Advances in Psychiatric Treatment (1997), vol. 3, pp. 46–51

Development of new antidepressants

Eleni Palazidou

The development of the first effective antidepressants in the late 1950s marked a turning point in the treatment of depressive illness. In 1957 the monoamine oxidase inhibitor (MAOI) iproniazid was discovered by chance, while searching for new antituberculous drugs. One year later the tricyclic antidepressant (TCA) imipramine was introduced, having been developed originally as an antipsychotic. A number of other drugs were subsequently added to these two groups of antidepressants, which dominated the field for the next three decades.

In the 1970s and 1980s some new antidepressant drugs such as mianserin, zimeldine, nomifensine, maprotiline and trazodone were introduced. However, it was the antidepressants developed in the late 1980s and the 1990s, more specifically the selective serotonin reuptake inhibitors (SSRIs), which seriously threatened the position of the TCAs as the first-choice drugs in the treatment of depression.

Neurotransmitter function in depression

The first-generation antidepressants served not only as effective treatments for depression, but also as investigative tools in the study of the biochemical basis of depression. A considerable body of knowledge has been accumulated over the years from both animal and clinical research, which used increasingly sophisticated methods such as receptor ligand technology and neuroimaging.

The introduction of receptor ligand technology in the 1970s allowed the examination of neurotransmitter receptor status. Significant changes in the density of the receptors and in second messenger production were demonstrated in animal experiments on long-term antidepressant drug treatment. The early experiments, limited to receptors within the noradrenergic system, led to the introduction of the 'β receptor down-regulation hypothesis' proposed by Sulser (1978), which challenged the hitherto universally accepted 'monoamine hypothesis' of depression. The latter assumed a reduction in brain noradrenaline and serotonin (5-hydroxytryptamine; 5-HT) concentrations as the cause of depression, therefore requiring an increase in the availability of these monoamines at the synaptic level to correct the deficit. The β receptor down-regulation hypothesis proposed that a pathological 'supersensitivity' of the brain β-adrenergic receptors was responsible for depressed mood state, and that this abnormality is corrected by antidepressant drug treatment, which leads to down-regulation (reduction in density) of β receptors.

Subsequent research findings, however, show that the picture is much more complex. Changes in the density and functional responsiveness of adrenergic receptors (the post-synaptic α_1 and pre-synaptic α_2 autoreceptors) as well as changes in the sensitivity of receptors within the serotoninergic (5-HT_2 and 5-HT_{1A} receptor subtypes) and other central neurotransmitter systems have been demonstrated after chronic (≥2 weeks) treatment with antidepressant drugs (Leonard, 1993), irrespective of their presumed pharmacological actions. The antidepressant drugs' ability to increase the availability of the neurotransmitter (noradrenaline or 5-HT) in the synaptic cleft, by means of either inhibition of reuptake into the neuronal terminal (TCAs and SSRIs) or prevention of its breakdown (MAOIs), is only the beginning of a cascade of events involving changes in the sensitivity of receptors at somatodendritic sites (5-HT_{1A} receptors) and at the pre- and post-synaptic levels, as well as changes in neuronal signal transduction beyond the receptor.

It is significant that the central neurotransmitter systems are functionally interdependent. The receptor changes described above are not limited to the neurotransmitter system targeted by the particular antidepressant (the serotoninergic system for SSRIs

Eleni Palazidou, MRCPsych, is Consultant Psychiatrist at the Royal London Hospital (St Clement's), 2A Bow Road, London E3 4LL, and Honorary Senior Lecturer at the Institute of Psychiatry, MRC Psychopharmacology Unit. She is particularly interested in the treatment of affective disorders.

or both the serotoninergic and adrenergic systems for TCAs and MAOIs). The close anatomical and physiological relationship between the neurotransmitter systems militates against the notion of the presence of two distinct biochemical depressive subtypes. Clinical studies provide further evidence against the view that there may be separate noradrenergic and serotoninergic depressive groups, with preferential response to adrenergic or serotoninergic agents, respectively (Montgomery, 1982; Emrich *et al*, 1987). Nevertheless, there are subgroups of patients with specific clinical features who appear to respond better to particular antidepressant drug groups.

