life ^b)	Washout 5 half-lives of SSRI. (Caution: fluoxetine)	DON'T COMBINE. Washout 5 half-lives of SSRI. (Caution: fluoxetine)
SNRI or mirtazapine	No washout – taper ^b	No washout – taper ^{b,c}	No washout – taper ^{b,c} . Monitor for noradrenergic effects ^d	CAUTION. Washout 5 half-lives.	DON'T COMBINE. Washout 5 half-lives.
MAOI (reversible)	CAUTION. Washout 2 days.	CAUTION. Washout 2 days.	CAUTION. Washout 2 days.	-	Stop & start new drug next day at a low dose
MAOI (irreversible)	CAUTION. Washout 10 days.	DON'T COMBINE. Washout 10 days.	DON'T COMBINE. Washout at least 14 days for SNRI and 10 days for mirtazapine ^c .	Start next day if low - moderate MAOI dose (otherwise taper)	DON'T COMBINE. Washout 10 days.

(a) More rapid switching may often be used in in-patients (except for reversible or irreversible MAOIs) with monitoring of symptoms.

(b) Taper first drug over 3 - 7 days prior to starting second antidepressant; consider starting second drug at reduced dose.

(c) Monitor for serotonergic side effects (e.g. sweating, nausea, hypertension, tachycardia, tachypnoea, diarrhoea, confusion, agitation, tremor, muscular rigidity)

(d) Monitor for noradrenergic side effects (e.g. hypertension, tachycardia, tremor, sweating, insomnia)