

# Commencing and changing antidepressants

By Dr Michelle Bellingan

## Learning objectives

After reading this article you should be able to:

- Describe signs and symptoms of depression.
- Provide appropriate advice to patients commencing antidepressant therapy.
- Provide appropriate advice to patients changing antidepressants.
- Recognise symptoms that warrant immediate referral to a doctor.

### Competencies addressed:

2.1.1.1, 3.1.4, 3.2.2, 4.3.3, 7.3.2



## Case study

*Agnes (43 years old) is a long-standing customer at your pharmacy. Her husband passed away suddenly two years ago and she has three teenage boys. She is an office manager and has previously told you that she leads a largely sedentary lifestyle because she 'doesn't have time to exercise'. Agnes now tells you that 'over the past couple of months everything has just become too much to cope with'. She has lost weight and is having trouble sleeping. Her doctor has diagnosed depression and Agnes presents you with a prescription for fluoxetine 20 mg each morning. Agnes has never taken an antidepressant before and asks numerous questions regarding depression and her medication.*

## Can you tell me more about depression?

Depression is a large cause of disability in Australia.<sup>1</sup> According to the 2007 National Survey of Mental

Health and Wellbeing, 4.1% of adults have a depressive disorder in any given month.<sup>2</sup> It is further estimated that about one in five people will experience at least a short period of depression at some stage in their life.<sup>3</sup> Depression occurs more commonly in women than men and most major depression begins in the late twenties.<sup>4</sup>

Many factors protect against, predispose to, or precipitate depression, including: genes, childhood experience, previous trauma, social and cultural supports, physical factors (including drugs) and stress.<sup>5</sup>

The symptoms of depression vary in severity from person to person. Table 1 summarises common symptoms of depression that range from feeling irritable to suicidal.<sup>3</sup> Despite depression manifesting in different ways, most people with depression experience significant disruption to their normal lifestyle.<sup>6</sup>

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Table 1. Common symptoms of depression<sup>3</sup>

<b>Emotional symptoms</b>
<ul style="list-style-type: none"> <li>• pervasive sadness</li> <li>• irritable mood</li> <li>• low, depressed mood</li> <li>• loss of enjoyment or pleasure</li> <li>• being aggressive or angry.</li> </ul>
<b>Cognitive symptoms</b>
<ul style="list-style-type: none"> <li>• worrying</li> <li>• feeling worthless</li> <li>• feeling hopeless</li> <li>• thinking about death frequently</li> <li>• guilt, self blame</li> <li>• indecision.</li> </ul>
<b>Physical symptoms</b>
<ul style="list-style-type: none"> <li>• inability to concentrate</li> <li>• fatigue or low energy nearly every day</li> <li>• significant change in weight or appetite</li> <li>• difficulty sleeping or excessive sleeping</li> <li>• increased sensitivity to pain</li> <li>• agitation.</li> </ul>
<b>Social symptoms</b>
<ul style="list-style-type: none"> <li>• withdrawing or deliberately isolating yourself.</li> </ul>

In the majority of cases, the prognosis for depression, where the person is being treated appropriately, is generally good. Studies have, however, identified that the probability of remission declines with increasing episode duration. Long term prognosis (i.e. probability of remission at six months and beyond) is strongly related to remission status at three months and only modestly related to various other clinical characteristics assessed at baseline (e.g. prior history of refractory depression, medical comorbidity and comorbid anxiety symptoms).<sup>7</sup> A patient's response to an antidepressant should therefore be assessed at three months. Should minimal improvement be evident, a change in antidepressant should be considered.

