

# Antidepressants

Jon Nash  
David Nutt

## Abstract

Recent years have seen a large increase in the prescription of antidepressants in the UK. This is a field in which both research and clinical practice are developing rapidly. A new generation of 'designer drugs' has largely replaced the tricyclic antidepressants and monoamine oxidase inhibitors, on grounds of safety and tolerability rather than improved efficacy. Drugs have been developed on the basis of the monoamine theory of depression, although the biological changes that are responsible for the development of depressive symptoms have yet to be clearly established. All of the antidepressants currently available act by enhancing the activity of monoamine neurotransmitters, either by reuptake inhibition, enzyme inhibition or activity at pre- or postsynaptic receptors. This contribution describes the pharmacology of the different classes of antidepressants, puts this in a context of clinical prescribing and current practice guidelines and considers likely future developments in the field.

**Keywords** antidepressant; bupropion; depression; dopamine; MAOI; mirtazapine; monoamine; noradrenaline; serotonin; SNRI; SSRI; TCA

The use of drugs for the treatment of mood disorders has a relatively short history and is still in a phase of rapid development. As is the case in many areas of psychiatry, the process of scientific advancement has followed a haphazard course. Early agents were the product of the serendipitous discovery that treatments for medical disorders also had beneficial effects on mood. Once the pharmacology of these agents had been fully understood, new agents were designed with specific actions on key neurotransmitter systems. These drugs are better tolerated, although not necessarily more effective, than their predecessors.<sup>1,2</sup>

The development of drugs such as the selective serotonin reuptake inhibitors (SSRIs) has coincided with a huge increase

**Jon Nash** MBChB MRCP MRCPsych is a Specialist Registrar in Learning Disability Psychiatry in Weston-super-Mare, UK. He was formerly Lecturer in Psychiatry of Old Age at the University of Bristol and has a research interest in the biology of stress and anxiety disorders. Conflicts of interest: none declared.

**David Nutt** FRCP FRCPsych FMedSci is Professor of Psychopharmacology at the University of Bristol, UK, and Honorary Consultant Psychiatrist, Avon and Wiltshire Partnership Trust. His research interests include drugs used to treat anxiety, depression and addiction, and the insights that the actions of these give on the underlying brain pathologies. Conflicts of interest: none declared.

## What's new?

- Clinical trial evidence for antidepressants has been collated as consensus statements and clinical guidelines
- Evidence is growing that antidepressants with actions on multiple neurotransmitters have a therapeutic advantage
- A new SNRI, duloxetine, has been licensed in the UK
- The NDRI bupropion (already available for smoking cessation) and melatonin agonist agomelatine are likely to be launched in the UK in the near future

in the prescription of antidepressants,<sup>3</sup> partly because of the increased emphasis on the detection and treatment of mood disorders in primary care and partly because of the expanding use of antidepressants for other psychiatric disorders. The most recently marketed antidepressants have actions on multiple neurotransmitters and may have superior efficacy compared with SSRIs in some patient groups. Psychiatrists therefore have a range of prescribing options that can be tailored to the needs of the individual patient. Nevertheless, it should be stressed that the biological changes leading to depressive symptoms are still not fully understood, and all drugs that are currently available mediate their actions via a small family of neurotransmitters, the monoamines.

## Monoamine theory of depression

The monoamine neurotransmitters serotonin (5-HT), noradrenaline and dopamine facilitate transmission in neural pathways that originate in nuclei of the brainstem and have descending projections to the autonomic nervous system and widespread ascending projections to the limbic system and cortex. These pathways control many aspects of behavioural function, including mood and anxiety responses. Early theories implicated a deficiency of monoamines in the biology of depression, as drugs that facilitate monoamine release were found to be antidepressant (e.g. amphetamine), while drugs that interfere with monoamine release cause depressive symptoms (e.g. reserpine).

