The new generation of antidepressants

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A major goal of antidepressant development is to improve on preceding drug classes with agents with better efficacy, tolerability and with more rapid onset of action. This article describes the new generation of antidepressants which have been recently introduced and also briefly describes possible future antidepressants which are currently being researched.

The total morbidity associated with depressive illness is second only to that of heart disease in developed countries (Murray and Lopez, 1997), and the financial consequences are massive both in terms of treatment and socioeconomic costs. Antidepressant drugs should be thought of as one of a range of resources to be used to obtain the best outcome for patients.

Major depression is one of the commonest illnesses affecting people in the UK, with a weekly prevalence of 2.3% (Jenkins et al, 1997). Mild depressive states are more common, with a UK weekly prevalence of 7.7% (Jenkins et al, 1997). Dysthymia has been reported to have a prevalence of 2.5% (Kessler et al, 1994). Depressive states frequently co-exist with physical illness (Wells et al, 1988) and other psychiatric disorders (Weissman et al, 1996). Treatment of depression can be extremely effective even in the context of psychosocial stressors.

TREATMENT

Antidepressants are effective in all phases of treatment of major depression of moderate and greater severity, including depression associated with physical illness. They have similar efficacy for the majority of patients with major depression.

Systematic reviews and meta-analysis suggest that the commonly available antidepressants have comparable efficacy in the majority of patients seen in primary care or outpatient psychiatric settings (Song et al, 1993; Anderson, 1997; Geddes et al, 1999).

Most antidepressant medications increase the activity of the serotonergic or the noradrenergic systems in the brain. They also have effects on other transmitter systems.

It is believed that antidepressant agents have a time lag of 2 weeks before they have any effect which is greater than placebo. Various pharmacological mechanisms have been suggested which may contribute to this delay in onset of antidepressant efficacy. Beta-adrenoceptor downregulation occurs in most cases after 2–4 weeks; this period coincides with the observed onset of action of antidepressant treatments. It has been suggested that this downregulation may be accelerated by a simultaneous action on both serotonergic and noradrenergic systems (Baron et al, 1988). A second suggested mechanism is autoinhibition by presynaptic 5-HT1A autoreceptors which only downregulate after chronic treatment with serotonergic agents (Blier et al, 1988).

Early antidepressant medications, e.g. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), are effective because they enhance either noradrenergic or serotonergic mechanisms. Unfortunately, they also block cholinergic, histaminergic and alpha-1-adrenergic receptor sites, interact with a number of other medications and bring about undesirable side-effects.

In the past decade, several chemically unrelated agents have been developed and introduced to supplement the early antidepressants. These include selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline re-uptake inhibitors (SNRIs), noradrenaline re-uptake inhibitors (NARIs), noradrenergic and specific serotonergic antidepressants (NASSAs), and selective and reversible monoamine oxidase inhibitors (RIMAs).

Strategies to find drugs that are as effective as the TCAs, but have better safety and tolerability profile, resulted in the development of these newer compounds. Most current antidepressants are monoamine based, and modulating monoamine activity as a therapeutic strategy continues to dominate antidepressant research. However, these newer antidepressants are far from ideal, resulting in undesirable side effects and requiring 2–6 weeks of treatment to produce a therapeutic effect.

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NEW ANTIDEPRESSANTS LICENSED IN THE UK

Selective serotonin re-uptake inhibitors

The relatively new SSRIs have become popular because of their better tolerance and side-effect profile. In inpatient studies, meta-analysis showed a significantly higher discontinuation rate as a result of adverse effects for TCAs compared with SSRIs. Drop-out rates as a result of treatment failure were equivalent (Anderson, 1998). In outpatient studies, discontinuation because of side effects is modestly but significantly more common with TCAs than SSRIs (Martin et al, 1997).

Indications: SSRIs are indicated for the treatment of depression, obsessive compulsive disorder (OCD) and panic disorder as well as many other disorders. The group has steadily expanded and includes fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram. SSRIs share almost no molecular features. Variations within the SSRI drug class, such as the selectivity ratios or serotonin *vs* noradrenaline uptake, elimination half-life, and affinity for 5-HT2 receptor have been identified and may be important determinants of efficacy, side effects and clinical use.

Pharmacokinetics: SSRIs' diverse chemical structures possess significantly different pharmacokinetic profiles (*Table 1*).

All SSRIs are metabolized in the liver by the cytochrome P45 (CYP) enzymes, specifically CYP 2D6. The most clinically significant drug–drug interaction results from inhibition of CYP 2D6, and these drugs may raise serum concentrations of a number of other drugs that are also metabolized by CYP 2D6, such as TCAs.

