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Antidepressants

By Dr Michelle Bellingan

Learning objectives

This article aims to provide the reader with an update of:

- The major theories that are hypothesised to explain the pathology of depression
- The pharmacodynamics of the new generation antidepressants
- The efficacy and onset of action of these newer antidepressants compared to the older antidepressants.

Competencies addressed: 3.1.2, 4.2.1

Depression is the fourth most common problem presenting to GPs in Australia. It is estimated that 10% of people may become depressed during their lives. This lifetime prevalence may be as high as 20% in women.[1] A recent study revealed that the most commonly prescribed medication for Australian women is antidepressants.[2] There are numerous neurochemical theories pertaining to the pathophysiology of depression and a corresponding variety of drugs used in the treatment of this complex condition. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and mianserin dominated the antidepressant market until the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, was approved by the FDA (United States) in 1988. Since then, four more SSRIs and four other new antidepressants, namely venlafaxine, duloxetine, reboxetine and mirtazapine, have been approved (refer to Table 1).

This increased armentorium of antidepressants could lead both patients and practitioners to pose the following questions:

- How do these newer antidepressants work?
- Are they more acceptable to patients in terms of side effects?
- Are these newer antidepressants more effective than the older agents?
- Do the newer antidepressants have a faster onset than the older agents?

This article will briefly address these questions.

Summary of pathology of depression

The cause of depression is yet to be fully elucidated. It has been proposed that depression may be due to decreased functional amine-dependent synaptic transmission.[4]

The Monoamine Hypothesis of Depression 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.[4] Different types of depression are still being debated, i.e. Patient A's depression may be largely as a result of a noradrenaline deficiency, Patient B may be depressed because of serotonin deficiency, whereas Patient C's depression might be due to a deficiency of both these neurotransmitters. Antidepressant therapy should therefore be individualised according to patient response.

The Monoamine Hypothesis of Depression cannot explain the delay in time of onset of clinical relief of depression of up to six to eight weeks. This is explained by the *Receptor Sensitivity Hypothesis*. Supersensitivity is a compensatory response of the postsynaptic neuron when it receives too little stimulation. The neuron attempts to make up for a lack of stimulation by increasing receptor responsiveness. Over time, the postsynaptic neuron may also compensate for the lack of stimulation by synthesising additional receptor sites.[4] This process is known as up-regulation. This up-regulated postsynaptic state is believed to be associated with the clinical symptoms of depression.

Pharmacodynamics of new generation antidepressants

All the antidepressants currently available have been developed in line with the Monoamine and Receptor Sensitivity Hypotheses. Despite having varied pharmacodynamic actions, antidepressants increase neurotransmitter levels in the synaptic cleft, which then prompts postsynaptic receptors to decrease in number (down-regulate) and decrease in sensitivity (desensitisation). Table 2 outlines the pharmacological differences among several of the older and newer antidepressants.

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Table 1. Antidepressant Drug Classes (adapted from AMH[3])

	Drug names	Trade names (examples only)
Older antidepressant classes		
Tricyclic antidepressants (TCAs)	Amitriptyline Clomipramine Dothiepin Doxepin Imipramine Nortriptyline Trimipramine	*Endep* *Anafranil, Placil* *Dothep, Prothiaden* *Deptran, Sinequan* *Tofranil, Tolerade* *Allegron* *Surmontil*
Monoamine oxidase reuptake inhibitors (MAOIs)	Moclobemide Phenelzine Tranylcypromine	*Amira, Aurorix, Clobemix, Mohexal, Maosig* *Nardil* *Parnate*
Other	Mianserin	*Lumin, Tolvon*
Newer antidepressant classes		
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	*Celapram, Celica, Ciazil, Cipramil, Citalobell, Citalopram, Talam, Talohexal* *Esipram, Lexapro* *Lovan, Prozac, Auscap, Fluohexal, Zactin, Fluoxebell* *Faverin, Luvox, Movox, Voxam* *Aropax, Extine, Paxtine* *Concorz, Sertra, Eleva, Zoloft, Xydep*
Serotonin noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine Duloxetine	*Efexor-XR* *Cymbalta*
Selective noradrenaline reuptake inhibitors (NARIs)	Reboxetine	*Edronax*
Noradrenergic and specific serotonergic antidepressant (NaSSA)	Mirtazapine	*Avanza, Mirtazon, Remeron, Axit30, Avanza SolTab*

Question 1. How do the newer antidepressants work?

Selective serotonin reuptake inhibitors

SSRIs block the amine pump for serotonin reuptake.[4] Paroxetine and sertraline are also associated with a down-regulation of postsynaptic beta-1-adrenoceptors.[5] The side-effects of SSRIs are largely associated with increased levels of serotonin interacting with postsynaptic 5-HT2 and 5-HT3 receptors. Stimulation of 5-HT3 receptors is responsible for nausea, diarrhoea and headache, which often occur at the start of treatment. Agitation, akathisia, anxiety, panic attacks, insomnia and sexual dysfunction may be related to an action at 5-HT2 receptors. Sexual dysfunction may also be due to disinhibition of the descending serotonin pathway from the brain stem through the spinal cord to neurons mediating spinal reflexes such as ejaculation and orgasm. The increased serotonin release inhibits sexual functioning.[5] During long term therapy, the most troublesome adverse effects are sexual dysfunction, weight gain and sleep disturbance.[6]

It is important to consider that the SSRIs have differing individual profiles (refer to Table 2).

