



# The role of medicines in the management of depression in primary care

A selective serotonin reuptake inhibitor (SSRI) is usually the first-line pharmacological treatment for patients with moderate to severe depression who have not responded sufficiently to non-pharmacological interventions. Other medicines, e.g. mirtazapine, venlafaxine or tricyclic antidepressants, may be considered in some cases. Patients should be followed-up in the first weeks after initiating an antidepressant to assess treatment response and any adverse effects

## KEY PRACTICE POINTS:

- Non-pharmacological interventions are essential in the management of patients with depression and should be continued if medicines are initiated
- Antidepressants are generally reserved for patients with moderate to severe depression
- There is little evidence separating the classes of antidepressants in terms of efficacy; adverse effects, safety and patient preference are used to guide treatment decisions
- The SSRIs citalopram, escitalopram, sertraline and fluoxetine are generally first-line choices, although mirtazapine may also be considered as a first-line option
- If a patient has not responded to an antidepressant after three weeks, consider switching to another medicine within the same class or another class
- Patients experiencing severe symptoms, marked functional impairment or who are at high risk of self-harm require intensive treatment and should be referred to mental health services
- It is recommended that antidepressants are continued for at least one year following a single episode of depression or for at least three years following recurrent episodes

This is a revision of a previously published article.

What's new for this update:

- Maprotiline and phenelzine have been discontinued
- Change to dosulepin funding status – funded with endorsement for patients taking this medicine prior to 1 June, 2019; no new patients should be initiated on dosulepin
- Imipramine 25 mg tablets are out of stock (as of 1 May, 2021); patients will need to switch to an alternative treatment, or some patients may be able to use the appropriate number of imipramine 10 mg tablets to make up the equivalent dose. No new patients should be initiated on imipramine.
- The latest information on the supply of medicines can be found on the PHARMAC website: <https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notice/?mType=all>

## When to consider medicines for patients with depression

Non-pharmacological interventions are the mainstay of treatment for patients with depression.<sup>1</sup> General practitioners can provide perspective and guidance to patients, help them develop coping strategies, encourage them to seek support from family and friends and direct them to community groups and online programmes, e.g. cognitive behavioural therapy or mindfulness programmes.

Assessment of a patient with depression may start with identifying contributing factors, such as social isolation, illness, financial stress or problems relating to relationships or employment (also see: "Tools for assessing patients with depression"). If a patient feels overwhelmed, the use of lists or electronic reminders can help to order responsibilities and provide a sense of control. Encourage patients to focus on one task at a time and to set aside time each day for an activity they enjoy. Writing down thoughts and feelings, i.e. "journaling", may be helpful for self-reflection, working through difficulties and gaining insight. Important decisions should be deferred while the patient is in a low mood. Some patients may feel stigmatised by a diagnosis of depression; they can be reassured that many people experience depression, having a diagnosis is the first step towards recovery and that they are doing the right thing by seeking help.


Non-pharmacological interventions for depression are centred on building mental strength and resilience. This includes:<sup>2</sup>

- Cognitive behavioural therapy
- Relaxation techniques, e.g. mindfulness
- Education about depression, e.g. depression is not a sign of weakness, it is a serious medical condition experienced by one in six people at some stage in their life
- Social support from whānau/family and friends
- Maintaining cultural, religious or spiritual connections
- Regular exercise, including group activities
- A healthy diet
- Addressing alcohol or drug intake
- Sleep hygiene – For further information, see: "I dream of sleep: managing adults with insomnia", [www.bpac.org.nz/2017/insomnia-1.aspx](http://www.bpac.org.nz/2017/insomnia-1.aspx)

 Examples of online patient resources for depression:

- [www.depression.org.nz](http://www.depression.org.nz) – a wide range of resources including an online programme ("The Journal"), personal stories and self-tests for depression and anxiety
- [www.mentalhealth.org.nz/get-help/a-z/resource/13/depression](http://www.mentalhealth.org.nz/get-help/a-z/resource/13/depression) – education and patient resources that can be viewed online, printed or ordered

- [www.beatingtheblues.co.nz](http://www.beatingtheblues.co.nz) – an online CBT programme for depression and anxiety; patients are referred via the ManageMyHealth portal


 For further information on differentiating short-term distress from depression, see: <https://bpac.org.nz/2019/ssri.aspx>

### Antidepressants are appropriate for patients with moderate to severe symptoms

Antidepressants are not routinely prescribed for patients with mild depression (see: "Tools for assessing patients with depression") as they will often respond to psychological interventions alone, especially in the early stages of illness.<sup>2,3</sup> In addition, the benefit of antidepressants is proportional to the severity of the depression, i.e. no benefit over placebo for mild depression, but a substantial benefit in patients with severe depression.<sup>4</sup>