Development of new drugs

The major progress made in our understanding of the psychopharmacology of antidepressant drugs and the function of central neurotransmitter systems in relation to mood state, guided the production of new antidepressants. The first antidepressants were discovered by serendipity, but subsequent antidepressant drug development has been to a great extent by design, with the noradrenergic and/or serotoninergic neurotransmitter systems as the primary targets.

In the 1970s and early 1980s the focus was on the noradrenergic neurotransmitter system, partly because of the greater understanding of its pharmacology, particularly in relation to receptor function and the impact of the β receptor down-regulation hypothesis of depression. The late 1980s and the 1990s saw a rapid growth in the pharmacology of the serotoninergic system. Several serotonin receptors were identified and the production of selective receptor agonists/antagonists allowed examination of these receptors. The introduction of the SSRIs was a turning point in the pharmacotherapy of depression, and the serotoninergic neurotransmitter system became the focus of study. More recently the SSRIs have been joined by other types of antidepressants such as the reversible monoamine oxidase inhibitors (RIMAs), the serotonin/noradrenaline reuptake inhibitor (SNRI) venlafaxine, and other novel drugs. The new-generation antidepressants differ from the older drugs in that they have a narrower pharmacological profile, increasing noradrenergic or serotoninergic activity, or both (Table 1), without significant direct effects on other central neurotransmitter systems. The main aims in the development of the new antidepressants (which, so far, have only partly been achieved) were:

(1) greater efficacy;
(2) absence of side-effects;
(3) lack of toxicity in overdose; and
(4) earlier onset of action.

Efficacy

None of the antidepressants presently available has shown significantly superior efficacy in the treatment of depression in randomised controlled trials or meta-analyses (see Anderson, 1997, this issue), although the possible superior efficacy in suicidality and the safety in overdose offer an advantage to the SSRIs over TCAs in patients who present suicidal risk. In general, between 50 and 70% of patients respond to the first antidepressant, irrespective of its pharmacological profile.

Table 1. Pharmacological actions of antidepressants

Antidepressant	Presumed mechanism of action	Undesirable pharmacological actions
TCAs	Noradrenaline and 5-HT reuptake inhibition	Anticholinergic; antihistaminic; α_1-adrenoceptor antagonism; direct membrane stabilisation
SSRIs	5-HT reuptake inhibition	
MAOIs	Irreversible inhibition of MAO-A and MAO-B	Interaction with tyramine and sympathomimetics; irreversible and non-selective MAO inhibition
RIMA: moclobemide (Manerix)	Reversible inhibition of MAO-A	
SNRI: venlafaxine (Effexor)	5-HT and noradrenaline reuptake inhibition	
Nefazodone (Dutonin)	5-HT reuptake inhibition and 5-HT_2 receptor antagonism	

5-HT, serotonin; MAO, monoamine oxidase; SSRIs – fluvoxamine (Faverin), fluoxetine (Prozac), paroxetine (Seroxat), sertraline (Lustral), citalopram (Cipromin); MAOIs – phenelzine (Nardil), isocarboxazid (Marplan), tranylcypromine (Parstelin); RIMA, reversible MAO inhibitor; SNRI, 5-HT/noradrenaline reuptake inhibitor.

https://doi.org/10.1192/apt.3.1.46 Published online by Cambridge University Press

Side-effects and safety in overdose

The older antidepressants are associated with a range of side-effects, which may affect compliance and render them potentially dangerous. The TCAs have a spectrum of pharmacological actions, many of which are seen as non-therapeutic and are responsible for their fairly extensive side-effect profile (Box 1).