### How do antidepressants work? How long will it take before I start feeling better?

The Monoamine Hypothesis states that depression is caused by a deficiency of monoamines, particularly noradrenaline and serotonin, in the synaptic cleft. According to

this hypothesis, depression can be alleviated by drugs that increase the availability of noradrenaline and serotonin. The Monoamine Hypothesis cannot, however, explain the delay in time of onset of antidepressants. This is explained by the Receptor Sensitivity Hypothesis. Super sensitivity is a compensatory response of the postsynaptic neuron when it receives too little stimulation due to a deficiency of noradrenaline and serotonin. Over time, the postsynaptic neuron increases receptor responsiveness and may also compensate for the lack of stimulation by synthesising additional receptor sites. This upregulated postsynaptic state is believed to be associated with the clinical symptoms of depression.<sup>8</sup>

Via various pharmacodynamic actions, all antidepressants increase neurotransmitter levels in the synaptic cleft which then prompts a down-regulation and desensitisation of postsynaptic receptors.

Although neurotransmitter levels increase rapidly after taking an antidepressant, post-synaptic receptor down-regulation takes a number of weeks. Pharmacists should take care to explain that antidepressant therapeutic effects are not immediate. Unrealistic expectations of how soon a patient will start feeling 'better' only compound the depressed patient's sense of hopelessness.

### How must I take/use the antidepressant?

Antidepressants should be taken regularly every day. It should be made clear to patients that antidepressant medications should be taken for a minimum of two to four weeks for a noticeable therapeutic effect<sup>9</sup> and that self-administration of higher doses will not result in a faster outcome. On the contrary, higher than prescribed doses will result in the amplification of side-effects, some of which are potentially dangerous.

Some antidepressants are highly sedative, whereas others may increase alertness. It is therefore important to take the medication as advised by a doctor or pharmacist (i.e. at night or in the morning). Should a dose be missed and the patient remembers when it is almost time for the next dose, the dose should be skipped and the next dose taken at the usual time. Patients

should be advised to not take a double dose to make up for the dose they have missed.<sup>10</sup>

Patients should also be counselled to continue taking the medicine even if feeling better and not to discontinue therapy without consulting their doctor.

### Will I have to take antidepressants for the rest of my life? Will I get addicted to them?

After a patient's first episode of major depression antidepressant therapy needs to continue for four to 12 months for maximum efficacy.<sup>11</sup> Treatment should continue for at least two years for repeated episodes or where there are other risk factors for relapse.<sup>6</sup> In the majority of cases of recurrent depression, continuous maintenance antidepressant treatment may be required.<sup>11</sup>

Concern about the addiction potential of antidepressants has arisen from an increasing volume of research characterising a withdrawal syndrome on cessation of treatment.<sup>12,13</sup> Such symptoms typically appear one to three days after termination of treatment and last seven to 14 days.<sup>14</sup>

The DSM-IV lists seven criteria that represent substance dependence.<sup>4</sup> To qualify for a diagnosis of substance dependence, an individual must meet at least three of these criteria. Withdrawal symptoms are only one criterion for dependence, and alone are not sufficient for a diagnosis of dependence. The essence of dependence is drug-seeking behaviour despite negative consequences – this behaviour is not apparent on cessation of an antidepressant.<sup>15</sup>

It is important to address Agnes' concerns regarding 'addiction' since non-adherence to medications is a significant barrier to the effective treatment of depression. Discontinuation rates of antidepressants within three months of treatment initiation can reach 68%.<sup>16</sup>

### Are antidepressants safe to take?

Side-effects vary depending on which antidepressant the patient has been prescribed. Common side-effects are outlined in Table 2. Studies have

shown that fear of side-effects and the actual occurrence of side-effects are the main reasons for not filling a second prescription of an antidepressant.<sup>17</sup> Since side-effects tend to manifest shortly after initiating therapy (while the therapeutic effects are delayed), it is vitally important that patients are made aware of common side-effects and their expected duration and, where possible, counselled on practical measures to manage side-effects.

