

# Choosing an antidepressant

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## SUMMARY

A biopsychosocial and lifestyle approach should be used when managing depression. Many patients seen in primary care do not require drug therapy.

Evidence-based treatments such as psychological therapies and antidepressant drugs are effective for depression. All patients should receive education about depression.

Shared decision making with the patient is critical if an antidepressant is prescribed. The choice of antidepressant depends on its efficacy and tolerability, the depressive presentation, patient preference and drug interactions.

## Introduction

Major depression is best conceptualised using a biopsychosocial and lifestyle model.<sup>1</sup> All those factors need to be considered when formulating a management plan. Lifestyle factors (such as alcohol or substance misuse, lack of exercise or poor sleep habits) that may be contributing to the onset and maintenance of the depressive episode need to be dealt with concurrently (see Table 1). There is a need to be mindful of any psychosocial factors, such as unemployment or interpersonal stress, that maintain the depression.

All patients should receive psychoeducation with a discussion about the symptoms of depression, contributing factors and management options. When appropriate this education can involve other people close to the patient.

## Specific treatments

While attending to lifestyle factors and providing psychoeducation may be helpful for some patients, others need more specific treatments. These are formulation-based psychological treatment and antidepressant drugs. The efficacy of psychological treatment, such as cognitive behavioural therapy, is equivalent to drug therapy in mild-moderate disease. Ideally, psychological treatment should be offered first, unless the patient refuses or is unable to access or afford psychological treatment, or expresses a strong preference for drug treatment. Sometimes there is a clear indication for prescribing an antidepressant drug.

## Indications for drug therapy

Antidepressant drugs are indicated for patients with:

- major depression (characterised by marked symptoms and functional impairment)
- melancholia (characterised by significant psychomotor symptoms – agitation or retardation)
- psychotic depression (depression with delusions or hallucinations).

Antidepressants are also indicated for patients who have had a previous good response to them and for when psychological therapies are not accessible or have been ineffective. Even if a drug is indicated, psychoeducation along with basic counselling is still required.

## Drug selection

The choice of antidepressant for a particular patient should be based on four major considerations:

- finding the right balance between efficacy and tolerability
- matching the antidepressant to the type of depression and its presenting features

**Table 1 Lifestyle factors and interventions for depression**

Potential lifestyle risk factors	Interventions
Poor sleep pattern	Encourage good sleep hygiene – regular bedtime and wake up time, bed is for sleep and not for other activities (TV, social media). There are useful apps that provide basic psychoeducation and a sleep diary.
Alcohol misuse	Encourage safe drinking. If there is heavy use and the patient is seeking treatment, refer to an addiction medicine service. If they are not seeking treatment, do a brief intervention.
Substance misuse	Provide psychoeducation about the harmful effects of substances, advise abstinence, formal counselling or refer to addiction medicine services.
Smoking	Encourage smoking cessation, and consider motivational interviewing and nicotine replacement therapy.
Unhealthy diet	Psychoeducation about healthy diet and the harms associated with processed food. Encourage Mediterranean diet and increased intake of fruit and vegetables.
Lack of exercise	Encourage regular exercise (e.g. daily walks), emphasising a graded approach to exercise.

- safety – risk of overdose, interactions with other drugs or medical disorders (some groups need special consideration, such as older patients and women during pregnancy and lactation, as the baby will be exposed to the antidepressant)<sup>2</sup>
- patient preference.

There is not yet sufficient evidence confirming that the choice of antidepressant should routinely be made using pharmacogenetic data. Patients, particularly those vulnerable to marketing messages, can be advised that, except in some very special cases, genetic testing is not essential. They can save money by not paying for genetic tests.