As more becomes known about the biology of monoamine systems, a complex picture is emerging. Although the predominant mechanism of action of antidepressant drugs is to increase synaptic availability of monoamines, this does not bring about an immediate lifting of mood, and the full onset of antidepressant effects may be delayed by 2–4 weeks. One reason for this is that the activity of homeostatic feedback mechanisms must be overcome before there is a net increase in monoamine activity.<sup>4</sup> This is illustrated by the action of reuptake inhibitors on the serotonergic neurone (Figure 1). The acute elevation of synaptic serotonin stimulates inhibitory presynaptic 5HT<sub>1A</sub> receptors and leads to a reduced firing rate of serotonergic cell bodies in the raphe nucleus. Chronic administration leads to desensitization of these receptors and eventually an increase in cell firing (Figure 2).

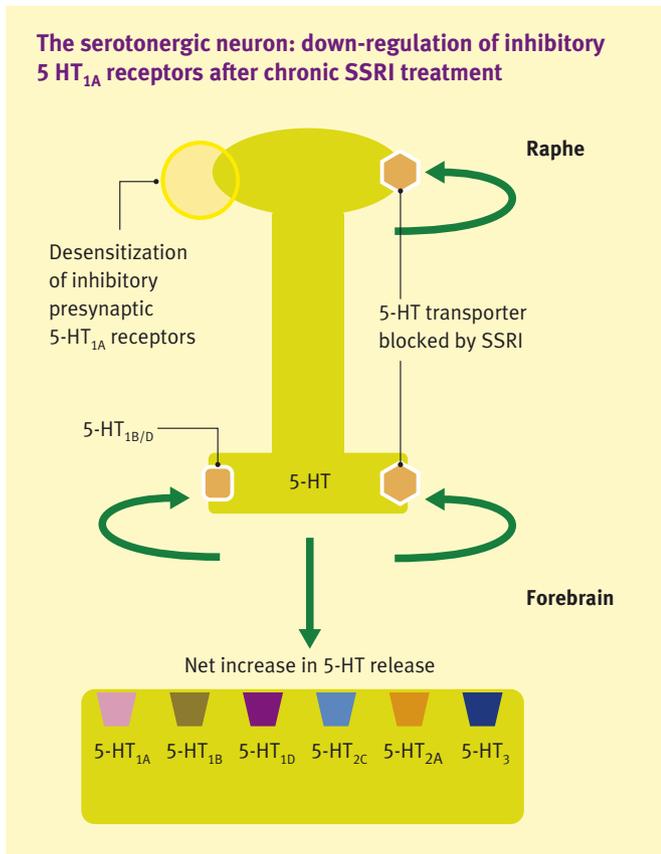


Figure 1

Increased synaptic monoamine activity may occur via several pathways, including decreased reuptake by blockade of transporters, decreased metabolism by inhibition of oxidative enzymes and increased release by blockade of inhibitory

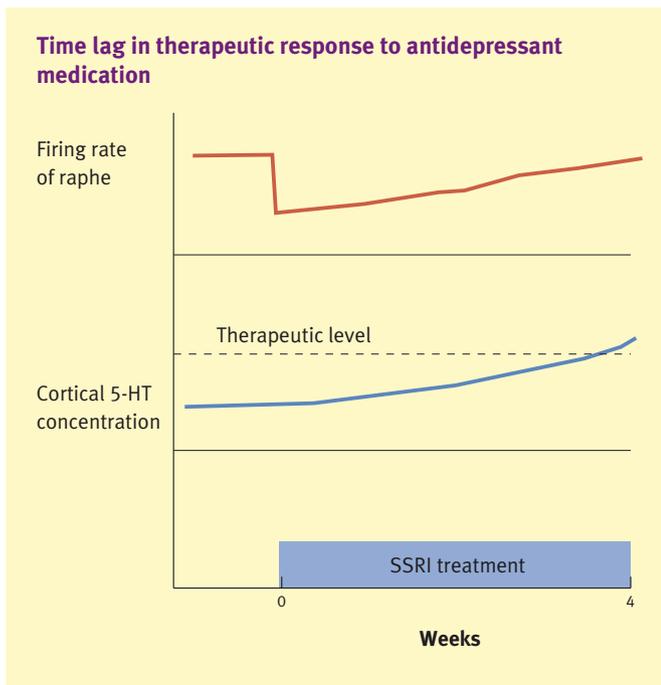


Figure 2

autoreceptors. Evidence from postmortem, neuroendocrine and neuroimaging studies suggests that depression is associated with abnormalities of postsynaptic monoamine receptor function, and some antidepressants have direct actions on these receptors.<sup>5</sup>