Because of their selectivity for the serotoninergic system, the SSRIs are largely devoid of other clinically significant pharmacological effects. However, they do have side-effects due to the effects of the SSRIs on the serotoninergic system and particular 5-HT receptors (Box 2); for example, nausea and vomiting are probably due to enhanced 5-HT_3 receptor activity. Meta-analyses comparing the tolerability of the side-effects of the TCAs with those of the SSRIs (see Anderson, 1997), and the adverse effects of newer and older antidepressants, and their interactions (Henry, 1997) are discussed elsewhere in this issue.

Costs

The cost of a month's treatment with the cheapest SSRIs (fluvoxamine, fluoxetine and paroxetine) is two and a half times that with the TCA dothiepin in therapeutic dose. It has been argued, however, successfully according to some studies, that when both direct and indirect costs are taken into account the overall expenditure is not higher when using SSRIs compared with TCAs (Boyer & Feigner, 1993). This issue is still highly contentious.

Box 1. Side-effect profile of TCAs

Anticholinergic
Dry mouth, blurred vision, urinary hesitancy, constipation, memory impairment, aggravation of narrow angle glaucoma

Antihistaminic
Sedation

α_1-adrenoceptor antagonism
Orthostatic hypotension

Cardiovascular effects
Sinus tachycardia, arrhythmias, conduction delays, sudden death

Other
Weight gain, sexual dysfunction, impaired cognitive and psychomotor processes skills, convulsions

Box 2. Side-effect profile of SSRIs

Nausea/vomiting
Abdominal pain
Dry mouth
Constipation/diarrhoea
Headache
Asthenia
Dizziness
Insomnia/somnolence
Sweating
Anorexia
Weight loss
Nervousness/agitation
Tremor
Convulsions
Dystonic reactions (paroxetine)
Sexual dysfunction (reduced libido, anorgasmia)

Earlier onset of action

Antidepressant drugs, in general, have a slow onset of action with noticeable clinical improvement only after two to four weeks of ongoing treatment. The reasons for this are not clear, as monoamine reuptake inhibition and monoamine oxidase inhibition take place within hours. It is argued that subsequent events in the complex process of neurotransmission are essential in effecting clinical improvement.

Several antidepressants have claimed an earlier onset of action but none has, as yet, demonstrated this incontrovertibly. It was hoped that drugs with higher selectivity acting directly on relevant receptors could achieve faster antidepressant effects. Drugs with adrenergic receptor selectivity such as the β agonists salbutamol and clenbuterol, and later the 5-HT_{1A} receptor agonists busiprone, gepirone and ipsapirone, were developed but they failed to compete effectively with established antidepressants in terms of clinical efficacy. The 5-HT_2 receptor agonist ritanserin, despite some early promise as an effective anti-dysthymia agent, had a similar fate.

Although desirable in that it reduces the possibility of side-effects, receptor selectivity by itself may also limit the antidepressant efficacy of the drug. Receptor selectivity may be more useful if combined with neurotransmitter reuptake inhibition, enhancing its antidepressant effects and at the same time reducing some undesirable side-effects. An example of such a drug available in the UK at present is nefazodone.

Amoxapine, which is structurally similar to maprotiline (a tricyclic with a fourth ring as a side

https://doi.org/10.1192/apt.3.1.46 Published online by Cambridge University Press

structure), and the SSRI paroxetine have been claimed to have faster action. Venlafaxine, one of the latest antidepressants, has shown some promise as having earlier onset of action but this requires further proof. Interestingly this drug down-regulates β receptors after a single dose exposure unlike other antidepressants which require continued exposure for >10 days for this to occur.

