Antidepressants

Based on NICE depression (2022, NG222), NICE dependence-forming medication (NG215) and CG113 and CG150.

Starting antidepressants

Remember: psychological therapies are often equally effective!

There is increasing recognition that withdrawal effects of antidepressants can be severe and long-lasting, and side-effects can be marked (DTB 2022;60:7). The 2022 NICE depression guidance goes to some lengths to emphasise the importance of counselling patients thoroughly before starting medication. NICE doesn't imply that antidepressants cause physical dependence and tolerance in the same way as opiates, but the concerns about withdrawal effects are significant enough that it has included them in its 2022 dependence-forming medication guideline.

Before prescribing an antidepressant, NICE says we should:

- Provide written information about the medication.
- Document the management plan in the clinical record and give a copy to the patient.

We should cover:

- Side-effects to be expected:
  - That these may occur before any benefits are seen.
  - That they usually ease over time.
- What next if the medicine is ineffective.
- The issues around withdrawal:
  - Missing doses may lead to withdrawal symptoms.
  - There can be difficulty in stopping this medicine, and how this might be managed.
- Safe storage.
- If appropriate, issues relating to pregnancy/planning a pregnancy.

Document the management plan in the clinical record **and give the patient a copy**. This should include:

- Indication and intended outcomes of treatment.
- Starting dose, and intervals between adjustments (the aim will be to use the lowest effective dose).
- Time to onset of action.
- Who to contact if there are problems.
- Anticipated duration of therapy and duration of each prescription.
- Risks of taking more than the prescribed dose, and symptoms and signs of an overdose (and what to do).
- Plans for reviewing the medication (where, when and by whom).

Creating a written, personalised management plan every time we start an antidepressant feels like a big ask. Until someone produces a nice personalised plan (like the Asthma UK Asthma Action Plan), individual practices may develop something themselves, and MIND has a good leaflet on antidepressants (see useful resources at the end of this article.) But, if you are running short of time, do bear in mind that the Patient Information Leaflet in the packet of antidepressants covers most of what NICE asks us to tell people about (admittedly requiring quite a high level of literacy, and sometimes in a rather anxiety-provoking way). Suggesting someone reads the leaflet in the packet would mean that you can then focus on the key elements that genuinely do need personalising – the dose, the follow-up arrangements, etc.

Choosing an antidepressant

- Various trials have tried to assess which is the best antidepressant, but this has usually been done through network meta-analyses rather than head-to-head trials, which introduces all kinds of risks of bias and error!
- **SSRIs are usually first line in primary care initiation.** They are safest in overdose.
- **Risk of side-effects** (monitor elderly more closely):
  - Increased bleeding risk: consider a PPI, e.g. older people, NSAIDs, aspirin.

  - Hyponatraemia risk, falls and fractures (especially in the elderly).
  - Sexual dysfunction.
  - Fatigue.
  - Weight gain.
- **Interactions** (especially if polypharmacy):
  - Citalopram and sertraline have fewer interactions.
  - Fluoxetine, paroxetine and fluvoxamine have greater risk of interactions.
- **How easy will they be to stop?** Paroxetine and venlafaxine have shorter half-lives; discontinuation symptoms are therefore more likely.
- **Has there been a response to a previous drug?**

The NICE depression guidance states that although the first choice will usually be an SSRI, it's acceptable to start a non-SSRI drug first line in severe depression. Non-SSRI antidepressants used in primary care include:

- SNRIs such as duloxetine and venlafaxine.
- Mirtazapine.

We should only usually use these drugs when there's a compelling reason not to pick an SSRI.

A 2019 BMJ review looked at managing depression in primary care, and summarised some of the available comparative data for antidepressants (remember, these analyses are highly problematic in terms of risks of bias and error) (BMJ 2019;365:l835).

- While the review found duloxetine, venlafaxine and mirtazapine **may** have better efficacy in depression compared with most SSRIs, it also suggested they have a higher side-effect burden and are more lethal in overdose.
- Mirtazapine was the most likely agent to cause weight gain and among the most sedative *(this tends to be seen particularly at **lower** doses).*
- Mirtazapine may be helpful for patients experiencing sexual problems while on other drugs as it was found to have the lowest incidence of sexual dysfunction among the antidepressants.