**Reuptake inhibitors**

Following release of the neurotransmitter into the synaptic gap, a specific transporter facilitates its reuptake into the presynaptic neurone (Figure 1). Several classes of antidepressant act primarily via inhibition of this reuptake process. They are distinguished firstly by their selectivity for the transporter over receptors for other neurotransmitters, and secondly by their relative affinity for blockade of the reuptake of each of the monoamines. Figure 3 compares the selectivity for reuptake inhibition of serotonin versus noradrenaline of various antidepressants. Interestingly, tianeptine, a drug that facilitates the reuptake of serotonin, also has antidepressant properties.

**Tricyclic antidepressants (TCAs)**

This heterogeneous group contains the earliest reuptake inhibitors. They are similar in structure to antipsychotics such as chlorpromazine and share the wide range of pharmacological actions of these drugs. In addition to reuptake inhibition of serotonin and noradrenaline, TCAs also antagonize postsynaptic  $\alpha_1$ -adrenoceptors, histamine ( $H_1$ ) receptors, muscarinic cholinergic receptors and serotonin ( $5-HT_2$ ) receptors. These actions are responsible for the excess in side effects and toxic effects in comparison with more selective drugs such as the SSRIs (Table 1). Maprotiline is a related tetracyclic drug that predominantly inhibits noradrenergic reuptake.

TCAs are still prescribed frequently as they have a wide spectrum of clinical use and it is doubtful that their efficacy has been exceeded by that of newer drugs. However, antidepressant efficacy is seen at doses equivalent to 150 mg and above of amitriptyline, and their relatively poor tolerability may lead to poor adherence to treatment or prescription of sub-therapeutic doses. Some countries have recorded a downward trend in suicide rates since prescription of SSRIs has superseded that of TCAs, and this may reflect a reduction in access to potentially lethal tablets in high-risk patients.<sup>6</sup>

**Selective serotonin reuptake inhibitors (SSRIs)**

Although the development of the TCAs resulted in drugs that had greater affinity for the reuptake blockade of either serotonin or noradrenaline, the SSRIs are considered to be the first ‘designer’ antidepressants as they are highly selective for the 5-HT transporter. They are effective in most mood and anxiety disorders (Table 1) and their use has generally superseded that of the TCAs due to their improved safety and tolerability.<sup>1</sup> Nevertheless, they are not without side effects, and some effects are particularly associated with individual drugs within the class; for example, fluoxetine has agonist activity at  $5-HT_{2C}$  receptors, causing headache, agitation and loss of appetite.

**Interactions:** SSRIs can interact with other serotonergic drugs, and of particular importance is the interaction with monoamine oxidase inhibitors (MAOIs), which can lead to the potentially

