Reuptake inhibitors for depression

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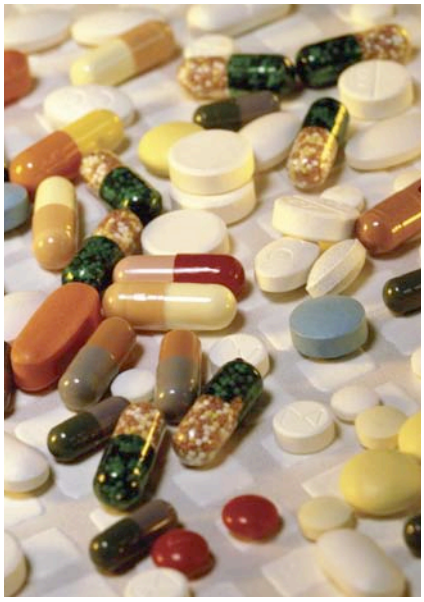
Most of the currently available antidepressants are monoamine neurotransmitter reuptake inhibitors. The development of drugs that are selective for either serotonin or noradrenaline, or both, has resulted in medications with better side effect profiles and reduced toxicity compared with the nonselective reuptake inhibitors, the tricyclic antidepressants.



The management of depression advanced greatly with the development of antidepressant agents based on neurotransmitter reuptake inhibition and, more recently, the development of reuptake inhibitors selective for specific neurotransmitters. These newer antidepressants have fewer side effects and less toxicity than the older agents. The pharmacology of the reuptake inhibitors, and particularly the newer drugs, is discussed in this article.

What are reuptake inhibitors?

Reuptake inhibitors are a group of drugs from several different classes whose mode of action involves blocking the reuptake of monoamine or other types of neurotransmitters from the synapse into the presynaptic neurone. The end effect is an increased synaptic concentration of neurotransmitter. The 'neurotransmitter hypothesis' of depression – that a deficit in monoamine neurotransmitter, notably noradrenaline and serotonin but also dopamine, underlies depression – infers that this increased concentration of synaptic monoamine neurotransmitter is responsible for the antidepressant effect. However, it is clear that this is not an adequate explanation for the antidepressant effect and that other mechanisms such as pre- and postsynaptic receptor effects and postsynaptic intracellular systems are also involved. Moreover, there are monoamine reuptake inhibitors that do not have antidepressant activity (for example, the weight reduction agent sibutramine.

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Classes of reuptake inhibitors

Most of the currently available antidepressants are reuptake inhibitors. The exceptions are the reversible and irreversible monoamine oxidase inhibitors (MAOIs; which inhibit the metabolism of monoamines) and the tetracyclic antidepressant mianserin and its analogue mirtazapine (which act by blocking presynaptic inhibitory receptors, thereby increasing the release of noradrenaline in the case of mianserin, and noradrenaline and serotonin in the case of mirtazapine).

Tricyclic antidepressants (TCAs) were the first antidepressants available that inhibited monoamine reuptake, and they are still widely used. They inhibit the reuptake of both serotonin and noradrenaline, but because they also interact with other postsynaptic receptors they are associated with considerable side effects and toxicity. The development of TCA-like drugs that are selective for either serotonin or noradrenaline, or both, has resulted in medications with better side effect profiles and reduced toxicity.

The selective reuptake inhibitors are classified as follows:

- selective serotonin reuptake inhibitors (SSRIs) – citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
- serotonin and noradrenaline reuptake inhibitors (SNRIs) – venlafaxine
- noradrenaline reuptake inhibitors (NARIs) – reboxetine.

Bupropion is a dopamine reuptake inhibitor and has antidepressant activity but is approved in Australia only for aiding smoking cessation (the mechanism by which it does this is unclear).

When are reuptake inhibitors used?

Reuptake inhibitors are indicated for the treatment of moderate to severe depression in adults, usually in conjunction with appropriate psychological management. Some of the SSRIs and SNRIs are also approved for the treatment of a variety of anxiety disorders in adults, such as generalised anxiety disorder, panic disorder, obsessive compulsive disorder and social phobia, and for premenstrual dysphoric disorder and post-traumatic stress disorder. There is evidence for the efficacy of some SSRIs for the treatment of bulimia. No antidepressants are approved for the

treatment of depression or anxiety in children and adolescents. The reuptake inhibitors available in Australia and their Therapeutic Goods Administration (TGA)-approved indications for use are listed in Table 1.