Fluoxetine: Fluoxetine is unique because it has a very long half-life. It is advisable to allow at least 5 weeks from the time of discontinuation of fluoxetine before starting treatment with a MAOI. Fluoxetine is licensed as an antibulimic agent as well as for the treatment of OCD. The antidepressant dose is 20 mg/day with no increase in efficacy at high doses. Patients with bulimia nervosa and OCD respond better to higher doses up to 60 mg/day.

Because of its long half-life, a delayed-release enteric coated formulation containing fluoxetine 90 mg has been developed for once-weekly oral administration. The efficacy and tolerability profile is similar to that of the daily formulation (Wagstaff and Goa, 2001), but it is not yet licensed for use in the UK.

Paroxetine: Paroxetine has early anxiolytic properties in addition to its antidepressant actions and is useful for patients with depression accompanied by anxiety. It is also licensed for the treatment of OCD, panic disorder, social phobia and post-traumatic stress disorder. Paroxetine has no active metabolite and a short half-life of about 21 hours. Withdrawal symptoms lasting up to 3 weeks have been described and it is advisable to taper off the dose slowly when stopping treatment. The maximum dose recommended for the treatment of depression is 50 mg/day. There have been infrequent reports of extrapyramidal side effects associated with paroxetine, mostly with patients who have underlying movement disorder. Dystonic movement of the face, tongue and eyes has also been reported.

Fluvoxamine: Fluvoxamine has a relatively higher incidence of nausea than other SSRIs but is more sedative. It is licensed for the treatment of depressive illness and OCD. The recommended daily dose is up to 300 mg/day.

Sertraline: Sertraline is licensed for the treatment of depressive illness and OCD. It is an effective antidepressant without sedative, anticholinergic, antidopaminergic or cardiotoxic effects. It has been reported to induce mania. The recommended daily dose is up to 200 mg/day.

Citalopram: Citalopram is not a potent inhibitor of the hepatic enzyme system cytochrome P45 and it is therefore less likely to cause clinically significant elevation in plasma levels of co-administered drugs, such as anticonvulsants and warfarin. The recommended dose is up to 60 mg/day. It has been said that citalopram may be the only true SSRI (Stahl, 1996). It does not enhance the sedation caused by alcohol and studies show that it decreases the number of drinking days and total amount of alcohol drinking (Naranjo, 1987).

Escitalopram: Escitalopram is a more highly selective version of citalopram, containing only the s-enatiomer rather than the racemic mixture of the active molecule. Escitalopram has been developed as a formulation for the treatment of major depressive episodes and panic disorder with or without agoraphobia. The recommended daily dose is 20 mg/day.

TABLE 1.
Pharmacokinetic profiles of selective serotonin-reuptake inhibitors

Drug	Time to peak plasma concentration	Half-life	Half-life of metabolite	Time to steady state
Fluoxetine	6–8 hours	4–6 days	4–16 days	28–35 days
Fluvoxamine	3–8 hours	15 hours	–	5–7 days
Paroxetine	5–6 hours	21 hours	–	5–10 days
Sertraline	4.5–8.5 hours	26 hours	62–104 hours	5–7 days
Citalopram	4 hours	35 hours	3 hours	7 days

Reversible inhibitors of monoamines

The new generation of monoamine oxidase inhibitors such as moclobemide are selective and reversible and they allow ingested tyramine to be metabolized. They, therefore, have fewer adverse effects and are better tolerated. Moclobemide has few significant drug interactions, although with the SSRIs there is a risk of serotonin syndrome and so this combination is best avoided. Moclobemide does not precipitate seizures or modify psychomotor performance and is therefore safe to use with epileptic patients (Stimemel and Dophliede, 1996). The recommended daily dose is a maximum of 600 mg and it is licensed for depressive illness and social phobia.

Serotonin and noradrenaline re-uptake inhibitors

Venlafaxine is the first antidepressant in this class; milnacipran is another antidepressant in this class which is waiting to be licensed in the UK. An immediate release form of venlafaxine has been established to be as effective and safe as the normal preparation. It is licensed for the treatment of depressive illness and generalized anxiety disorder. Studies (Clerc et al, 1994) suggest that venlafaxine is more effective than fluoxetine in patients with major depression with melancholia. Some reports (Entsuah et al, 1996), which examined relapse rate during long-term treatment, showed that cumulative relapse rate at both 6 and 12 months was significantly lower for venlafaxine-treated *vs* placebo-treated depressed patients in the pooled analysis, but more research is required to support these claims. This raises an interesting possibility that drugs inhibiting both serotonin and noradrenaline reuptake may have superior efficacy to single reuptake inhibitors.

The maximum recommended daily dose is 375 mg in divided doses; blood pressure monitoring is advisable with higher doses.