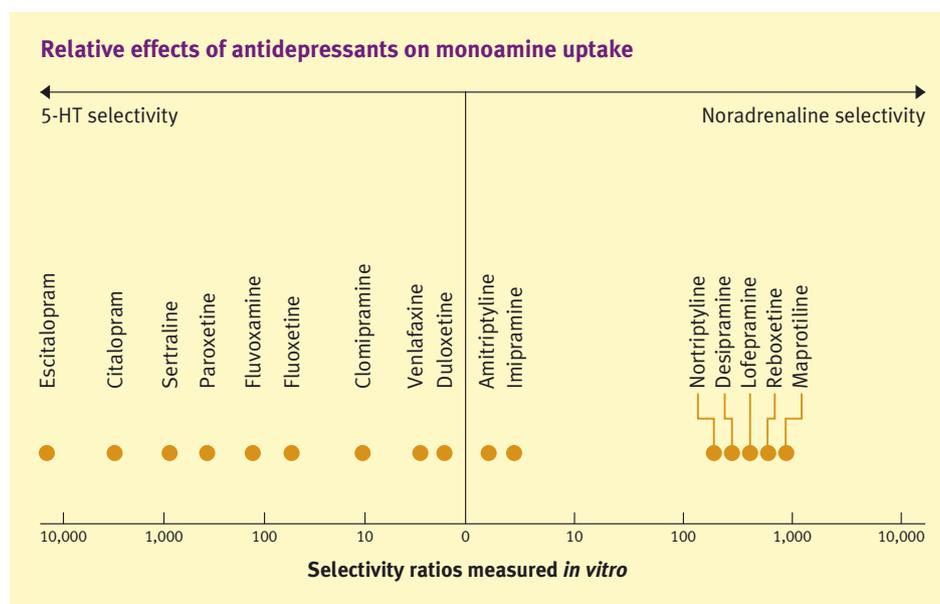


Figure 3

lethal 'serotonin syndrome', comprising restlessness, irritability, tremor, sweating and hyperreflexia.<sup>7</sup> There should be a washout of 2 weeks between discontinuing MAOI therapy and starting an SSRI, and a washout of 1–2 weeks should follow SSRI discontinuation (5 weeks for fluoxetine). SSRIs have variable potential for drug interactions via hepatic cytochrome P450 enzymes, with escitalopram having the lowest potential for interactions.

**Side effects:** controversies surrounding the use of SSRIs have been brought to public attention recently.<sup>8</sup> Agitation is a well-recognized side effect, but anecdotal reports and some study findings have associated the initiation of SSRI therapy with suicidal thoughts and aggressive behaviour. The scientific basis for this association continues to be hotly debated, but it does not appear that SSRI treatment is associated with an overall increase in suicidality at a population level.

SSRIs have also been subject to claims in the lay media that they have 'addictive' properties. This unfortunate confusion is due in part to the risk of relapse when treatment is discontinued, and to the occurrence of a specific discontinuation syndrome in some patients. The most common symptoms are dizziness, nausea and headache, and although the 'SSRI discontinuation syndrome' has received prominent attention, a similar syndrome has been reported with most antidepressant classes (Table 1). It is more common in drugs with a short half-life (such as paroxetine among the SSRIs) and when long-term therapy is discontinued rapidly. Core features of addiction, such as craving and drug-seeking behaviour, are clearly not part of the syndrome.

#### Selective serotonin and noradrenaline reuptake inhibitors (SNRIs)

Following on from the SSRIs has come a class of drugs with additional inhibitory activity at noradrenaline reuptake sites. SNRIs vary in their relative affinities for the serotonin and noradrenaline transporters. At low doses, venlafaxine has predominantly serotonergic effects, with significant noradrenergic uptake blockade

occurring at daily doses of 150 mg and above. Duloxetine is more balanced in its serotonergic and noradrenergic effects. Tolerability is similar to that of the SSRIs, although at higher doses monitoring for elevated blood pressure is required. It is probable that the dual mechanism of action confers added antidepressant efficacy, as there is growing evidence that response rates for the SNRI venlafaxine are higher than for SSRIs in some patient groups, particularly those with more severe depression.<sup>9,10</sup> The same is true of amitriptyline and clomipramine, TCAs with similar actions to venlafaxine (Figure 3).

#### Other reuptake blockers

The first selective noradrenaline reuptake inhibitor (NARI) to be marketed was reboxetine, an effective antidepressant with reasonable tolerability. Its activity is similar to that of the TCAs desipramine, lofepramine and nortriptyline. It is not yet possible to identify individual patients who benefit from noradrenergic rather than serotonergic drugs, although noradrenergic drugs tend to have alerting and energizing effects that may be useful in some cases. Bupropion is a drug that inhibits the reuptake of dopamine and noradrenaline. It has good antidepressant efficacy<sup>11</sup> and is licensed as an extended-release preparation in the USA and most of Europe, although it is currently licensed in the UK only for nicotine withdrawal.