Medicines are generally reserved for patients with depression that is moderate to severe or for those who have not responded to non-pharmacological interventions.<sup>1</sup> Depression and anxiety frequently co-exist and anxiety often precedes the onset of depression.<sup>2</sup> If a patient presents with depression and symptoms of anxiety, the priority is generally to treat the depression first,<sup>3</sup> although medicines used to treat patients with depression, i.e. SSRIs, are also often effective in relieving anxiety.<sup>2</sup>

Patients with severe depression, marked functional impairment or who are at high risk of self-harm or suicidal behaviour should be referred to mental health services as they require intensive treatment. Substance misuse, stressful events and a history of self harm greatly increase the risk of suicide in patients with depression.<sup>5</sup> However, risk factors for suicide are often not helpful in predicting an attempt and open questions followed by specific questions about suicidal intent, where appropriate, are encouraged.<sup>5</sup>

 For further discussion about identifying and managing suicide risk in primary care see: "Suicide prevention: what can primary care do to make a difference?" see: <https://bpac.org.nz/2017/suicide.aspx>

### Manage the patient's expectations of the effectiveness of antidepressants

The goal in treating patients with depression or anxiety is a complete remission of symptoms with full recovery of function and improved resilience, i.e. a reduced likelihood of recurrence.<sup>2,6</sup>

<sup>6</sup> A healthy lifestyle is an important and ongoing component of treatment and ideally, medicines will be withdrawn after the patient has recovered.

It is important that patients do not view medicines as a "quick fix" for mental health problems. Patients need to know

that it will take several weeks of adherence to pharmacological treatment before any benefit occurs and that they may not respond to the first medicine they are prescribed.

Encourage patients to think of medicines as a therapeutic trial with treatment reviewed regularly. If patients understand at the outset that pharmacological treatment is likely to be temporary, future discussions about reducing doses or withdrawing treatment may be easier.

## A selective serotonin reuptake inhibitor is often the first-line pharmacological treatment

The first-line medicine for patients with depression is generally a SSRI, e.g. citalopram, escitalopram, sertraline or fluoxetine (Tables 1 and 2).<sup>1, 2</sup> This recommendation is based on a reduced risk of adverse effects and toxicity in overdose, rather than evidence of superior effectiveness over other classes of antidepressant.<sup>1</sup> As a rule, paroxetine is prescribed less frequently as it is associated with more anticholinergic effects, sedation and discontinuation syndrome, compared with other SSRIs.<sup>2, 8, 9</sup> However, it is not possible to predict how a patient will respond to an antidepressant, therefore if they have previously benefited from a specific antidepressant, reinitiating the same medicine is advisable.

There are no guidelines for selecting a particular SSRI as there is little clinical trial data separating the SSRIs in terms of efficacy and the results of meta-analyses have been contentious. The adverse effect profile, potential for medicine interactions, ease of withdrawal and prescriber experience, can be used to guide discussions regarding medicine choice (Table 1).

## Minimising the adverse effects of SSRIs

The adverse effects of SSRIs are broadly similar across the class and include sexual dysfunction, nausea, anxiety, insomnia, sweating, agitation, electric shock sensations, hypomania and worsening depression.<sup>10</sup>

**Sexual dysfunction occurs in 30% or more of people taking SSRIs.**<sup>2</sup> Paroxetine is more likely than other SSRIs to cause sexual dysfunction, particularly delayed ejaculation.<sup>8</sup> Sexual dysfunction in patients who have otherwise responded positively to a SSRI may be resolved by reducing the dose or switching to another SSRI, especially if taking paroxetine. An alternative is switching to bupropion, which may alleviate the sexual dysfunction (unapproved indication – see below).<sup>11</sup>


**Gastrointestinal disturbances are experienced by 10–30% of patients taking SSRIs.**<sup>2</sup> Nausea may be reduced by taking the SSRI with food. Sertraline is more likely to be associated with diarrhoea than other SSRIs.<sup>8</sup> The use of SSRIs is associated with an approximate three-fold increased risk of gastrointestinal

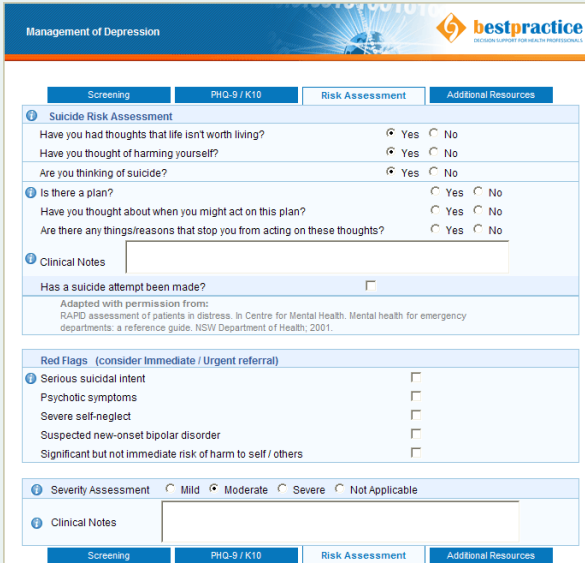
## Tools for assessing patients with depression