The risk of suicide is inherent in depression and may persist until significant remission occurs. Patients should be closely monitored for clinical worsening and suicidality (suicidal ideation and suicidal behaviours), especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania and mania have been reported in patients being treated with antidepressants. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidality impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation or behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the antidepressant, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.<sup>19</sup>

The risk of serotonin syndrome is another important point to be addressed in patients prescribed antidepressant therapy. Serotonin toxicity is characterised by neuromuscular excitation (clonus, hyperreflexia, myoclonus, rigidity), autonomic stimulation (hyperthermia, tachycardia, diaphoresis, tremor, flushing) and changed mental state (anxiety, agitation, confusion). There are several drug mechanisms that cause excess serotonin in the central

nervous system, but severe serotonin toxicity only occurs with combinations of drugs acting at different sites, most commonly a monoamine oxidase inhibitor and a serotonin reuptake inhibitor. Less severe toxicity occurs with other combinations, overdoses and even single-drug therapy in susceptible individuals. To minimise the risk of serotonin toxicity, patients taking antidepressants should be counselled to always advise their doctor or pharmacist prior to initiating any new prescription or over-the-counter drugs. Patients should also be aware that certain recreational drugs (e.g. amphetamines and ecstasy) are serotonin-releasing drugs and pose the risk of serotonin toxicity if taken concurrently with antidepressants.<sup>20</sup>

### What if the antidepressant doesn't help me?

Despite antidepressants being effective in the treatment of depression, non-response remains a major clinical problem. It is reported that 30% of patients do not respond to antidepressants at all, while another 30% respond only partially without reaching full remission.<sup>21</sup>

Patients who report an unsatisfactory response to initial antidepressant treatment should be re-assessed in terms of their diagnosis and treatment plan. Lack of adherence to the treatment plan should be considered and perpetuating psychosocial factors need to be reviewed.<sup>22</sup> The following measures may be considered in patients who fail to respond to initial antidepressant therapy: a change in antidepressant, psychotherapy or lifestyle measures (e.g. exercise, meditation, relaxation techniques, stress management, support groups and self-help programmes). Should a second antidepressant also fail to elicit a response, augmentation with lithium may be considered. Electroconvulsive therapy (ECT) should be reserved for severe, refractory depression.<sup>1,2,22</sup>

### My GP has recommended I see a counsellor. Do you think it would be worth going if these tablets are going to make me feel better anyway?

Various psychotherapies are available as sole treatments or adjuncts to antidepressant medication. Interpersonal therapy, cognitive-

behavioural therapy, behavioural therapy and brief dynamic therapy have all been used in the treatment of mild to moderate depression. Antidepressants can eliminate many of the symptoms of depression, whereas psychotherapy is best at assisting the patient in day-to-day coping skills that can prevent relapse.<sup>24</sup>

Cognitive-behavioural therapy (or, to a lesser extent, interpersonal therapy) plus medication is reported to give better results than either treatment alone<sup>25</sup> for depression or for comorbid anxiety and depressive disorders.<sup>26</sup> Despite the combination of medication and psychotherapy yielding good results, patients with severe depression require antidepressant therapy or ECT prior to engaging in meaningful psychotherapy.<sup>22</sup>

### Would increasing my physical activity help me feel better?

Feeling tired and demotivated are common symptoms of depression. Exercise is often the last thing individuals feel like doing when they are depressed. Studies have, however, shown that individuals who exercise regularly experience fewer symptoms of depression and anxiety than those who do not exercise regularly. Research also suggests that exercise can further assist depression in individuals who have responded only partially to an antidepressant.<sup>27</sup> In this particular scenario, Agnes should be encouraged to build up her physical activity gradually. She could start with a 10–15 minute walk each morning and gradually increase this to 30 minutes per day.