Secondary care antidepressants

Secondary care antidepressants include MAOIs, tricyclic antidepressants (TCAs) (when used in depression) and vortioxetine.

Vortioxetine is a novel agent that has multimodal actions on serotonin receptors and inhibits serotonin reuptake. NICE says it should only be started when there's been an inadequate response to two antidepressants, and NICE's technology appraisal for this drug states that it's "likely to be used predominantly in secondary care".

Secondary care may also use two antidepressants in combination, but NICE is clear this shouldn't be done in primary care.

A 2022 meta-analysis found that adding a drug such as mirtazapine to a SSRI, SNRI or TCA did improve outcomes in both first-line use for severe depression and depression not responding to a single drug (JAMA Psychiatry 2022;79:300). *This may lead to psychiatry using dual therapy more often and earlier, which feels at odds with the trend elsewhere in depression to reduce prescribing!*

Drug treatment options (based on NICE guidance)

Remember: for many of these conditions, psychological therapies are first line!

	First-line drug therapy	Second-line drug therapy
Depression	• **Usually an SSRI,** although in 'more severe' depression, it's an option to start other drugs first line such as an SNRI or mirtazapine (see *Depression* article).	• If, after 4 weeks of treatment, there has been no response, increase dose or switch to another SSRI or any other antidepressant suitable for primary care (see above). • Do not use St. John's wort.
Generalised anxiety disorder (GAD)	• SSRI. • NICE suggests that **sertraline** is most cost-effective.	• Alternative SSRI or SNRI. • Consider pregabalin only if these are not tolerated.

		• Do not use benzodiazepines except as a short-term measure in a crisis. • Do not use antipsychotics.
Social anxiety	• Offer antidepressant only if CBT declined. • Sertraline or escitalopram if drug therapy required. • Paroxetine licensed but high risk of discontinuation symptoms so not recommended.	• Paroxetine, venlafaxine, fluvoxamine.
Panic	• **Any SSRI** licensed for panic disorder, i.e. citalopram, sertraline, paroxetine, escitalopram.	• **Alternative SSRI or imipramine/clomipramine** (off-label). • Do not use antipsychotics, benzodiazepines or sedating antihistamines.
Obsessive–compulsive disorder (OCD)	• **Any SSRI** – all equally effective. • Higher doses often needed and longer duration (up to 12w) for an initial response.	• Swap to alternative SSRI or clomipramine. • Occasionally, antipsychotics used as adjuncts (secondary care).
Body dysmorphic disorder	• SSRIs: **fluoxetine** recommended first line. • Higher doses often needed and longer duration (up to 12w) for an initial response.	• Swap to alternative SSRI or clomipramine. • Buspirone sometimes used as adjunct alongside SSRI (secondary care).
Post-traumatic stress disorder (PTSD)	• Drug therapy is less clinically and cost-effective than psychological therapy so **use only as second-line treatment**. • If offering drug therapy: **any SSRI** or **venlafaxine** (note: only sertraline and paroxetine have a UK licence for PTSD).	• Antipsychotics such as risperidone may be used to augment other approaches in adults with severe or disabling symptoms and poor response to other treatments (specialist only).

Frequency of review on drug therapy

Depression	Review at 2w, then 2–4 weekly over first 3m.	**<u>If the patient is under 25 (some sources say under 30)</u>**, review within 1w of starting (because of higher risk of suicidal ideation) and more frequently thereafter, especially in the first month.
GAD	2–4 weekly over first 3m.	
Social anxiety		
Panic	Review after 2, 4, 6 and 12w, then every 2–3 months.	

Troubleshooting with antidepressants

- **Side-effects early in treatment** are usually mild. Reassurance that they will settle is often all that is needed.
  - With SSRIs, the commonest side-effects are nausea (often worse when hungry and relieved by a little snack), dry mouth and a temporary slight increase in anxiety levels.
  - If patient willing to continue, offer additional monitoring/support.
  - If side-effects intolerable, stop/swap antidepressants (see below).
- **Significant increased agitation:**
  - Assess for psychotic features and anxiety, and consider offering a short-term (2w) benzodiazepine to help with initial SSRI-induced increase in anxiety/agitation that is not amenable to psychological therapies.
  - Do not use benzodiazepines in those with chronic anxiety (risk of addiction).
- **No improvement in depressive symptoms:**
  - *Check expectations; not likely to be suddenly back to normal!*

- Improvements often seen after 2–4w.
- What does improvement look like? Often manifests as little patches of feeling a bit better against a background of ongoing low mood, rather than gradually feeling progressively and uniformly a bit better with time.