**The PHQ-9 questionnaire** is a validated tool to detect and assess the severity of depression that takes less than five minutes to complete.<sup>7</sup> The PHQ-9 tool can also be used to monitor the patient's response to treatment. Available from: [www.cqaimh.org/pdf/tool\\_phq9.pdf](http://www.cqaimh.org/pdf/tool_phq9.pdf)

**The GAD-7 questionnaire** can be used to assess the severity of illness in patients with generalised anxiety. Available from: [www.nzgp-webdirectory.co.nz/site/nzgp-webdirectory2/files/pdfs/forms/GAD-7\\_Anxiety.pdf](http://www.nzgp-webdirectory.co.nz/site/nzgp-webdirectory2/files/pdfs/forms/GAD-7_Anxiety.pdf)

**The anxiety and depression checklist (K10)** is a simple tool for assessing patients with symptoms of depression and anxiety. Available from: [www.beyondblue.org.au/the-facts/anxiety-and-depression-checklist-k10](http://www.beyondblue.org.au/the-facts/anxiety-and-depression-checklist-k10)

 *bestpractice* offers a range of electronic decision support tools for assessing and managing patients with depression. These modules are part of a nationally funded suite of resources available free-of-charge to all primary care practices in New Zealand. There are separate modules for managing adults, elderly people, young people and women in the antenatal and postnatal periods with depression. The assessment incorporates the PHQ-9 and GAD-7 questionnaires and the K10 checklist. For further information, see: [www.bestpractice.net.nz/feat\\_mod\\_NatFunded.php](http://www.bestpractice.net.nz/feat_mod_NatFunded.php)



Management of Depression

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Screening PHQ-9 / K10 Risk Assessment Additional Resources

**Suicide Risk Assessment**

Have you had thoughts that life isn't worth living?  Yes  No

Have you thought of harming yourself?  Yes  No

Are you thinking of suicide?  Yes  No

**Is there a plan?**  Yes  No

Have you thought about when you might act on this plan?  Yes  No

Are there any things/reasons that stop you from acting on these thoughts?  Yes  No

**Clinical Notes**

Has a suicide attempt been made?

Adapted with permission from:  
RAPID assessment of patients in distress. In Centre for Mental Health. Mental health for emergency departments: a reference guide. NSW Department of Health; 2001.

**Red Flags (consider Immediate / Urgent referral)**

Serious suicidal intent

Psychotic symptoms

Severe self-neglect

Suspected new-onset bipolar disorder

Significant but not immediate risk of harm to self / others

**Severity Assessment**  Mild  Moderate  Severe  Not Applicable

**Clinical Notes**

Screening PHQ-9 / K10 Risk Assessment Additional Resources

bleeding.<sup>12</sup> A proton pump inhibitor is recommended for older patients who are concurrently prescribed a SSRI with a non-steroidal anti-inflammatory drug (NSAID) or aspirin, or for patients with a history of gastrointestinal bleeding.<sup>3,12</sup>

**Central nervous system adverse effects are experienced by 10–30%** of patients taking SSRIs,<sup>2</sup> often in the first days or weeks of treatment.<sup>10</sup> These may include akathisia, i.e. anxiety, restlessness and agitation, fatigue or apathy (which can be mistaken for a relapse), insomnia and increased sensitivity to alcohol.<sup>10</sup> Ask patients to report these symptoms, as a change to another class of medicine may be appropriate. Dosing SSRIs in the morning may reduce insomnia, although this practice is not supported by evidence.

**Suicidal thoughts may develop in a small number of patients taking SSRIs** during the first two to four weeks of treatment, particularly in those aged under 25 years.<sup>2</sup> The risk

of suicide during this period may be increased by SSRI-induced akathisia.<sup>13</sup> The possibility of suicidal thoughts should be discussed with all patients, with instructions given to report symptoms promptly and numbers provided for emergency support services. Young patients should be specifically asked about the development of suicidal thoughts in the first week of treatment with a SSRI. A safety plan should be put in place, ensuring that the patient has identified a support person that they can contact at any time if they are feeling suicidal.