### Case study

*Agnes returns to your pharmacy after three months fluoxetine therapy. Her doctor has now changed her treatment to mirtazapine 15 mg at night. Agnes informs you that the fluoxetine made her feel 'dreadful'. She was 'very anxious, had recurrent headaches and experienced more trouble sleeping than before'. Agnes also reports attending a single counselling session. She 'felt no different' after spending an hour with the counsellor and has never returned.*

Table 3. Recommendations for antidepressant changeover<sup>11,28,29</sup>

Drug	Recommendation	Rationale
<b>Category A changeover</b>		
Fluoxetine Phenelzine Tranycypromine	<ul style="list-style-type: none"> <li>gradual withdrawal generally unnecessary; withdrawal symptoms very unlikely</li> <li>wait for &gt; 10–14 days before starting the next antidepressant</li> <li>consider hospitalisation during washout/changeover if severely depressed</li> </ul>	Drug (or metabolites) with long half-life or persistent effects
<b>Category B changeover</b>		
TCA's SSRIs (except fluoxetine) Mianserin Mirtazapine	<ul style="list-style-type: none"> <li>withdraw gradually to prevent withdrawal symptoms (particularly if higher dose or long-term use); usually reduce dose by 25% per day</li> <li>wait for 2–4 days before starting the next antidepressant</li> <li>consider hospitalisation during washout/ changeover if severely depressed</li> </ul>	Drug (or metabolites) with intermediate half-life of 24–48 hours
<b>Category C changeover</b>		
Duloxetine Moclobemide Reboxetine Venlafaxine Desvenlafaxine	<ul style="list-style-type: none"> <li>duloxetine, venlafaxine, desvenlafaxine; withdraw gradually to prevent withdrawal symptoms</li> <li>reboxetine, moclobemide: withdrawal symptoms not reported</li> <li>wait for 1–2 days before starting the next antidepressant</li> </ul>	Drug (or metabolites) with short half-life of < 18 hours

### How should I change from my previous antidepressant to this new one?

When changing from one antidepressant to another, the need for a wash-out period should always be considered. The absence of a wash-out period can lead to serious adverse effects due to the interaction between the initial antidepressant and the subsequently prescribed drug. Of particular concern is the risk of serotonin syndrome. Table 3 outlines the recommendations for antidepressant changeover.

In this particular scenario, Agnes should be counselled to stop taking the fluoxetine capsules for 10–14 days before initiating the mirtazapine therapy. Fluoxetine's very long half-life would minimise the risk of withdrawal symptoms. Re-emphasise the benefits of psychotherapy as an adjunctive therapy to the antidepressant and explain that the benefits of therapy are not immediately apparent.

### Where can I find more information on depression?

Table 4 provides the details of some of the organisations patients may be referred to for further information. Depressed individuals in urgent need of assistance should be encouraged to call Lifeline on 13 11 14.

### Table 4. Useful Websites<sup>3</sup>

<b><a href="http://www.beyondblue.org.au">www.beyondblue.org.au</a></b> Information on depression, anxiety and bipolar disorder
<b><a href="http://www.blackdoginstitute.org.au">www.blackdoginstitute.org.au</a></b> Specialist information on depression and bipolar disorder
<b><a href="http://www.depressionservices.org.au">www.depressionservices.org.au</a></b> Information and online forums with 24 hour peer support and moderation for individuals living with depression

### Key learning points

- Since poor adherence is a major problem with the use of antidepressants, pharmacists can play a vital role in counselling

patients on the expected time to therapeutic onset and potential adverse effects (particularly those likely to present on commencement of treatment).

- The adjunctive role of psychotherapy and positive lifestyle interventions in the management of depression should be explained and encouraged.

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27. Black Dog Institute. Fact Sheet – Exercise and Depression. [www.blackdoginstitute.org.au/docs/ExerciseandDepression.pdf](http://www.blackdoginstitute.org.au/docs/ExerciseandDepression.pdf) (Accessed 16/04/2010).
28. AusDI Advanced – CYMBALTA® (Duloxetine HCl capsules) Product Information.
29. Aus DI Advanced – EDRONAX® (Reboxetine mesilate tablets) Product Information.

## Questions

A score of 4 out of 5 attracts 1 credit point.