Practically, what should we do? Check the table below for a simple guide:

Depression			Other indications
2–4 weeks	3–4 weeks	Over 4 weeks	6–8 weeks
• Check compliance.	• Increase support. • Consider increase dose or changing drug.	• Increase dose OR • Change drug OR • Add psychosocial intervention.	• Consider switching to alternative antidepressant.

- **Seizure risk:** a DTB review of the impact of antidepressants on seizures concluded that the risk of seizures is generally low for antidepressants used at therapeutic doses in those with no seizure history, but is not zero. The risk is 1 in 100 to 1 in 1000 for sertraline and amitriptyline, and 1 in 1000 to 1 in 10 000 for citalopram, fluoxetine and venlafaxine (DTB 2020;58(9):137).

Withdrawal symptoms

All classes of antidepressants can cause withdrawal symptoms; these are experienced by more than half (56%) of people stopping SSRI treatment, with rates varying between individual drugs. Antidepressants used in higher doses, for longer periods of time and with shorter half-lives (e.g. paroxetine) are more likely to cause a more severe withdrawal (BJGP 2023;73:138).

NICE (2022, NG215) is clear that we should counsel patients about the potential for withdrawal effects **before starting an antidepressant drug**, which includes discussing non-pharmacological approaches to treatment.

NICE depression guidelines (2022, NG222) say that withdrawal symptoms usually resolve within 1 to 2 weeks. However, a systematic review suggests that many patients will experience withdrawal symptoms for longer than two weeks, and it is not uncommon for people to experience withdrawal for several months (Addict Behav 2019; 97:111-12).

Withdrawal effects range from mild to severe, and often appear within a few days of dose reduction or stopping. Common symptoms experienced during withdrawal include:

- Restlessness, irritability, anxiety.
- Insomnia, unsteadiness, sweating.
- GI upset, palpitations, headaches.
- Fatigue, arthralgia/myalgia.
- Altered mood or sensation.
- Severe withdrawal may even include suicidal ideation.

It is important to recognise withdrawal symptoms so that we do not misdiagnose a relapse of the original problem. The patient may also become fearful to stop the antidepressant, leading to an unnecessarily extended treatment duration (DTB 2020;58(1):5). Relapse can be distinguished from withdrawal by (BJGP 2023;73:138):

- Asking about symptoms such as sensory disturbance, muscle pain and nausea, which are unlikely to be features of depressive relapse.
- Establishing the timeline: withdrawal typically begins within days of antidepressant cessation, whereas relapse takes weeks to months.
- Restarting the antidepressant usually rapidly relieves withdrawal symptoms, whereas improvement usually takes weeks to months after a relapse.

We can reduce the risk of antidepressant withdrawal by:

- **Slowly tapering the dose**. NICE (2022, NG222) doesn't specify a timeframe for tapering but says the rate of withdrawal should be patient-led, ensuring that any withdrawal symptoms are tolerable before the next reduction. A review in the BJGP suggests using a gradual, stepwise rate of reduction over a long period of time spanning months or even years, particularly if the patient has been taking antidepressants for a long time (BJGP 2023;73:138). Dose reductions should be proportionate to the existing dose, such as lowering by 25% or 50%, so

that changes become incrementally smaller over time. In people with marked withdrawal, a slower tapering regime may be needed, such as reducing by 5 or 10%, with longer periods between dose changes.
- **Consider using liquid preparations** at lower doses to enable smaller changes in dose.

It is also important to keep the pharmacokinetics of the antidepressant in mind:
- Venlafaxine and paroxetine have short half-lives and need the slowest reductions.
- Fluoxetine has a longer half-life and may be reduced more quickly (although not stopped abruptly). Alternate-day dosing may be used at lower doses.

Managing withdrawal symptoms

If withdrawal symptoms occur, we should explain that:
- These symptoms are common.
- Relapse does not usually happen as soon as you stop taking an antidepressant or lower the dose.
- For mild symptoms, offer additional monitoring/support.
- For significant symptoms, consider reintroducing antidepressant/reverting to previous dose. Once withdrawal symptoms have settled, consider more gentle dose reduction.
- Discuss coping strategies for managing distressing symptoms, for example exercise, mindfulness and sleep hygiene.