**Balancing efficacy with tolerability**

The efficacy of antidepressant drugs has been confirmed in a network meta-analysis.<sup>3</sup> Each antidepressant was compared with other antidepressants using data from randomised placebo-controlled trials. ‘Dual-acting’ antidepressants that target more than one neurotransmitter system, such as the serotonin noradrenaline reuptake inhibitors (SNRIs) and tricyclics, are more efficacious than ‘single-action’ drugs, such as the selective serotonin reuptake inhibitors (SSRIs) like sertraline and escitalopram, based on the odds ratio of achieving a 50% response (see Table 2).<sup>3</sup> This meta-analysis also examined the acceptability of the various antidepressants by comparing the drop-out rates in clinical trials. While this is a useful metric of acceptability, the rates of adverse effects for each antidepressant are more useful in clinical practice.

Table 3 summarises the common adverse effects ranked according to a ‘limitation’ score for each of the antidepressant classes. The frequency of adverse effects can vary greatly between antidepressant classes, due to having different mechanisms of action. There are fewer differences between drugs in the same antidepressant class, although there are some exceptions.

In general, for an uncomplicated mild-moderate depression, the first choice of antidepressant should be a drug that will be well tolerated and has good efficacy. The ease of switching treatment<sup>4</sup> should be considered because the first antidepressant may not lead to full remission, requiring the patient to change to a different antidepressant.<sup>5</sup>

For patients with a severe depression or melancholia (characterised by significant psychomotor change), the prime consideration is efficacy rather than tolerability. The first choice will then be one of the more potent antidepressants, generally a dual mode-of-action drug, such as an SNRI or a tricyclic antidepressant.

**Table 2 Efficacy of antidepressants compared to placebo**

Antidepressant	Odds ratio	95% confidence interval
Amitriptyline	2.13	1.89–2.41
Mirtazapine	1.89	1.64–2.20
Duloxetine	1.85	1.66–2.07
Venlafaxine	1.78	1.61–1.96
Paroxetine	1.75	1.61–1.90
Fluvoxamine	1.69	1.41–2.02
Escitalopram	1.68	1.50–1.87
Sertraline	1.67	1.49–1.87
Vortioxetine	1.66	1.45–1.92
Agomelatine	1.65	1.44–1.88
Fluoxetine	1.52	1.40–1.66
Citalopram	1.52	1.33–1.74
Clomipramine	1.49	1.21–1.85
Desvenlafaxine	1.49	1.24–1.79
Reboxetine	1.37	1.16–1.63

Efficacy is given as the odds ratio of achieving a response (>50% reduction in severity). These studies generally used the typical dose to treat depression (although some of the studies were ‘dose finding’ studies in which lower doses were used).

Source: adapted from reference 3

**Matching the antidepressant to the clinical presentation**

Antidepressants differ in the specific symptoms that they target, so it is possible to choose an antidepressant according to the patient’s clinical presentation. It is also possible to use the adverse effects to target specific symptoms. For example, mirtazapine is sedating, so it is an option for patients with significant insomnia. Mirtazapine is also associated with weight gain so it may be useful for major depression accompanied by significant weight loss.<sup>6</sup> In short-term trials, the serotonin modulator vortioxetine benefited patients who had major depression with marked cognitive deficits.<sup>7</sup>

The choice of an antidepressant also depends, to some degree, on the symptom profile of the patient or a specific subtype of depression.<sup>8</sup> Table 4 lists the antidepressants that are preferred for different depressive symptom profiles. Many patients with major depression in primary care also have significant symptoms of anxiety or have a comorbid anxiety disorder. The antidepressant of choice

Table 3 Antidepressant adverse effects and their limitations on use

Class	Major adverse effects				Ease of switching (half-life)
	Weight gain	CNS effects – sedation/agitation	Sexual	Withdrawal syndrome	
Selective serotonin reuptake inhibitors (SSRIs)	•	••	•••	••†	••
Serotonin noradrenaline reuptake inhibitors (SNRIs)	•	••	•••	•••	••
Serotonin modulator (vortioxetine)	•	•	••	••	•••
Noradrenaline reuptake inhibitor (reboxetine)	•	•	••	•	••
Tricyclic antidepressants (TCAs)	•••	•••	•••	•••	•••
Reversible inhibitor of monoamine oxidase A (moclobemide)	•	••	•	•	•••
Tetracyclic (mianserin)	••	••	•	••	•
Noradrenergic and specific serotonergic (mirtazapine)	•••	•••	••	••	•
Monoamine oxidase inhibitors (MAOIs)	••	•••	••	••	•••
Melatonergic (agomelatine)	•	•	•	•	•