Overview of antidepressants currently licensed in the UK

TCAs

The antidepressant properties of the TCAs are dependent on their ability to inhibit the reuptake of noradrenaline and serotonin into the neuronal terminal and enhance adrenergic transmission. The rest of their pharmacological actions are not only redundant but also responsible for a range of side-effects (Box 1). In the 1960s and 1970s modifications were made to the chemical structure of existing drugs, aiming to reduce these undesirable actions. The secondary amines, desipramine and nortriptyline, were produced from the tertiary amines, imipramine and amitriptyline, respectively. These drugs had relatively fewer side-effects, being less anticholinergic and less sedative, while retaining similar antidepressant efficacy to that of the parent drug. Nevertheless, some of these side-effects have been used to clinical advantage; for example, the sedative effects of the tertiary amines in agitated, insomniac patients.

Dose range of the TCAs

The established therapeutic dose is 125–150 mg/day. There is no good evidence that doses of 75 mg or less have any acute antidepressant clinical benefit. Although antidepressant drug monitoring is available and tentative therapeutic concentrations suggested, the benefit of these levels is probably more relevant in preventing toxicity and checking on compliance rather than for therapeutic monitoring.

TCAs have a relatively narrow therapeutic index and cardiotoxicity can occur at doses of only about 10 times the therapeutic dose. Furthermore, in patients who are slow metabolisers toxicity may occur even with therapeutic doses. It has been argued for these reasons that therapeutic monitoring of TCA blood levels should be more widely used (Preskorn & Jerkovich, 1990; Preskorn, 1993).

In addition to the TCAs already mentioned, there are others which merit mention:

Nortriptyline is the only TCA shown to have a therapeutic window (50–170 mg/ml); doses achieving plasma levels outside this range are less effective.

Clomipramine is a potent and preferentially 5-HT reuptake inhibitor and has been successfully used to treat obsessive–compulsive disorder (OCD), especially prior to the introduction of the SSRIs.

Maprotiline is a more selective noradrenaline reuptake inhibitor than the other TCAs. Unfortunately, it is associated with a higher incidence of seizures in overdose and also in standard doses, and this has limited its clinical use.

Lofepramine is a major advance in the development of TCAs as it has much fewer side-effects. It has minimal sedative and psychomotor side-effects and, most importantly, it appears to be safe in overdose.

SSRIs

In general, the SSRIs have a wider spectrum of clinical effects influencing, in addition to the depressed mood, functions such as eating behaviour, anxiety, impulsive behaviour, aggression and OCD, and some are marketed for some of these indications.

Certain pharmacokinetic/pharmacodynamic interactions need to be considered before using the SSRIs in combination with other psychotropic drugs. Caution is required when using lithium augmentation in resistant depression and it is advisable slowly to increase the dose of lithium, monitoring carefully its blood levels, as fluoxetine may affect lithium plasma concentrations. However, the lithium plus fluoxetine combination has been widely used, quite successfully and without significant problems with lithium concentrations. Particular caution is required when SSRIs are used in combination with TCAs, as SSRIs impair the metabolism of TCAs by interfering with the cytochrome p450 2D6 (Crewe *et al*, 1992). It is advisable to reduce the dose of the TCA, especially in the elderly, and plasma drug level monitoring may be needed if higher doses are required. Although MAOIs can be used safely, with caution, in combination with the TCAs in the treatment of resistant depression, the combination of the SSRIs with the MAOIs can potentially have very serious consequences and should not be used in clinical practice. The potent 5-HT reuptake inhibition (SSRIs) coupled with the prevention of 5-HT breakdown (MAOIs) can cause undesirably high serotoninergic activity and lead to the serotonin syndrome, which is potentially fatal (see Henry, 1997, this issue).

Unlike the TCAs, the SSRIs have very dissimilar chemical structures. They are all effective antidepressants but differ in their pharmacokinetics, dose range, side-effect profile, etc.

https://doi.org/10.1192/apt.3.1.46 Published online by Cambridge University Press

Fluvoxamine has a relatively higher incidence of nausea than other SSRIs but is more sedative and the manufacturer promotes its sleep-improving properties.