**Citalopram and escitalopram are contraindicated in patients with QT-prolongation**, i.e. a QT value greater than 450 milliseconds for adult males and 470 milliseconds for adult females.<sup>14</sup> If a patient has multiple risk factors or cardiac disease, ECG testing is recommended prior to initiating citalopram or escitalopram, and after any dose increases, or at any time the patient develops symptoms of an arrhythmia, e.g. dizziness, palpitations, syncope or seizures.<sup>10</sup>

**Table 1:** A summary of the comparative advantages and disadvantages of individual SSRIs; suggested order of preference, however, prescribers need to take into account individual patient circumstances.

SSRI	Advantages	Disadvantages
<b>Citalopram</b>	<ul style="list-style-type: none"> <li>Lowest potential for medicine interactions compared with other SSRIs</li> </ul>	<ul style="list-style-type: none"> <li>Contraindicated in patients with QT prolongation</li> <li>Moderate risk of discontinuation syndrome</li> </ul>
<b>Escitalopram</b>	<ul style="list-style-type: none"> <li>Low potential for medicine interactions compared with fluoxetine and paroxetine</li> </ul>	<ul style="list-style-type: none"> <li>Contraindicated in patients with QT prolongation</li> <li>Some evidence of an increased risk of hyponatraemia, compared with SSRIs other than sertraline</li> </ul>
<b>Sertraline</b>	<ul style="list-style-type: none"> <li>Low potential for medicine interactions compared with fluoxetine and paroxetine</li> <li>Lowest infant exposure while breastfeeding</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhoea is more frequent, compared with other SSRIs</li> <li>May require titration due to a wide dose range, i.e. 50–200 mg, daily</li> <li>Some evidence of an increased risk of hyponatraemia, compared with SSRIs other than escitalopram</li> </ul>
<b>Fluoxetine</b>	<ul style="list-style-type: none"> <li>Discontinuation syndrome is rare</li> <li>A missed dose is less likely to cause a relapse due to a long half-life</li> <li>The only SSRI with some evidence of efficacy in patients aged under 18 years</li> </ul>	<ul style="list-style-type: none"> <li>Highest potential for medicine interactions</li> <li>Switching to another antidepressant is more problematic due to long half-life</li> <li>Least preferred while breast feeding</li> </ul>
<b>Paroxetine</b>	<ul style="list-style-type: none"> <li>Some evidence that it has the lowest risk of QT prolongation compared to other SSRIs<sup>16</sup></li> </ul>	<ul style="list-style-type: none"> <li>Sexual dysfunction, particularly delayed ejaculation, is more frequent compared to other SSRIs</li> <li>Discontinuation syndrome can be severe</li> <li>High potential for medicine interactions</li> <li>May cause more anticholinergic adverse effects than other SSRIs</li> </ul>

Risk factors for QT prolongation include:<sup>15</sup>

- Female gender
- Older age
- Structural heart disease
- Hypokalaemia
- Hypomagnesaemia
- Concurrent use of other medicines that may prolong the QT interval, e.g. omeprazole

 Remember that escitalopram is prescribed at half the dose of citalopram as it is the S-enantiomer and active component of racemic citalopram.

## Antidepressants to consider if the adverse effects of SSRIs are a concern

**Mirtazapine** is a noradrenergic and specific serotonergic antidepressant (NaSSA),<sup>2</sup> and is a first-line alternative to a SSRI. There is evidence that mirtazapine has a faster onset of action than SSRIs, meaning that some patients may experience greater benefit in the first two to four weeks of treatment.<sup>8</sup> Mirtazapine is associated with somnolence, which may be an undesirable adverse effect for some patients, but beneficial for others who are having difficulty sleeping.<sup>9</sup> Patients treated with mirtazapine may experience increased appetite and weight gain, e.g. 0.8 – 3 kg after six to eight weeks of treatment, which may or may not be a desirable effect. Other adverse effects include dry mouth and constipation.<sup>2,8</sup> There are rare case reports of agranulocytosis in patients taking mirtazapine, although the frequency is unknown.<sup>17</sup> Agranulocytosis is most likely to occur in the first four to six weeks of treatment.<sup>17</sup> If patients present with fever, sore throat, stomatitis or other signs of infection mirtazapine should be ceased and a full blood count requested.<sup>17</sup>

In summary, mirtazapine:

- May have a faster onset than a SSRI
- Causes sleepiness
- Causes increased appetite and weight gain
- May be associated with dry mouth, constipation and, in rare cases, agranulocytosis