#### Enzyme inhibitors

These drugs offer an alternative mechanism for increasing the synaptic availability of serotonin, noradrenaline and dopamine. The metabolism of these neurotransmitters within the presynaptic nerve terminal is inhibited by antagonism of monoamine oxidase enzymes. Antidepressant efficacy is similar to that of reuptake inhibitors but there is a distinct side-effect profile. The different mechanism of action of these drugs offers a strategy for treatment-resistant depression, and they have a historical clinical use in atypical depression.

### Properties of antidepressant classes

Drug class	Antidepressant agents available in UK	Other clinical uses	Safety	Tolerability	Discontinuation syndrome
TCA and related drugs	Amitriptyline Amoxapine Clomipramine Dothiepin Doxepin Imipramine Lofepramine Maprotiline Nortriptyline Trimipramine	Obsessive–compulsive disorder Panic disorder Neuralgia Nocturnal enuresis	Cardiac and neurological toxicity in overdose Potential for toxic interactions	Significant burden: anticholinergic and antihistamine effects, postural hypotension, sexual dysfunction	Widely reported
SSRI	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Anxiety disorders	Low overdose toxicity Varying potential for toxic drug interactions	Side effects include nausea, dizziness and sexual dysfunction	Reported Most common with paroxetine Least common with fluoxetine
SNRI	Venlafaxine Duloxetine	Anxiety disorders Urinary incontinence	Low overdose toxicity	Side effects include nausea, dizziness and sexual dysfunction	Reported
NDRI	Bupropion	Smoking cessation	Neurological toxicity in overdose Potential for toxic drug interactions	Side effects include headache, tremor and anxiety	Reported
NARI	Reboxetine	Sleep disorders	Low overdose toxicity Low potential for toxic interactions	Side effects include dizziness and urinary symptoms	Not widely reported
SARI	Trazodone	Insomnia	Lower overdose toxicity but potential for drug interactions	Side effects include sedation, postural hypotension, priapism	Not widely reported
MAOI	Isocarboxazid Phenelzine Tranylcypromine	Panic disorder Social anxiety disorder	Significant overdose toxicity High potential for toxic interactions including hypertensive ‘cheese’ reaction	Significant side-effect burden: dizziness, postural hypotension, headache, anticholinergic effects	Reported
RIMA	Moclobemide	Social anxiety disorder	Low potential for toxicity Risk of interactions at higher doses	Well-tolerated	Not widely reported
NaSSA	Mirtazapine Mianserin		Mirtazapine has low potential for toxicity and interactions	Side effects include sedation and weight gain	Not reported

**Table 1**

#### Classical monoamine oxidase inhibitors (MAOIs)

MAOIs bind so irreversibly to monoamine oxidase enzymes that metabolic activity can be restored only by the synthesis of fresh enzymes over several weeks. Their clinical use is limited by their significant side-effect profile and overdose toxicity. Of particular concern is the risk of hypertensive crisis following the ingestion of foods containing tyramine (the ‘cheese reaction’) or drugs with sympathomimetic properties. The need for a washout

period when switching to or from other antidepressants has been mentioned above.

#### Reversible inhibitors of monoamine oxidase A (RIMA)

The available drug in this class (moclobemide) does not require a lengthy washout period as it binds competitively to the enzyme and so can be displaced by the neurotransmitter substrates. It is selective for MAO-A and is less likely to cause hypertensive

reactions, although dietary precautions should be observed above 900 mg per day as it becomes less selective at higher doses. Moclobemide has advantages in safety and tolerability over the classical MAOIs but has not demonstrated similar efficacy in treatment-resistant depression.

### Receptor blockers

These drugs share the property of blockade of inhibitory presynaptic  $\alpha_2$ -adrenoceptors, resulting in an increase in the synaptic release of serotonin and noradrenaline, as well as acting at various postsynaptic receptors including the serotonin 5-HT<sub>2</sub> receptor. This receptor mediates the agitation seen with other serotonergic antidepressants, so drugs in this class tend to have calming effects.

#### Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). It increases synaptic release of serotonin and noradrenaline via blockade of presynaptic inhibitory  $\alpha_2$ -adrenoceptors, as well as blocking postsynaptic 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors and H<sub>1</sub> histamine receptors. It is an anxiolytic antidepressant with a unique side-effect profile. Whilst lacking serotonergic effects such as nausea, agitation and sexual dysfunction, it can cause sedation, increased appetite and weight gain. Tolerance to the sedative properties usually occurs and, paradoxically, higher doses tend to be less sedating, as increased noradrenaline release is thought to offset histamine blockade. It is safe in overdose, interactions with other drugs are rare and discontinuation symptoms have not been reported. Mianserin is sometimes classified with mirtazapine as it blocks  $\alpha_2$ -adrenoceptors and 5-HT<sub>2</sub> receptors. It also blocks postsynaptic  $\alpha_1$ -adrenoceptors and has sedative properties.

#### Trazodone

Trazodone is structurally related to TCAs and is classed as a serotonin antagonist and reuptake inhibitor (SARI). It combines weak serotonin reuptake inhibition with blockade of multiple monoamine receptors, including presynaptic  $\alpha_2$ -adrenoceptors and postsynaptic 5-HT<sub>2A</sub> receptors and  $\alpha_1$ -adrenoceptors. It is highly sedating due to its 5-HT<sub>2</sub> blockade, antihistamine and anticholinergic effects. A related drug, nefazodone, is a selective 5-HT<sub>2</sub> blocker and SSRI which demonstrated antidepressant and anxiolytic properties but was recently withdrawn in the UK because of a risk of hepatic toxicity.

### Clinical prescribing

Ideal prescribing occurs in the context of a careful diagnostic assessment, including identification of comorbidity such as substance misuse or anxiety disorder which might modify the treatment plan. The choice of treatment should be negotiated with the patient after a full discussion of the risks and benefits of the available options for medical and psychological therapy. The likely duration of treatment and plans for discontinuation should be highlighted before treatment is initiated.

The choice of antidepressant drug will depend on factors including symptom profile, treatment history and individual

concerns about side effects. Differences in efficacy between drugs are relatively small and for uncomplicated cases of moderate severity the decision will be based largely on safety and tolerability. The possibility of pharmacokinetic interactions with other medications should be considered and appropriate care must be taken when switching between drugs. The clinician can be supported by the use of evidence-based guidelines, such as those produced by the British Association for Psychopharmacology,<sup>9</sup> the Maudsley Hospital<sup>12</sup> and the National Institute for Clinical Excellence.<sup>13</sup>

### Future developments

In the near future, developments are likely to remain focused on monoamine neurotransmitters, with the aim of finding agents that are either more effective, better tolerated or that have a faster onset of action than existing options. As evidence grows that drugs with actions on multiple neurotransmitters have therapeutic advantages over the SSRIs, new agents are likely to have this property. The current limited use in the UK of duloxetine and bupropion is therefore likely to increase, and a further novel antidepressant, agomelatine, is close to being launched. Agomelatine is an agonist of melatonin receptors and antagonist of 5-HT<sub>2C</sub> receptors, and in early studies has shown positive effects on anxiety and sleep symptoms, with good tolerability.<sup>14</sup> New selective blockers of dopamine and noradrenaline reuptake are in development, as well as compounds that are 'triple reuptake blockers' for all three monoamines. Serotonin release may also be promoted by drugs which act at 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. Selegiline, a specific inhibitor of monoamine oxidase B, has antidepressant effects, and an interesting feature of this drug is that it can be delivered via a transdermal patch.<sup>15</sup> Alternative methods of drug delivery or new controlled-release preparations of existing drugs are likely to be tried in an attempt to improve drug compliance.

