

New antidepressants

A number of new antidepressants have recently become available, and some fit the profile described above. They were designed to possess those properties of the TCAs that are thought to be responsible for their antidepressant action without the properties responsible for the TCAs' cardiovascular side-effects and unwanted effects related to their blockade of muscarinic and histaminergic receptors. The result was 'cleaner' drugs such as venlafaxine (Efexor), which blocks the reuptake of both NA and 5HT, and reboxetine (Edronax), which blocks the reuptake of NA⁴.

It is less clear, however, that it is necessary to block the re-uptake of noradrenaline and/or serotonin in order to produce an antidepressant effect; some new agents,

Mirtazapine (Zispin), one of the latest compounds to become available in the UK, has a novel mechanism of action that may help in the elucidation of this question⁵. Although mirtazapine primarily increases the availability of NA through blockade of the α_2 adrenergic autoreceptors of the cell bodies in the locus coeruleus, it also by the same mechanism increases the release of 5HT from the cell bodies of raphe nuclei. It seems therefore that there is a 'cross-talk' between the noradrenergic and serotonergic systems of the brain and, although more complicated than initially thought, the monoamine hypothesis still appears to be the most plausible explanation for the mode of action of antidepressants.

Depression in the elderly

What are the implications for clinicians managing older people with depression? The clinical presentation of depression in the elderly varies considerably. It is sometimes difficult to distinguish between concurrent medical illnesses like chronic pain or cardiovascular disease, neuropsychiatric conditions such as dementia, normal life stresses associated with later life such as bereavement, retirement or lack of intellectual stimulation, and the effects of ongoing pharmacological treatment like antihypertensives or steroids. In addition, these conditions often co-exist with depression⁶.

Then, once a diagnosis of depression has been established, the prescriber is faced with a number of pertinent questions regarding the choice of the most appropriate drug. For example, what are the age-related differences in the pharmacokinetics of the various drugs? What is known about their safety, tolerability and efficacy?⁷

After the age of 65, absorption, transport, metabolism, distribution and excretion of drugs undergo various changes which are not homogeneous and should be seen as tendencies rather than absolute laws⁸. For example, the rate of metabolism in the liver can be influenced by changes in the hepatic blood flow, microsomal enzyme activity, hepatic illness or concurrent use of other pharmacological agents. The volume of distribution in the body also increases with age and the half-life of drugs is extended. Differences in sensitivity to drugs between individuals can also be explained by varying changes in the structure of brain, such as neuronal death or alterations in the enzyme activity of membranes. The clinician should therefore not be dogmatic when prescribing to an elderly depressed patient but should be alert to individual patient differences.

Table 1: Mode of action of newer antidepressants

Name (brand)	Type	Mode of action
Fluvoxamine (Faverin)	SSRI	Inhibit re-uptake of serotonin
Fluoxetine (Prozac)		
Sertraline (Lustral)		
Paroxetine (Seroxat)		
Citalopram (Cipramil)		
Venlafaxine (Efexor)	SNRI	Inhibits re-uptake of noradrenaline and serotonin
Reboxetine (Edronax)	NARI	Inhibits re-uptake of noradrenaline
Nefazodone (Dutonin)	SARI	Blocks 5HT-2a post-synaptic receptors Inhibits re-uptake of serotonin (moderately)
Mirtazapine (Zispin)	NaSSA	Blocks α_2 adrenergic auto- and hetero-receptors Enhances release of noradrenaline and serotonin

SSRI = selective serotonin re-uptake inhibitor; SNRI = serotonin & noradrenaline re-uptake inhibitor; NARI = noradrenaline re-uptake inhibitor; SARI = serotonin antagonist and reuptake inhibitor; NaSSA = noradrenergic & specific serotonergic antidepressant

although effective in the treatment of depression, act predominantly through other mechanisms. Nefazodone (Dutonin) is a moderate SSRI and it is thought to exercise its effect mainly through blockade of the postsynaptic 5HT-2a receptors⁹, which may lead to increased 5HT-1a function as well as promoting a good sleep and anxiety profile.