**Bupropion** is a noradrenaline reuptake inhibitor (NDRI) which is approved for use as a smoking cessation medicine, but can also be used for the treatment of patients with depression. As this is an unapproved indication, it is a second-line treatment to SSRIs and mirtazapine. There is no evidence that bupropion is more effective than SSRIs for the treatment of depression. However, the noradrenergic activity of bupropion may mean that it is useful for patients with depression who report fatigue as a predominant symptom.<sup>2</sup> Bupropion is not associated with sexual dysfunction so it may also be preferable in patients who are experiencing SSRI-induced sexual dysfunction.<sup>11</sup> Bupropion

is associated with a small amount of weight loss therefore it may be preferred over mirtazapine as an alternative to SSRIs by patients who are concerned about weight gain.<sup>11</sup> The stimulating effect of bupropion means that it is less likely than mirtazapine to be beneficial for patients with problems sleeping.<sup>2</sup> Dry mouth and nausea are also associated with the use of bupropion.<sup>2</sup>

Document the discussion in the patient's notes before prescribing bupropion. The concurrent use of bupropion with other medicines that lower seizure threshold is not recommended and bupropion is contraindicated in patients with a history of seizures.<sup>9</sup>

In summary, bupropion:

- Is used to treat depression as an unapproved indication
- May counteract fatigue, but may also contribute to insomnia
- Does not cause sexual dysfunction
- Does not cause weight gain
- May cause dry mouth and nausea

 For further information, see: "Upfront: Unapproved medicines and unapproved uses of medicines: keeping prescribers and patients safe", available from: [www.bpac.org.nz/BPJ/2013/March/unapproved-medicines.aspx](http://www.bpac.org.nz/BPJ/2013/March/unapproved-medicines.aspx)

## Other antidepressants are often prescribed to patients with more severe symptoms

Venlafaxine and tricyclic antidepressants (TCAs) are second-line treatments for patients with depression, and moclobemide (a reversible mono-amine oxidase inhibitor [MAOI]) may be a third-line option in some cases.<sup>2</sup> These recommendations are based on the tolerability and toxicity profiles of the medicines.

### Venlafaxine is effective but is more toxic than the SSRIs

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI) that may be more effective than SSRIs for patients with severe depression.<sup>2</sup> The adverse effects of venlafaxine are similar to the SSRIs and include sexual dysfunction, headache, sweating and gastrointestinal symptoms.<sup>2</sup> However, venlafaxine is recommended as a second-line treatment for patients with depression or anxiety, due to the potential for additional cardiac complications or seizures in overdose and an increased risk of discontinuation syndrome.<sup>2,6</sup> The major safety concern is the potential for dose-related hypertension due to inhibition of noradrenaline reuptake;<sup>18</sup> blood pressure monitoring every three months is recommended. Uncontrolled hypertension is a contraindication to the use of venlafaxine.<sup>9</sup> An observational study comparing the fatality rate in overdoses of TCAs, venlafaxine and SSRIs found that venlafaxine was substantially less toxic than the TCAs, but considerably more toxic than the SSRIs.<sup>19</sup>

**Table 2:** Recommended use of fully-subsidised antidepressants for patients with depression, adapted from Malhi *et al* (2015).<sup>2</sup>

Recommendation	Medicine	Class	Main mechanism of action	May be useful for patients with depression and the following features:
<b>First-line</b>				
	Sertraline, citalopram, escitalopram, fluoxetine, paroxetine,	Selective serotonin reuptake inhibitors (SSRIs)	Selective blockade of 5-HT reuptake	Anxiety
	Mirtazapine	Noradrenergic and specific serotonergic antidepressant (NaSSA)	Blockade of 5-HT at 5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptors and blocks 5-HT <sub>3</sub> receptors and alpha <sub>2</sub> -adrenoceptors	Insomnia, weight loss, reduced appetite
<b>Second-line</b>				
	Bupropion (unapproved indication)	Noradrenaline reuptake inhibitor (NDRI)	Blockade of noradrenaline and dopamine transporters	Fatigue, sexual dysfunction
	Venlafaxine	Serotonin-noradrenaline reuptake inhibitor (SNRI)	Blockade of 5-HT and noradrenaline reuptake and subsequent increase in prefrontal dopamine	Severe depression or treatment resistant depression
	Amitriptyline, clomipramine, nortriptyline	Tricyclic antidepressants (TCA)	Broad: all cause blockade of noradrenaline reuptake. Some block 5-HT reuptake and 5-HT receptors and other receptors types	Insomnia, severe depression or co-morbid pain

### Tricyclic antidepressants are often appropriate for patients with severe depression

TCAs are generally a second-line option for patients with depression as patients may be less adherent to treatment due to adverse effects, compared with SSRIs, and TCAs are more toxic in overdose.<sup>2,3</sup> However, in patients with severe depression or with insomnia or chronic neuropathic pain a TCA may be more effective than an SSRI.<sup>2</sup>