Switching antidepressants

From Maudsley Prescribing Guidelines in Psychiatry, 2008, Wiley

<table>
<tr><td>Switching to →
Switching from ↓</td><td>Any SSRI or venlafaxine</td><td>Mirtazapine</td></tr>
<tr><td>Any SSRIs except fluoxetine</td><td>Stop old drug and start the new one the next day.</td><td rowspan="3">Cross taper: reduce dose of old drug, start new drug at low dose and titrate up (as old drug comes down) at weekly increments.</td></tr>
<tr><td>Fluoxetine (longer half-life)</td><td>Stop fluoxetine, wait 4–7d, then start new drug.</td></tr>
<tr><td>Venlafaxine</td><td>Stop old drug and start the new one the next day.</td></tr>
<tr><td>Mirtazapine (more serotonergic than other drugs)</td><td>Cross taper: reduce dose of old drug, start new drug at low dose and titrate up (as old drug comes down) at weekly increments.</td><td>–</td></tr>
<tr><td colspan="3">For all other swaps: take advice! Too-rapid switching can result in serotonin syndrome: confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus.
MAOIs (e.g. isocarboxazid, moclobemide, phenelzine, tranylcypromine) need really careful management. NEVER initiate in primary care!
Do NOT combine antidepressants without advice from a consultant psychiatrist. A psychiatrist may choose to augment the action of an antidepressant with lithium, an antipsychotic, an alternative antidepressant or (for <2w duration) a benzodiazepine. Do not use antiepileptics or thyroxine for augmentation.</td></tr>
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Stopping antidepressants

- **Review risks and benefits periodically, keeping in mind that stopping too soon can increase the risk of relapse.**
  - **For depression, social anxiety and panic disorder:** consider stopping when well for 6m or longer (see 'Continuing vs. stopping antidepressants after remission' in our *Depression* article for more on this).
  - **For generalised anxiety disorder:** continue for at least 12m as the risk of relapse is high.
  - **For OCD and body dysmorphic disorder:** review and consider stopping treatment 12m after remission (symptoms are not clinically significant and the person is fully functioning), taking into account the severity and duration of initial illness, number of previous episodes and presence of residual symptoms.
- Make a plan for dose reduction, and counsel patients about withdrawal symptoms (see 'Troubleshooting', above).

Antidepressants: common and important interactions

This is not an exhaustive list, but covers common/important interactions (this is from the old 2009 NICE depression guideline, but we summarise it here as we think it's really useful).

Medication	Recommended antidepressant(s)
NSAIDs	**Do not normally offer SSRIs** (bleeding risk). Unclear how great the risk is with short-term NSAID use. If no suitable alternatives, offer gastroprotective medicines (e.g. PPI) with the SSRI. Consider mirtazapine, trazodone, mianserin, reboxetine or moclobemide.
Aspirin	**Use SSRIs with caution** (bleeding risk): if no alternative, offer SSRI with PPI cover. Consider mirtazapine, trazodone, mianserin or reboxetine.
Warfarin or heparin	**Do not normally offer SSRIs** (bleeding risk). Consider mirtazapine (INR may slightly increase).
Triptans for migraine	**Do not offer SSRIs** (increased risk of serotonin syndrome). Offer mirtazapine, trazodone, mianserin or reboxetine.
Tamoxifen	**Do not use fluoxetine, paroxetine or duloxetine. Other SSRIs are safe.** Why? Tamoxifen is a pro-drug, and conversion to the active metabolite (endoxifen) is through the cytochrome P450 system (CYP2D6 enzyme). Therefore, drugs that inhibit CYP2D6 reduce the availability of the active drug, endoxifen. These drugs are: **fluoxetine, paroxetine, duloxetine, bupropion, quinidine** (an antiarrhythmic) **and cinacalcet** (used by endocrinologists and renal team for some on dialysis). A cohort study showed an increased risk of death in those who were taking paroxetine for at least 40% of the time there were on tamoxifen: **1 extra breast cancer death for every 20 women (range 12–46 women) within 5y of stopping tamoxifen** (BMJ 2010;340:c693). In 2016, a cohort study did not confirm this increased risk, but the follow-up in this study was for a median of 2.2 years which is probably insufficient to look for a disease such as cancer (BMJ 2016;354:i5014)!
MAO-B inhibitors (e.g. selegiline, rasagiline)	**Do not normally offer SSRIs.** Offer mirtazapine, trazodone, mianserin or reboxetine.
Theophylline, clozapine, methadone or tizanidine	**Do not normally offer fluvoxamine.** Offer sertraline or citalopram.
Flecainide or propafenone	**Offer sertraline as the preferred antidepressant.** Mirtazapine and moclobemide may also be used.
Atomoxetine	**Do not offer fluoxetine or paroxetine.** Offer a different SSRI.
Antiepileptics	Fluoxetine inhibits metabolism of antiepileptics, including lamotrigine, phenytoin and valproate. Citalopram, venlafaxine and TCA do not (DTB 2020;58(9):137).