Gastrointestinal side effects are most frequently reported. Fluvoxamine and sertraline are associated with the highest frequency of GI disturbances.

Serotonin noradrenaline reuptake inhibitors

SNRIs selectively block the reuptake of both serotonin and noradrenaline into the presynaptic bulb. Weak effects on dopamine reuptake have also been reported.[5] It should be noted that the increased dopamine levels are not of significance in terms of the amelioration of depressive symptoms. Unlike the TCAs, however, SNRIs have less alpha-1, cholinergic or H1 receptor blocking properties. In particular, SNRIs have fewer cardiac effects, hence they are safer in overdose than TCAs.

It should be noted that the reuptake effects of venlafaxine are dose dependent. At low doses (<150 mg/day), the drug acts like the SSRIs. At intermediate to high doses, the additional effects of noradrenaline reuptake become more significant.[5]

Nausea, agitation, sexual dysfunction and insomnia at low doses of venlafaxine are probably as a result of effects on postsynaptic serotonergic receptors. At intermediate to high doses, additional adverse effects such as raised blood pressure and headache are observed.[5] These effects are probably due to an action on the noradrenaline transporter.

Selective noradrenaline reuptake inhibitors (NARIs)

The prototype drug in this class, reboxetine, selectively inhibits the reuptake of noradrenaline. It has been proposed that reboxetine may be more effective in noradrenaline deficiency syndrome (e.g. depression associated with fatigue, apathy, cognitive and somatic disturbances), or nonresponders to SSRIs.

Adverse effects of reboxetine include urinary retention, dry mouth, sweating, parasthaesia and constipation. Other noradrenergic effects include: increased diastolic blood pressure, increased heart rate, insomnia and headache.[3]

Genitourinary problems occurring within five weeks of commencing therapy have been described in numerous Adverse Drug Reactions Advisory Committee (ADRAC) reports. Patients prescribed reboxetine should be asked about symptoms of urinary obstruction and sexual dysfunction soon after commencing therapy.[7]

Noradrenergic and specific serotonergic antidepressants

With the exception of the MAOIs, all antidepressants have inhibitory effects at the monoamine reuptake pump (either for serotonin, noradrenaline or both). Mirtazapine is

pharmacologically unique in that it is an alpha-2-antagonist on the presynaptic bulb. By inhibiting this autoreceptor, mirtazapine counteracts negative feedback on the release of neurotransmitters from storage vehicles, thereby promoting neurotransmitter release. Mirtazapine also antagonises post-synaptic 5-HT2 and 5-HT3 receptors thereby minimising the more common adverse effects associated with the SSRIs. Despite having less of the traditional serotonergic side effects, mirtazapine use is frequently associated with increased appetite, weight gain, sedation, weakness and peripheral oedema.[3]

Question 2. Are the new generation antidepressants more acceptable to patients in terms of side-effects?

The new generation antidepressants tend to have more tolerable side effect profiles than TCAs and MAOIs. As outlined above, these drugs are by no means devoid of significant side effects. On average, 61% of patients taking second-generation antidepressants experience at least one side effect. The most common are nausea, vomiting, constipation, diarrhoea, dizziness, headache and sleeplessness.[8]

Venlafaxine is associated with a higher incidence of nausea and vomiting than the SSRIs. This drug is also more likely to be discontinued due to adverse effects. Sertraline is more likely to cause diarrhoea than citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine or venlafaxine. Mirtazapine leads to a higher incidence of weight gain than fluoxetine, paroxetine or venlafaxine.[8]

Question 3. Are these newer antidepressants more effective than the older agents?

Despite working in different ways and having different adverse effect profiles, antidepressants have always been regarded as being equally efficacious or equipotent. None of the newer antidepressants have been shown to be more effective than the tricyclics with which they have been compared.[4] Recently published meta-analyses have, however, questioned the equipotency of the newer antidepressants.[9] One of these studies analysed results of 117 randomised controlled trials from 1991–2007, which compared the effects of 12 new generation antidepressants in more than 25,000 patients with major depression. The drugs tested were bupropion*, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran**, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine.[10]

* only available as nicotine replacement in Australia
** not available in Australia

Sertraline and escitalopram were reported to score highly in terms of efficacy and acceptability, while reboxetine was shown to be significantly less efficacious than the other 11 drugs studied in the meta-analysis. Mirtazapine and escitalopram were also found to be more efficacious than the other drugs tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations of treatment than did duloxetine, fluvoxamine, paroxetine, reboxetine and venlafaxine.[10]

Despite these new claims, it should be considered that patients respond in a highly individualised manner to antidepressants. Sertraline and escitalopram might not be effective or appropriate in all patients.