The next phase of antidepressant development should see agents that have their activity via other neurochemical pathways.<sup>16</sup> Likely targets for manipulation include the actions of oestrogens and stress hormones of the hypothalamic-pituitary-adrenal axis, which are both known to interact with monoamine systems; other neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA); and CNS peptides such as neuropeptides, insulin growth factor and brain-derived neurotrophic factor. As the expanding market for antidepressants favours investment from pharmaceutical companies it is likely that new compounds will continue to emerge. ◆

### REFERENCES

- 1 Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 2000; **58**: 19–36.
- 2 MacGillivray S, Arroll B, Hatcher S, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *Br Med J* 2003; **326**: 1014.
- 3 Munoz-Arroyo R, Sutton M, Morrison J. Exploring potential explanations for the increase in antidepressant prescribing in

- Scotland using secondary analyses of routine data. *Br J Gen Pract* 2006; **56**: 423–28.
- 4 Blier P. The pharmacology of putative early-onset antidepressant strategies. *Eur Neuropsychopharmacol* 2003; **13**: 57–66.
  - 5 Nutt DJ. The neuropharmacology of serotonin and noradrenaline in depression. *Int Clin Psychopharmacol* 2002; **17**(suppl 1): S1–12.
  - 6 Nutt DJ. Death by tricyclic: the real antidepressant scandal? *J Psychopharmacol* 2005; **19**: 123–24.
  - 7 Gillman PK. A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action. *Biol Psychiatry* 2006; **59**: 1046–51.
  - 8 Nutt DJ. Death and dependence: current controversies over the selective serotonin reuptake inhibitors. *J Psychopharmacol* 2003; **17**: 355–64.
  - 9 Anderson IM, Nutt DJ, Deakin JFW. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2000; **14**: 3–20.
  - 10 Shelton C, Entsuah R, Padmanabhan SK, Vinall PE. Venlafaxine XR demonstrates higher rates of sustained remission compared to fluoxetine, paroxetine or placebo. *Int Clin Psychopharmacol* 2005; **20**: 233–38.
  - 11 Clayton AH. Extended-release bupropion: an antidepressant with a broad spectrum of therapeutic activity? *Expert Opin Pharmacother* 2007; **8**: 457–66.
  - 12 Taylor D, Paton C, Kerwin R. The 2005–2006 Maudsley prescribing guidelines, 8th edn. London: Taylor & Francis, 2005.
  - 13 National Institute for Clinical Excellence. Depression: management of depression in primary and secondary care. Clinical Guideline 23. London: National Collaborating Centre for Mental Health, 2004.
  - 14 Zupancic M, Guilleminault C. Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs* 2006; **20**: 981–92.
  - 15 Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. *J Clin Psychopharmacol* 2006; **26**: 579–86.
  - 16 Rosenzweig-Lipson S, Beyer CE, Hughes ZA, et al. Differentiating antidepressants of the future: efficacy and safety. *Pharmacol Ther* 2007; **113**: 134–53.

#### FURTHER READING

- Bennett PN, Brown MJ. Clinical pharmacology, 9th edn. Edinburgh: Churchill Livingstone, 2003.  
(*The definitive pharmacology textbook.*)
- Carlsson A. A half-century of neurotransmitter research: impact on neurology and psychiatry. In: Jornvall H, ed. Nobel lectures, physiology or medicine 1996–2000. Singapore: World Scientific Publishing Co., 2003.  
(*An overview of monoamine physiology from a pioneer in the field.*)
- Goodwin GM, Young AH. The British Association for Psychopharmacology guidelines for treatment of bipolar disorder: a summary. *J Psychopharm*; **17**(suppl): 3–6.  
(*Evidence-based clinical guidelines for the use of antidepressants in bipolar disorder.*)
- Potokar JP, Thase ME, eds. Advances in the management and treatment of depression. London: Martin Dunitz, 2003.  
(*Contains chapters on various clinical uses of antidepressants.*)
- Stahl SM, Muntner N. Essential psychopharmacology of depression and bipolar disorder. Cambridge: Cambridge University Press, 2000.  
(*Illustrated textbook of antidepressant pharmacology.*)