Fluoxetine is unique among the SSRIs in that it has an active metabolite, norfluoxetine, which has a very long half-life. This can be an advantage (as forgetting to take the occasional dose will not significantly affect the drug's plasma concentration) and a drawback (as it delays beginning certain drug treatments that have dangerous interactions with fluoxetine, for several weeks). It is advisable to allow at least five weeks from the time of discontinuation of fluoxetine prior to starting treatment with an MAOI. Some patients experience a degree of agitation in the early stages of treatment, although in the long term it has anxiolytic properties. Fluoxetine is licensed as an antibulimic agent as well as for treatment of OCD. The antidepressant dose is 20 mg/day, with no increase in efficacy at higher doses. Patients with OCD and bulimia respond better to higher doses (40–60 mg).

Paroxetine has early anxiolytic properties in addition to its antidepressant actions and is useful in patients with depression accompanied by anxiety. Recently it has been licensed also for the treatment of OCD. Paroxetine has no active metabolites and a short half-life (10–21 hours); withdrawal symptoms lasting up to three weeks have been described and it is advisable to taper off the dose slowly on withdrawal. The effective dose is 20 mg/day, with evidence of increased efficacy up to 40 mg. The maximum dose recommended by the manufacturers for the treatment of depression is 50 mg. There have been infrequent reports of extrapyramidal side-effects associated with paroxetine, mostly in patients with underlying movement disorders. Dystonic movements of face, tongue and eyes have also been reported.

Sertraline and citalopram were introduced more recently and are comparable to the other SSRIs in efficacy.

MAOIs

The major problems encountered with MAOIs (phenelzine, isocarboxazid, tranylcypromine) were their potentially dangerous interactions with tyramine-containing foods and with certain drugs (indirectly acting sympathomimetics, some narcotic analgesics, TCAs), due to their lack of selectivity. Irreversible binding to monoamine oxidase means that MAOIs require a washout period (of at least 2 weeks) to permit resynthesis of monoamine oxidase.

RIMAs

The new-generation MAOIs, such as moclobemide, have the advantages that they are selective (MAO-A but not MAO-B inhibitors) and reversible (RIMAs). Selectivity does not affect their antidepressant properties as MAO-A preferentially metabolises noradrenaline and 5-HT, the substrates of antidepressant action, while it significantly reduces the possibility of side-effects. Tyramine is metabolised by both MAO-A and MAO-B, and by inhibiting one form only the potential for the 'cheese reaction' (see Henry, 1997, this issue) is significantly reduced. The reversibility of their action on enzyme inhibition allows the monoamine oxidase to free itself promptly after the treatment is stopped, with no need for the lengthy washout period needed by the old MAOIs. This allows relaxation of dietary restriction and concomitant use of other drugs. The potential for serotonin syndrome, however, is not reduced and concomitant administration with SSRIs should be avoided.

The MAOIs have been advocated for use in depressive states associated with prominent phobic features. Moclobemide appears, according to meta-analyses, to be as effective as a TCA in agitated anxious depression and in endogenous and non-endogenous depression.

SNRIs

Venlafaxine is the only SNRI currently available. It essentially has the pharmacological effects of the TCAs on 5-HT and noradrenaline reuptake but is devoid of actions on other sites responsible for the side-effects of the TCAs. It has some promise as a potentially rapidly acting antidepressant and as an effective treatment for resistant depression, but more research is required to support these claims.

Nefazodone

Nefazodone is a novel antidepressant with a chemical structure related to trazodone and a distinct pharmacological profile. It has dual action on the serotonergic system; it is a relatively weak 5-HT reuptake inhibitor and a potent 5-HT_2 receptor antagonist. This combination enhances 5-HT_{1A}-mediated neurotransmission, an effect which may be beneficial in the treatment of depression.