1. After a patient's first major depressive episode antidepressant therapy needs to continue for a minimum of:
  - a) 2 years.
  - b) 1 year.
  - c) 4 months.
  - d) 2 months.
2. Which of the following is **not** a potential adverse effect experienced in patients commencing a SSRI?
  - a) Headache.
  - b) Constipation.
  - c) Increased anxiety/agitation.
  - d) Transient nausea.
3. Which of the following antidepressant regimens is **least** likely to result in a withdrawal syndrome upon discontinuation?
  - a) Desvenlafaxine 50 mg daily.
  - b) Clomipramine 200 mg daily.
  - c) Fluoxetine 40 mg daily.
  - d) Paroxetine 20 mg daily.
4. Identify the **correct** process whereby a moderately depressed patient's therapy is changed from moclobemide to venlafaxine.
  - a) Gradually withdraw moclobemide over a period of one week; wait for a further 1–2 days before starting venlafaxine.
  - b) No need to gradually withdraw moclobemide; it may be discontinued and venlafaxine started within 1–2 days.
  - c) Gradually withdraw moclobemide over a period of one week; wait for a further 10–14 days before starting venlafaxine.
  - d) Gradually withdraw moclobemide over a period of one week; wait for a further 2–4 days before starting venlafaxine.
5. Which of the following statements would be **incorrect** when counselling a patient on the commencement of an antidepressant?
  - a) Adverse effects are likely to be experienced prior to any therapeutic benefits.
  - b) It is important to catch up missed doses – even if this means doubling up the dose when you remember.
  - c) Report any worsening depression or suicidal feelings to your doctor.
  - d) Do not stop taking the antidepressant at your own discretion.

## Conferences

### Reaching New Heights

20–22 August

Pharmacy Women's Congress 2010  
Wrest Point Hotel, Hobart Tasmania  
Email: [events@qldguild.org.au](mailto:events@qldguild.org.au)

Website:

[www.pharmacywomenscongress.com.au](http://www.pharmacywomenscongress.com.au)

### The Third Annual Pharmaceutical Law Conference

30–31 August

Sydney Harbour Marriott  
Email: [info@iir.com.au](mailto:info@iir.com.au)

Website: [www.iir.com.au/pharmalaw](http://www.iir.com.au/pharmalaw)

### The Australasian Conference for Compounding Pharmacists (ACCP),

11–12 September

Swissotel, Sydney

Website: [www.accp.net.au](http://www.accp.net.au)

### Pharmacy 2010 – The Pharmacy Management Conference

15–18 September

Hamilton Island, Queensland  
Email: [pharmacyconference@acclaimsemm.com.au](mailto:pharmacyconference@acclaimsemm.com.au)

Website:

[www.pharmacyconference.com.au](http://www.pharmacyconference.com.au)

### Quality of medicines in a globalised world: dreams and reality

14–15 October

Prague, Czech Republic

Organised by the European Directorate for the Quality of Medicines & HealthCare, Council of Europe. Website: [www.edqm.eu/en/Quality-of-medicines-in-a-globalised-world-Dreams-and-reality-Prague-Czech-Republic-1049.html](http://www.edqm.eu/en/Quality-of-medicines-in-a-globalised-world-Dreams-and-reality-Prague-Czech-Republic-1049.html)

### Pharmacy Australia Congress Star performance – the future for pharmacy

28–31 October

Melbourne Convention Exhibition Centre  
Website: [www.pac10.com.au](http://www.pac10.com.au)

### 23rd Federation of Asian Pharmaceutical Associations (FAPA) Congress

5–8 November

Taipei International Convention Centre, Taiwan

Website: [www.fapa2010-taiwan.com](http://www.fapa2010-taiwan.com)

### FIP Pharmaceutical Sciences 2010 World Congress

14–18 November

Morial Convention Centre, New Orleans, USA

Website: [www.pswc2010.org](http://www.pswc2010.org)

### 2010 ASMI Conference

18 November

Further details to be announced

Website: [www.asmi.com.au/events/default.aspx](http://www.asmi.com.au/events/default.aspx)