Adverse effects associated with TCAs include central nervous effects, e.g. sedation, fatigue or agitation, anticholinergic effects, e.g. dry mouth, tremor, and weight gain.<sup>2</sup> Less frequently, TCAs have been associated with cardiac adverse effects which can be lethal in overdose, including tachycardia, postural hypotension, slowed cardiac conduction, and seizures.<sup>2</sup> TCAs are contraindicated in the first six months following a myocardial infarction and should be used with caution in patients with cardiovascular disease.<sup>9</sup>

Considerations when selecting a TCA for patients with depression include:<sup>2,20,21</sup>

- Amitriptyline or clomipramine may be the most effective antidepressants for patients with severe depression, however, they are more likely than other TCAs to produce anticholinergic adverse effects
- Nortriptyline is the least toxic TCA with less potential to interact with other medicines and may be preferred in patients with chronic neuropathic pain or resistant depression requiring combination treatment
- Imipramine is the least sedating TCA (see: “Medicines update 2021: shortages, discontinuations and funding changes”)
- Dosulepin (dothiepin) is the most toxic TCA and should generally be avoided (see: “Medicines update 2021: shortages, discontinuations and funding changes”)

## Medicines update (as of 1 May, 2021): shortages, discontinuations and funding changes

**Imipramine (Tofranil)** is a tricyclic antidepressant. PHARMAC have notified that imipramine **25 mg tablets are out of stock**. As an alternative chemically equivalent brand has not been sourced, no new patients should be initiated on imipramine and patients who are currently taking imipramine 25 mg will need to switch to an alternative treatment or, depending on the dose they were on, make up the equivalent dose with 10 mg tablets. For example, consider using the appropriate number of imipramine 10 mg tablets to make up the equivalent dose over 48 hours (i.e. alternating 70 mg one day and 80 mg the next to equate to a previous daily dose of 75 mg). The practicality and risk of medicine errors associated with taking multiple tablets per day and alternating the dosing on different days must be considered. Switching patients who are established on imipramine to another antidepressant must be carefully managed; refer to the NZF (see link below) for recommendations on switching to another tricyclic antidepressant or class of antidepressant.

N.B. The supplier has advised that there is sufficient stock of the 10 mg tablets to manage increased demand during the out of stock period. It is unknown how long the out of stock period will last. The 10 mg tablets are not scored, and doses may be inaccurate if the tablets are broken.

**Maprotiline hydrochloride (Ludimil)** is a tricyclic-related (tetracyclic) antidepressant. This medicine has been **discontinued** and may have limited availability; Ludimil is the only brand of maprotiline approved by Medsafe. It is estimated that this will affect about 70 patients in New Zealand. Since 1 September, 2020, maprotiline has not been funded for new patients, however, maprotiline is currently subsidised by endorsement for patients who were taking it prior to this date. Stock of Ludimil 25 mg tablets has now expired, the current stock of Ludimil 75 mg tablets expires at the end of July, 2021, and there will be no new stock. Both tablet strengths are to be delisted from 1 August, 2021. Patients taking maprotiline should be switched to an alternative antidepressant; refer to the NZF (see link below).

**Phenelzine sulphate (Lupin)** is a monoamine oxidase inhibitor (Section 29, unapproved medicine). This medicine has been **discontinued** and supplies ran

out in 2020, affecting approximately 100 patients. The Mental Health Subcommittee of the Pharmacology and Therapeutics Advisory Committee advised PHARMAC that tranylcypromine sulphate would be an appropriate alternative, however, treatment changes would need to be individualised for each patient.<sup>22</sup> All patients should now have switched to an alternative treatment; discuss any issues regarding treatment options or change of treatment with a psychiatrist.

**Dosulepin (Mylan brand)**, a tricyclic antidepressant, is **subsidised by endorsement** for patients who were prescribed dosulepin [dothiepin] hydrochloride prior to 1 June, 2019. New patients should not be initiated on dosulepin. N.B. The Dopress brand of dosulepin has been discontinued; supplies ran out in early 2020.

👁️ For further information on medicine supply issues and updates, see: <https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notice/>

👁️ For further information on switching antidepressants, see: [https://nzf.org.nz/nzf\\_2225#nzf\\_10138](https://nzf.org.nz/nzf_2225#nzf_10138)

👁️ For further information on switching phenelzine to another antidepressant, see: [https://www.ranzcp.org/files/communications/medicine-alerts/phenelzine-switching-advice-\\_final-11052020.aspx](https://www.ranzcp.org/files/communications/medicine-alerts/phenelzine-switching-advice-_final-11052020.aspx)