There have been no reports of priapism, a recognised side-effect of trazodone, in clinical trials with nefazodone. Furthermore, sexual dysfunction was reported much less frequently than with other antidepressants; this might be related to 5-HT_{2A} receptor blockade.

https://doi.org/10.1192/apt.3.1.46 Published online by Cambridge University Press

Conclusions

In summary, the targets set in the production of the new-generation antidepressants have only partially been met:

(1) efficacy – no antidepressant has demonstrable superiority over the old tricyclics;
(2) side-effects – a different set of side-effects are associated with the new-generation antidepressants, which on balance appear to be better tolerated by patients;
(3) safety in overdose – this is the major advantage of the new drugs over the old antidepressants;
(4) earlier onset of action – there is some promise of faster action with some newer antidepressants but this needs confirmation.

References

Anderson, I. (1997) Lessons to be learnt from meta-analyses of newer versus older antidepressants. *Advances in Psychiatric Treatment*, **3**, 57–62.

Boyer, W. F. & Feigner, J. P. (1993) The financial implications of starting treatment with a selective serotonin reuptake inhibitor or tricyclic antidepressant in drug-naive depressed patients. In *Health Economics of Depression* (eds B. Jönsson & J. Rosenbaum), pp. 65–75. Chichester: Wiley.

Crewe, H. K., Lennard, M. S., Tucker, G. T., *et al* (1992) The effect of selective serotonin reuptake inhibitors on cytochrome P4502D6(CYP2D6) activity in human liver microsomes. *British Journal of Clinical Pharmacology*, **34**, 262–265.

Emrich, H. M., Berger, M., Riemann, D., *et al* (1987) Serotonin reuptake inhibition vs. norepinephrine reuptake inhibition: A double-blind differential-therapeutic study with fluvoxamine and oxaprotiline in endogenous and neurotic depressives. *Pharmacopsychiatry*, **20**, 60–63.

Henry, J. A. (1997) Toxicity of newer versus older antidepressants. *Advances in Psychiatric Treatment*, **3**, 40–44.

Leonard, B. E. (1993) Comparative pharmacology of new antidepressants. *Journal of Clinical Psychiatry*, **54** (suppl. 8), 3–15.

Montgomery, S. (1982) The non-selective effects of selective antidepressants. *Advances in Biochemistry and Pharmacology*, **31**, 49–56.

Preskorn, S. H. (1993) Sudden death and tricyclic antidepressants (TCAs): A rare adverse effect linked to high plasma levels. *Nordic Journal of Psychiatry*, **47** (suppl. 30), 49–55.

Preskorn, S. H. & Jerkovich, G. S. (1990) Central nervous system toxicity of tricyclic antidepressants: Phenomenology, course, risk factors and role of therapeutic drug monitoring. *Journal of Clinical Pharmacology*, **10**, 88–95.

Sulser, F., Vetulani, J. & Mobley, P. L. (1978) Mode of action of antidepressant drugs. *Biochemical Pharmacology*, **27**, 257–261.

Multiple choice questions

1. The following statements are true:
   a the SSRIs are more effective than the TCAs in major depression
   b the TCAs are more effective than the SSRIs in major depression
   c the new-generation antidepressants have an earlier onset of action.

2. The following antidepressants are unsafe in overdose:
   a amitriptyline
   b paroxetine
   c dothiepin.

3. The following antidepressant combinations are potentially dangerous and should be avoided:
   a tricyclics and lithium
   b SSRIs and lithium
   c SSRIs and MAOIs.

4. The following statements are true:
   a sexual dysfunction is not a side-effect of the SSRIs
   b sexual dysfunction can occur in treatment with TCAs
   c cognitive and psychomotor processing can be affected by treatment with TCAs.

5. Serotonin syndrome:
   a is a common side-effect of the second-generation antidepressants
   b can occur when MAOIs are combined with SSRIs
   c is potentially fatal.

MCQ answers

1	2	3	4	5
a F	a T	a F	a F	a F
b F	b F	b F	b T	b T
c F	c T	c T	c T	c T

https://doi.org/10.1192/apt.3.1.46 Published online by Cambridge University Press