Table 1. Reuptake inhibitors available in Australia[1]

Reuptake inhibitor	TGA approved indications
SSRIs	
Citalopram (Celapram, Ciazil, Cipramil, Talam, Talohexal)	Major depression
Escitalopram (Lexapro)	Major depression; social anxiety disorder (social phobia), generalised anxiety disorder
Fluoxetine (Auscap, Fluohexal, Fluoxebelle, Lovan, Prozac, Zactin)	Major depression; obsessive compulsive disorder; premenstrual dysphoric disorder
Fluvoxamine (Faverin, Luvox, Movox, Voxam)	Major depression in adults; obsessive compulsive disorder in adults, adolescents and children ≥8 years
Paroxetine (Aropax, Oxetine, Paxtine)	Major depression; obsessive compulsive disorder; panic disorder; social anxiety disorder/ social phobia; generalised anxiety disorder; post-traumatic stress disorder
Sertraline (Concorz, Eleva, Xydep, Zoloft)	Major depression; panic disorder; social phobia (social anxiety disorder) in adults; obsessive compulsive disorder in adults and children ≥6 years; premenstrual dysphoric disorder
SNRIs	
Venlafaxine (Efexor, Efexor-XR)	Major depression; and for extended release formulation (Efexor-XR), also generalised anxiety disorder, social anxiety disorder
NARIs	
Reboxetine (Edronax)	Major depression
TCAs	
Amitriptyline (Endep, Tryptanol)	Major depression; nocturnal enuresis
Clomipramine (Anafranil, Placil)	Major depression; obsessive compulsive disorders and phobias in adults; cataplexy associated with narcolepsy
Dothiepin (Dothep, Prothiaden)	Major depression
Doxepin (Deptran, Sinequan)	Major depression
Imipramine (Melipramine, Tofranil)	Major depression; nocturnal enuresis in children >5 years
Nortriptyline (Allegron)	Major depression
Trimipramine (Surmontil)	Major depression

How are they used?

TCAs as a rule have a linear dose response and therefore they can sometimes be more effective in high doses. However, safety and cardiotoxicity then need careful monitoring and specialist supervision is important.

For SSRIs in general, the starting dose is the therapeutic dose and dosage titration is often not necessary. SSRIs have a relatively flat dose–response curve, meaning that increasing the dose beyond the recommended range is unlikely to increase efficacy for most patients. High doses, however, can be necessary for the treatment of obsessive compulsive disorder.

SNRIs have more of a linear dose response than SSRIs, and titration upwards can usually be expected to increase the response rate. Venlafaxine exhibits mostly serotonergic activity at low to moderate doses and only has significant noradrenergic activity in high doses, so it is only at high doses that it acts as an SNRI.

To lessen initial side effects and improve tolerance, it may be helpful to start any antidepressant with a low dose and then increase the dose gradually. For elderly patients, initial doses should be low and care should be taken to avoid excessively high doses.

Dosing guidelines for the newer reuptake inhibitors are given in Table 2. Once daily dosing is appropriate for most reuptake inhibitors, although dividing the dose sometimes improves tolerance. Morning dosing is suitable for most patients and can prevent excessive night-time stimulation and insomnia, although many patients are comfortable with evening dosing. Reboxetine and the immediate release formulation of venlafaxine are given twice daily.

What needs monitoring?

With all reuptake inhibitors, it is important to monitor symptoms and clinical progress as well as side effects and compliance. In more severe cases, careful monitoring for suicidal thoughts or behaviour is necessary; the first two weeks after starting treatment for depression is the period of

greatest risk for suicide.

In the elderly, monitoring for confusion/delirium and hyponatraemia is prudent.

What are the common side effects?

The common side effects of the SSRIs and SNRIs include nausea, headache, agitation, insomnia, increased sweating and sexual dysfunction (anorgasmia, decreased libido). Less common but important side effects with these inhibitors are bruxism (tooth grinding), myoclonic jerks and subtle cognitive effects such as 'apathy syndrome' and impaired concentration. The NARI reboxetine is associated with anxiety, agitation, insomnia and urinary hesitancy or retention.

The side effects tend to be dose related and often will settle to an acceptable level over one to two weeks; some, however, can be persistent and poorly tolerated. Switching to an alternative drug in the same class may be useful to manage side effects, as not all reuptake inhibitors have the same side effects in a particular individual. Occasionally, patients will have immediate and severe agitation due to excessive serotonin sensitivity, and will be unable to tolerate any serotonergic drug.