Table 2. Pharmacological differences among several antidepressants[4]

Drug	Sedative action	Anti-muscarinic action	Block of amine pump for:	
			Serotonin	Nora-drenaline
TCAs				
Amitriptyline	+++	+++	+++	++
Clomipramine	+++	++	+++	+++
Desipramine	+	+	0	+++
Doxepin	+++	+++	++	+
Imipramine	++	++	+++	++
Nortriptyline	++	++	+++	++
SSRIs				
Citalopram, Escitalopram	0	0	+++	0
Fluoxetine	+	+	+++	0, +
Fluvoxamine	0	0	+++	0
Paroxetine	+	0	+++	0
Sertraline	+	0	+++	0
SNRI				
Venlafaxine	0	0	+++	++
NaSSA				
Mirtazapine	+++	0	0	0

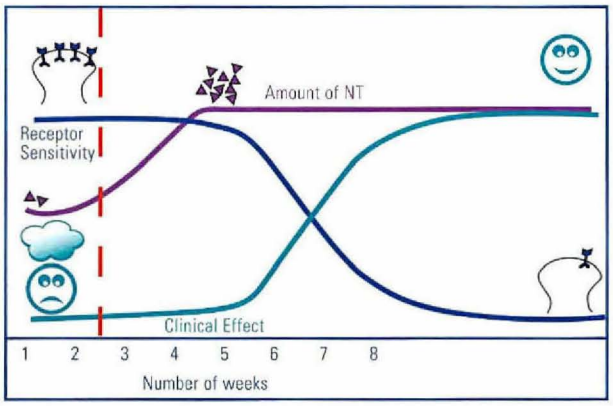
Question 4. Do the newer antidepressants have a faster onset than the older agents?

Speed of onset of antidepressants is clinically important for many reasons. Delayed onset means that depression, its associated disability and, for some patients, the potential risk of suicide continue. Early onset of effects may improve future compliance and thus outcomes.[11]

As depicted in Figure 1, neurotransmitter levels show an increase within the first week of antidepressant therapy. It may however take six to eight weeks before patients experience therapeutic benefits. It is hypothesised that the rate-limiting step in this process is the down-regulation of up-regulated receptors.

Several antidepressants have claimed an earlier onset of action but none has, as yet, demonstrated this incontrovertibly.[12,13]

Figure 1. Postulated neurotransmitter receptor hypothesis of antidepressant action



Adapted from: Stahl SM. Stahl's Essential Psychopharmacology, Neuroscientific Basis and Practical Applications, 3rd ed. USA: Cambridge University Press, 2008.

Post hoc analyses of comparisons between SSRIs and dual-action antidepressants such as mirtazapine, venlafaxine and duloxetine indicate that the dual-action drugs may have a faster onset of action.[13,14] Current data do not clearly support claims that one drug reduces the symptoms of depression faster than another, though the existing literature suggests that escitalopram displays some superiority in terms of rapidity of action.[13]

Conclusion

Until substantiated, neither efficacy nor speed of onset of action appears to be substantially altered in the newer generation antidepressants.[5] The search therefore continues for a 'magic bullet': the drug that will rapidly and safely meet the high expectations created by the word 'antidepressant'. Pharmacists have an essential role in counselling patients regarding their antidepressant medications. Realistic expectations should be discussed whilst still being mindful of the significant percentage of patients who might show a powerful, and sometimes almost immediate, placebo response to antidepressants. Furthermore, the benefits of psychotherapeutic intervention in conjunction with antidepressant therapy should also be emphasised.

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Questions

(A score of 3 out of 4 attracts three quarters of a credit point.)

1. Identify the **incorrect** statement pertaining to the use of SSRIs.

a) Sertraline has a higher risk of diarrhoea than any of the other SSRIs.
b) The side-effects of SSRIs are largely associated with the increased levels of serotonin interacting with postsynaptic 5-HT1 receptors.
c) During long-term therapy, the most troublesome side effects of SSRIs are nausea, diarrhoea and headache.
d) (b) and (c).
e) (a) and (b).

2. Which of the following antidepressants have a dual-action?

a) Duloxetine.
b) Reboxetine.
c) Mirtazapine.
d) All of the above.
e) (a) and (c).

3. Identify the **correct** statement pertaining to venlafaxine.

a) At low doses, venlafaxine's adverse effects are probably as a result of an effect on postsynaptic adrenergic receptors.
b) At doses above 150 mg daily, adverse effects are associated with serotonergic receptors.
c) Venlafaxine is safer in overdose than amitriptyline.
d) Venlafaxine has a lower incidence of nausea and vomiting than SSRIs.
e) Venlafaxine is an alpha-2-antagonist on the presynaptic bulb.

4. Antidepressants have varying actions at the monoamine reuptake pump. Identify the **incorrect** statement with regard to this statement.

a) Fluvoxamine only inhibits serotonin reuptake.
b) Mirtazapine inhibits serotonin, noradrenaline and dopamine reuptake.
c) Reboxetine only inhibits noradrenaline reuptake.
d) Duloxetine inhibits noradrenaline and serotonin.