## Monoamine-oxidase inhibitors are occasionally used for patients with atypical symptoms

MAOIs are classified as reversible, i.e. moclobemide, or non-reversible, i.e. tranylcypromine (see: "Medicines update 2021: shortages, discontinuations and funding changes"). MAOIs are seldom prescribed in primary care. Non-reversible MAOIs are almost exclusively reserved for patients under the care of a psychiatrist due to the risk of adverse effects and interactions with other medicines.<sup>3,9</sup> MAOIs may be considered for patients with atypical depression, i.e. those with a reactive mood, marked fatigue, weakness, hypersomnia, excessive eating, weight gain, and extreme sensitivity to personal rejection.<sup>2</sup>

## Combining antidepressants requires caution and experience


Combinations of antidepressants may be prescribed to patients with depression who have not responded to monotherapy; regimens are often initiated or overseen by a psychiatrist.<sup>2</sup> When combining antidepressants, treatment choice is generally guided by pharmacological knowledge, clinical experience and the limited amount of available evidence.<sup>2</sup> Some experts recommend the use of low-dose TCAs, e.g. nortriptyline 10–25 mg, in combination with citalopram or sertraline, if the patient's response has been suboptimal. Mirtazapine is sometimes used in combination with a SSRI, venlafaxine or a TCA, and lithium is sometimes prescribed with TCAs, SSRIs or other antidepressants.<sup>2</sup> Patients taking combinations of antidepressants should be monitored closely for adverse effects, particularly in the first weeks of treatment. Table 2 summarises the main pharmacological options for the management of depression in primary care.<sup>2, 20, 21</sup>


## Prescribing antidepressants safely and effectively

Begin by prescribing at the lowest recommended dose to reduce the risk of adverse effects. Patients should be prepared for transient adverse effects during the first days and weeks of treatment.<sup>10</sup> Tolerance to adverse effects, and adherence to treatment, may be improved by framing their onset as a signal that the medicine is working and providing reassurance that they are likely to diminish. A "start low, go slow" approach is recommended with TCAs, with the initial dose reduced by 50% in older patients.<sup>9</sup>

 Patient information sheets for individual medicines are available from the NZF: [www.nzf.org.nz](http://www.nzf.org.nz)

**Serotonin syndrome is a potentially life-threatening condition** suggested by a classic triad of autonomic, mental and neuromuscular symptoms and signs, including myoclonus, agitation and shivering.<sup>9</sup> Serotonin syndrome can occur with high doses of SSRIs or concurrent use of medicines with serotonergic activity, e.g. a SSRI with tramadol, mirtazapine, bupropion, pethidine, a MAOI, lithium or St John's Wort.<sup>10</sup> A washout period is required when switching between SSRIs and MAOIs.<sup>9</sup>

 Use the NZF interactions checker to look for potentially significant interactions before prescribing another medicine to a patient who is taking an antidepressant, available from: [www.nzf.org.nz](http://www.nzf.org.nz)


 For information on prescribing antidepressants to **women who are pregnant or breastfeeding**, see: <https://bpac.org.nz/2019/perinatal-depression.aspx>

## Prescribing antidepressants to younger patients: limited evidence of efficacy

Non-pharmacological treatments are always preferred for depression and/or anxiety in patients aged under 18 years. There is limited evidence supporting the use of antidepressants in young people and prescribing is unapproved. The majority of any benefit from antidepressants in young people is attributable to the placebo effect.<sup>23</sup> Psychological interventions should be continued alongside antidepressants if a medicine is initiated.

In patients aged under 18 years fluoxetine is the preferred medicine for moderate to severe depression,

as it is the only antidepressant with clinical data showing that the benefits outweigh the risks in this age group.<sup>24</sup> Discussion with a child and adolescent psychiatrist or a paediatrician is recommended before prescribing. Young people who are prescribed antidepressants should be closely monitored for suicidal thoughts or behaviour.<sup>24</sup>

 Further information is available from: "The role of medicines for the treatment of depression and anxiety in patients aged under 18 years" [www.bpac.org.nz/BPJ/2016/March/depression-anxiety-under18.aspx](http://www.bpac.org.nz/BPJ/2016/March/depression-anxiety-under18.aspx)



## Early follow-up after initiation is essential

After an antidepressant is initiated, the patient should be followed up within one to two weeks to assess their response and monitor for adverse effects.<sup>2</sup> Response to antidepressants varies, although a clinical benefit can usually be expected in the first two to three weeks of treatment with a therapeutic dose; remission generally requires at least six weeks of treatment.<sup>2</sup>

## Optimising antidepressant treatment

If after two to three weeks the patient's symptoms have improved somewhat, treatment should be continued and response reassessed again in one month.<sup>2</sup> A subsequent plateau indicates that the patient has partially responded and an increase in dose should be considered.<sup>2</sup> However, SSRIs generally have a flat dose-response curve and increasing the dose will not necessarily improve their efficacy.<sup>2</sup>

### When to consider switching medicines

If the patient has had no response to a therapeutic dose of an antidepressant after at least three weeks of treatment, a switch to another medicine may be appropriate, once the diagnosis has been reconsidered and treatment adherence confirmed.<sup>2</sup> As many as two-thirds of patients with depression who are prescribed an antidepressant may not respond adequately to initial treatment.<sup>27</sup> Switching antidepressants may also be necessary for patients who find the adverse effects of the initial medicine intolerable.