- Minimal limitation
- Some limitation
- Marked limitation

† There is little variation in the severity of adverse effects within classes of antidepressants (but patients may differ in the adverse effects they experience). One exception is the withdrawal symptoms following discontinuation of SSRIs. There is an absence of withdrawal symptoms for fluoxetine but very severe withdrawal symptoms for paroxetine.

Table 4 Symptoms and initial antidepressant choice

Symptoms	Preferred antidepressant
Anxiety	Selective serotonin reuptake inhibitors Moclobemide
Weight loss, reduced appetite	Mirtazapine Mianserin
Sleep disturbance, insomnia	Agomelatine Mirtazapine Mianserin Tricyclic antidepressants
Sexual dysfunction	Agomelatine
Blunting, anhedonia, demotivation	Selective serotonin reuptake inhibitors Serotonin noradrenaline reuptake inhibitors Agomelatine Monoamine oxidase inhibitors Reboxetine
Melancholia, severe depression	Serotonin noradrenaline reuptake inhibitors Tricyclic antidepressants Vortioxetine Monoamine oxidase inhibitors
Pain	Duloxetine Tricyclic antidepressants
Cognitive difficulties	Vortioxetine

here is an SSRI.<sup>9</sup> For patients with a melancholic depression, which has a clear biological underpinning characterised by vegetative symptoms and psychomotor change such as agitation or retardation, a dual-action antidepressant should be the first option. The tricyclic antidepressants or duloxetine may be used in certain neuropathic pain conditions. While they can be prescribed for patients with pain and associated depression, the doses of a tricyclic used to treat major depression need to be higher than those used for adjunctive therapy in pain management.

**Safety considerations**

Patients with depression can often have suicidal thoughts and may try to commit suicide. This needs to be considered when prescribing an antidepressant. A suicidal patient should not be given quantities of a drug that could be fatal in an overdose. The SSRIs have a much lower potential lethality than the tricyclic antidepressants.

Ask about any other drugs the patient may be taking to avoid potential interactions. For example, there is an increased risk of serotonin toxicity when taking SSRIs in combination with tramadol, St John’s wort or monoamine oxidase inhibitors (MAOIs). SSRIs are also associated with increased bleeding due to changes in platelet function. Caution is therefore needed if they are taken with anticoagulants or non-steroidal anti-inflammatory drugs (NSAIDs). With the

increased risk of bleeding, there is a need to consider any comorbid conditions that may add to this risk. In order to limit potential drug and disease interactions, it is recommended that prescribers only use a few antidepressants that they know and understand well.<sup>10</sup>

### Patient preference

A key consideration is patient preference. Adherence to antidepressants is essential to ensure remission of the depression. A significant proportion of patients will stop their antidepressant.<sup>11</sup> Adherence is improved if the patient is involved in the decision about which treatment to take. This involves a discussion about the expected benefits of the antidepressant and its potential adverse effects. Some adverse effects, such as sedation, may be more acceptable to patients, but others such as weight gain may be less acceptable. Be aware that patients might have misinformation from the internet or through word of mouth that the adverse effects of an antidepressant

are 'dreadful and nobody should ever take it'. In such situations, it is essential to listen to the patient's concerns and present them with clear and accurate information about the drug, including providing them with consumer fact sheets. This approach will improve adherence.

### Conclusion

After deciding that a patient needs to take an antidepressant, the choice of drug depends on the severity and symptom pattern of the depressive episode. There has to be a balance between efficacy and tolerability, which also considers patient safety and preference. <

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