Insomnia can be successfully managed with simple sleep hygiene, but the temporary addition of a hypnotic may be necessary. The addition of a sedating antidepressant to treat SSRI-induced insomnia is not appropriate because of the risks of drug interactions and serotonin syndrome (see below).

What are the important interactions and precautions?

Drug interactions

There are important potential drug interactions between SSRIs and other medications because of either the inhibitory effects of SSRIs on liver (cytochrome P450) enzymes or the risk of the serotonin syndrome. Prescribers need to be familiar with the more important and clinically relevant of these. For example, SSRIs will inhibit the metabolism of TCAs, leading to increased serum levels and potential tricyclic toxicity.

SSRIs should not be prescribed concurrently with tricyclics, MAOIs or other serotonergic compounds such as SNRIs, mirtazapine, clomipramine, hypericum (St John's wort) and tramadol because of the risk of serotonin syndrome. (The serotonin syndrome is characterised by changes in mental status and motor and autonomic function. It most commonly occurs as the result of two or more drugs that enhance serotonergic neurotransmission by different mechanisms being administered in combination or taken in overdose, although it may rarely occur following overdose of a single agent.)

Table 2. The newer reuptake inhibitors: dosing guidelines

Drug	Initial dose	Recommended dose range	Comment
SSRIs			
Citalopram	20 mg once daily	20 to 60 mg/day	–
Escitalopram	10 mg once daily	10 to 20 mg/day	–
Fluoxetine	20 mg once daily (morning)	20 to 60 mg/day (in two divided doses, morning and noon, if >20 mg/day)	Use up to 80 mg for obsessive compulsive disorder
Fluvoxamine	50 mg once daily (evening)	50 to 300 mg/day (in two or three divided doses if >150 mg/day)	–
Paroxetine	20 mg once daily	20 to 60 mg/day	Use upper dose range for anxiety disorders
Sertraline	50 mg once daily	50 to 200 mg/day	–
SNRI			
Venlafaxine	Immediate release formulation, 37.5 mg twice daily; extended release formulation, 75 mg once daily	Immediate release formulation, 75 to 375 mg/day; extended release formulation, 75 to 225 mg/day	–
NARI			
Reboxetine	4 mg twice daily	8 to 10 mg/day	Halve starting dose and dose range in the elderly and in patients with renal and/or hepatic impairment

When changing from one antidepressant to another it is important to observe the recommended washout period to avoid drug interactions.

Precautions

A withdrawal syndrome can occur with the abrupt cessation of any antidepressant and a tapered withdrawal is always necessary. This is particularly important for the serotonergic antidepressants (SSRIs, SNRIs and mirtazapine). Paroxetine and venlafaxine have been associated with particularly prominent discontinuation symptoms and the tapered withdrawal may need to extend over several weeks to minimise discomfort. Common withdrawal symptoms include dizziness, a light-headed feeling, irritability, general malaise and insomnia.

Recently, concerns have been raised about the possible connection between certain SSRIs and the development of suicidal thoughts and behaviour, particularly in adolescents. While further research is needed, there is sufficient concern to recommend careful monitoring for the emergence or worsening of suicidal thoughts during the initial two to three weeks after commencing any antidepressant.

Conclusion

Antidepressants are believed to exert their therapeutic effect by increasing the synaptic concentration of neurotransmitters, principally noradrenaline and serotonin. Reuptake inhibition is one mechanism by which this can be achieved. The newer reuptake inhibitors, because of their greater selectivity, have significant advantages in safety and side effects compared with the original reuptake inhibitors, the tricyclics. The successful treatment of the more severe forms of depression will usually involve antidepressant medication. An understanding of the mechanisms of action of the various antidepressants will assist the clinician in appropriate drug selection for the individual patient. MT

Reference

1. MIMS Australia. Issue No. 1 2006 (February/March). Sydney: CMPMedica Australia.

DECLARATION OF INTEREST: Dr Lyndon serves on advisory boards for Eli Lilly, Lundbeck and Synofi-Synthelabo and is involved in industry sponsored clinical trials for AstraZeneca and GlaxoSmithKline. He frequently delivers industry sponsored lectures and educational symposia and has been sponsored by various pharmaceutical companies to attend overseas meetings. He is a member of the organising committees for several annual psychiatric conferences sponsored by various pharmaceutical companies.