It is possible to switch between some SSRIs, e.g. citalopram and escitalopram immediately, however, more complex strategies may be required for other medicine combinations, e.g. switching from fluoxetine requires a washout period and cross-tapering is required when switching between TCAs.<sup>2,9</sup> If a patient has not responded to a SSRI, a switch to another class is recommended, e.g. mirtazapine, venlafaxine, or a TCA.<sup>2</sup>

Referral to a psychiatrist is recommended for patients with symptoms that have not improved after optimising psychological interventions and trialling two antidepressants.

 Information on switching between specific antidepressants is available in the NZF: [www.nzf.org.nz/nzf\\_2225](http://www.nzf.org.nz/nzf_2225)

## Withdrawing antidepressants following remission

It is appropriate to consider withdrawing antidepressants from patients who are coping well one year after recovery from a single episode of depression or at least three years after recovery from multiple episodes.<sup>2</sup> Patients should be monitored for symptoms of a relapse for at least six months following antidepressant withdrawal.

## Prescribing antidepressants to older patients: risk of hyponatraemia and decreased bone mineral density

Antidepressants are often prescribed to older patients at lower doses as they may be more sensitive to medicines and at an increased risk of falls, compared with young patients. However, it is important that dosing is sufficient for the medicine to have a therapeutic effect.

The use of antidepressants increases the risk of hyponatraemia, particularly in older patients taking SSRIs or SNRIs.<sup>2, 10, 25</sup> There is some evidence that this risk may be greatest in patients taking sertraline or escitalopram.<sup>25</sup> Additional risk factors for hyponatraemia include female sex, low body weight, cirrhosis, or the concurrent use of diuretics or omeprazole.<sup>10</sup> Most cases of hyponatraemia occur in the first four weeks of treatment.<sup>10</sup> Before prescribing a SSRI or venlafaxine to an older, frail patient their plasma sodium levels should be tested:<sup>10</sup>

- At baseline
- After two weeks and again at three months of treatment
- After a dose increase or the addition of other medicines that may cause hyponatraemia

Hyponatraemia at baseline may, depending on the cause, be treated before the antidepressant is initiated with fluid restriction, increased salt intake or diuretics. If hyponatraemia develops in the absence of symptoms, treatment can continue with the patient closely monitored for dizziness, nausea, lethargy, confusion, cramps and seizures.<sup>10</sup>

The use of antidepressants is associated with decreased bone mineral density and increased fracture risk.<sup>26</sup> The clinical significance of this association is hard to assess as depression itself is associated with reduced health and increased fracture risk, however, the risk is higher in patients taking SSRIs, compared with patients taking TCAs.<sup>26</sup> A pragmatic approach would be to consider the long-term use of antidepressants as an additional risk factor for reduced bone mineral density when assessing the future fracture risk of older patients.

## Abrupt cessation of antidepressants can cause discontinuation syndrome

Antidepressant discontinuation syndrome can develop in some patients who have taken antidepressants for longer than six weeks, if cessation is abrupt.<sup>27</sup> Patients may experience a range of adverse effects while withdrawing from a SSRI, SNRI or TCA, including “flu-like” symptoms due to anticholinergic withdrawal, nausea, lethargy, dizziness, ataxia, electric shock-like sensations, anxiety, irritability and sleep disturbances.<sup>27</sup> Withdrawal from paroxetine or venlafaxine, in particular, can be associated with severe symptoms.<sup>27</sup> Conversely, patients rarely experience problems withdrawing from fluoxetine due to its long-half life and active metabolite, although interactions with other medicines may persist for several weeks.<sup>9, 27</sup> Withdrawal from MAOIs can be problematic and patients may experience agitation, irritability, mood disorders, cognitive impairment and occasionally psychosis and delirium.<sup>27</sup> Where possible, antidepressants should be slowly decreased over at least four weeks before being withdrawn.

Patients should be prepared for the possibility of withdrawal symptoms and reassured that they are likely to resolve in a few weeks. If a patient is experiencing severe withdrawal symptoms the antidepressant can be reintroduced and subsequently withdrawn with a slower taper.<sup>28</sup> Patients who are experiencing difficulties withdrawing from a SSRI or venlafaxine may benefit from a switch to, or the addition of, fluoxetine with stabilisation for at least one month followed by a gradual reduction of the dose over the following months.

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