Citalopram and escitalopram: two drug dilemmas

There are 2 issues to be aware of when prescribing citalopram:

- Citalopram may interact with cocaine and cause hypertension, and further increase the risk of bleeding and subarachnoid haemorrhage.
- Citalopram (and escitalopram) can prolong the QT interval and should not be used with other drugs that also prolong the QT interval.

Citalopram and cocaine

An MHRA warning in July 2016 (MHRA Drug Safety Update, July 2016) was issued after a man died from a subarachnoid haemorrhage. It concluded that there were plausible mechanisms for citalopram and cocaine to interact and cause hypertension and increase the risk of bleeding, which may have led to the fatal SAH. We are advised to ask about illicit drug use when prescribing, and particularly the risk of cocaine with citalopram.

Citalopram/escitalopram and the QT interval

Do not use citalopram/escitalopram with other drugs that prolong the QT interval. This includes (not an exhaustive list) (Oxford Health Medicine Information Bulletin 2011;9:3):

- Mental health drugs:
  - Other antidepressants: tricyclics, trazodone and venlafaxine.
  - All antipsychotics, but highest risk with haloperidol and pimozide.
  - Lithium: with greater risk if lithium levels are raised.

- Methadone: especially doses above 100mg.
- Other drugs:
  - Antibiotics: macrolides (erythromycin, etc.), ampicillin, quinolones (ciprofloxacin, etc.), co-trimoxazole.
  - Azoles: including fluconazole.
  - Antihistamines: particularly astemizole and mizolastine.
  - Antiarrhythmics: including amiodarone, dronedarone, sotalol and quinidine.
  - Quinine: especially at higher doses.
  - Antimalarials: mefloquine, chloroquine, artemether/lumefantrine.

What about the other SSRIs? In therapeutic doses, fluoxetine, paroxetine and sertraline do not prolong the QT interval. However, in overdose, fluoxetine and sertraline may be associated with long QT:

Current recommended MAXIMUM doses are (Drug Safety Update 2011;5:5)		
	18–65y	>65y
Citalopram	40mg	20mg
Escitalopram	20mg	10mg

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Antidepressants

- Remember: psychological treatments are often at least as effective as antidepressants.
- The harms of antidepressants, including significant side-effects and issues at withdrawal, are being increasingly recognised.
- A shared understanding of benefits and harms, timescale for benefits, duration of treatment, potential for withdrawal symptoms and side-effects is particularly important, and should be discussed and documented every time.
- Imperfect trials and meta-analyses have tried to determine the 'best' antidepressants, but it is difficult to draw firm conclusions.
- In general in primary care, SSRIs are first line because they are safest in overdose. Remember the risks:
  - Bleeding.
  - Hyponatremia.
  - Falls and fractures in the elderly.
  - Weight gain, fatigue and sexual dysfunction.
  - Drugs with shorter half-lives, e.g. venlafaxine and paroxetine, can be trickier to stop and may need to be weaned down particularly slowly.
- We should not combine antidepressants in primary care without advice from secondary care.
- Ensure treatment duration is sufficient:
  - For depression, social anxiety and panic disorder: consider stopping when well for 6m.
  - For generalised anxiety disorder: consider stopping when well for 12m.
- There are numerous common and important interactions (see table).

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Useful resources:

Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- Mind – comparing antidepressant half-lives
- Mind – antidepressant side-effects
- Mind - antidepressant withdrawal effects

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