Noradrenergic and specific serotonergic antidepressants

Mirtazapine: This enhances noradrenergic transmission by acting as an antagonist and blocking alpha-2-autoreceptors, with the net effect of increasing synaptic levels of noradrenaline and serotonin. It specifically enhances 5-HT1 neurotransmission and blocks 5-HT2A and 5-HT3 receptors, therefore, increasing synaptic serotonin concentration. It also increases 5-HT neuronal firing by acting on alpha-1-adrenergic receptors on serotonergic neuronal cell bodies.

It has a relatively high affinity for H1 receptors leading to weight gain and sedative effects. It has a weak affinity for muscarinic receptors.

The recommended daily dose is up to 45 mg/day before sleep. Cautions include increased risk of neutropenia and agranulocytosis, increased risk of side effects in those with cardiac disease or hepatorenal insufficiency, and potentiation of other sedatives.

Nefazodone: In addition to selective serotonin reuptake inhibition, nefazodone also antagonizes 5-HT2A and 5-HT2C receptors. It also inhibits noradrenaline uptake. There is no evidence of sexual dysfunction. It promotes slow wave sleep. It is usually administered twice a day in a dose of 300–500 mg/day.

Nefazodone causes nausea, headache and drowsiness as often as other SSRIs. One Spanish study quantified the risk of hepatic toxicity associated with different antidepressants and concluded that the risk ranged from 1.28 cases per 100 000 patient-years for sertraline to 28.96 cases per 100 000 patient-years with nefazodone (Garcia-Pondo et al, 2002). A recent study (Hicks et al, 2002) has found that nefazadone improves sleep in early treatment compared with paroxetine in patients with moderate to severe depression. These effects are seen within the first 2 weeks of treatment and diminish thereafter.

Noradrenaline re-uptake inhibitors

Reboxetine selectively inhibits noradrenaline re-uptake without inhibiting serotonin or dopamine re-uptake. It is effective in treating patients with mild to severe depression and it is better than placebo in maintaining remission in depressed patients. The daily recommended dose is up to 12 mg in divided doses. Clearance of reboxetine and its metabolites is reduced in patients with renal or hepatic insufficiency requiring 50% dose reduction. Common side effects include constipation, insomnia and impotence. Although it has been associated with an increasing heart rate, the clinical significance of these findings is unknown, and reboxetine is not associated with any electrocardiographic abnormalities.

St John's Wort (*Hypericum perforatum*) is a flowering plant that grows as a common weed in many countries. Its antidepressant properties relate to its ability to inhibit re-uptake of numerous neurotransmitters, including serotonin, noradrenaline and dopamine. There is a moderate amount of evidence to suggest that St John's Wort is better than placebo in the short-term management of mild to moderate depressive illness, but there is increasing concern over reports of drug interactions (Kelly, 2001).

The cost of a month's treatment with the cheapest SSRIs is 2.5 times that with TCAs. However, it has been argued successfully that when both direct and indirect costs are taken into account, the overall expenditure is not higher when using SSRIs compared with TCAs (Boyer and Feigner, 1993).

SAFETY IN OVERDOSES AND DISCONTINUATION SYNDROME

The major advantage of the new generation of antidepressants over the old antidepressants is safety in overdoses, particularly with respect to cardiovascular effects. Discontinuation symptoms have been reported after sudden cessation of SSRIs and other antidepressants. These symptoms usually last about 1–2 weeks, but some patients experience difficulties for longer periods. It is therefore wise to use slow withdrawal after long-term administration of any antidepressant drugs if clinically possible (Singh, 2003).

CONCLUSIONS

Possible future antidepressants are being researched. Neuropeptides, e.g. thyrotropin-releasing hormone, or antagonists of neuropeptide receptors, e.g. the tachykinin NK (1) receptor, have undergone clinical tests. Also, the results of novel developmental approaches have suggested that modulation of N-methyl-D-aspartate (NMDA), neuropeptide (substance P and corticotrophin-releasing factor) receptors and the intracellular messenger system may provide a new set of potential therapeutic targets. The progress made in genome research would enable success in pharmacogenomic approaches. This would be possible through the use of high-density single nucleotide polymorphism (SNP) maps to correlate a patient's genetic information with his or her response to a certain drug. Current and future drugs will target proteins, and only a minor fraction of SNPs produce protein alterations that ultimately account for the clinical phenotype (Holsboer, 2001). HM

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KEY POINTS

- The new generation of antidepressants has no demonstrable superiority over the old tricyclic antidepressants.
- There is some promise of faster action with some newer antidepressants but this needs confirmation.
- A different set of side effects is associated with the new generation of antidepressants, which appear to be better tolerated by patients.
- Abrupt withdrawal of antidepressant can provoke discontinuation symptoms.
- Antidepressant research faces exciting new opportunities in the post-genomic era.