## Treatment of depression – drug therapies and ECT

### GENERAL QUESTIONS

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8.81 I found that patients who have received diazepam for their symptoms are reluctant to try antidepressants, and when they do they invariably encounter side-effects and discontinue treatment saying, ‘Valium is the only thing that works for me and lets me live a normal life’. It is a very difficult problem to handle, and I wonder if you have any advice?

FLUPENTIXOL

8.82 How does flupentixol work as an antidepressant?

8.83 I sometimes use flupentixol to treat patients with mild depression coupled with anxiety. I would not use it to treat severe depression, and I think of it as a ‘gentle’ antidepressant. Am I right in my thinking?

ANTIPSYCHOTICS

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8.85 Depression and schizophrenia may coexist. How would you treat this combination?

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8.94 Do patients have to consent to each individual treatment?
8.95 Does consent still have to be sought when a patient is in hospital under a section of the Mental Health Act?

8.96 How dangerous is ECT?

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8.98 What advantages does it offer over traditional ECT?

**PQ PATIENT QUESTIONS**

8.99 What types of treatment are available for depression?

8.100 Will I become dependent on antidepressants?

8.101 Will it be difficult stopping antidepressant therapy?

8.102 Do I have to inform the DVLA that I am taking antidepressants?

8.103 Why do I have to go on taking tablets once I feel better?

8.104 Should my child stop taking Seroxat immediately?
GENERAL QUESTIONS

8.1 GPs are being asked to diagnose and treat depression effectively, yet there are so many different drugs available it is difficult to know which one to choose. What general advice would you give about drug treatment?

Get to know a limited number of antidepressants well and how to use them effectively. A good guide would be to use those widely used by your local psychiatric service. This should coincide with the antidepressants that are available on your local formularies. It would be useful to have one that is slightly sedative, another that is relatively neutral, a third where the dose can be titrated up from a low starting dose to a full therapeutic dose. Possibly one with a different biochemical (e.g. SSRI/SNRI) profile could be a second-line treatment if the first-line treatment does not work. Two or three antidepressants used on a regular basis are probably sufficient. The differences in efficacy among the many antidepressants on the market are generally slight, and centre mainly on side-effect profiles rather than efficacy, but in clinical practice there are many patients who appear to benefit from one and not another antidepressant, so there appear to be differences that are hard to define from known pharmacological characteristics.

Characteristics of a variety of antidepressants are given in Table 8.1.

8.2 The newer antidepressants are considerably more expensive than the older tricyclics. Do you think this expense is justified in terms of safety, efficacy and compliance?

Yes. The newer antidepressants are certainly safer both in routine practice and in overdose. They lack the cholinergic side-effects which lead to constipation and urinary problems. They lack cardiotoxicity and, with a few notable exceptions, have minimal psychomotor impairment and do not interact with alcohol. They are much less toxic than tricyclics in overdose.

The question of efficacy is less clear on direct comparison, but when the issue of compliance is added, there are distinct advantages. If patients take the full dose of medication for an adequate period of time, they are more likely to benefit from the treatment. Most newer antidepressants can be given at a therapeutically effective dose from the first day of treatment. Often one dose per day is sufficient, thus avoiding the need to titrate the dose up or for multiple dosings, both of which are a deterrent to good compliance. On that basis, efficacy is likely to be improved because of better
### TABLE 8.1 Characteristics of some antidepressants

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose range daily</th>
<th>Type</th>
<th>Depression</th>
<th>Depression with anxiety</th>
<th>OCD</th>
<th>Panic</th>
<th>Social phobia</th>
<th>Relapse prevention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Cipramil)</td>
<td>20–60 mg</td>
<td>SSRI</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>50–250 mg</td>
<td>TCA</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not in epilepsy, recent heart attack</td>
</tr>
<tr>
<td>Dothiepin/Dosulepin</td>
<td>75–225 mg</td>
<td>TCA</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td>Dothiepin/Dosulepin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tried and tested</td>
</tr>
<tr>
<td>Escitalopram (Cipralex)</td>
<td>10–20 mg</td>
<td>SSRI</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>20–60 mg</td>
<td>SSRI</td>
<td>•</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bulimia</td>
</tr>
<tr>
<td>L-tryptophan (Optimax)</td>
<td>3–6 g</td>
<td>Amino acid</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EMS risk* Adjunct to treatment of severe depression</td>
</tr>
<tr>
<td>Maprotiline (Ludiomil)</td>
<td>25–150 mg</td>
<td>NaRI</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not sedative Probably OK for breast feeding No obvious cognitive impairment</td>
</tr>
<tr>
<td>Mirtazapine (Zispin)</td>
<td>15–45 mg</td>
<td>NaSSA</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sedative, hypnotic Weight gain, less sexual dysfunction</td>
</tr>
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TABLE 8.1 (cont’d) Characteristics of some antidepressants

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose range daily</th>
<th>Type</th>
<th>Depression</th>
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<th>Panic</th>
<th>Social phobia</th>
<th>Relapse prevention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moclobemide (Manerix)</td>
<td>300–600 mg</td>
<td>RIMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No sexual impairment</td>
</tr>
<tr>
<td>Paroxetine (Seroxat)</td>
<td>20–60 mg</td>
<td>SSRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTSD</td>
</tr>
<tr>
<td>Phenelzine (Nardil)</td>
<td>15–45 mg</td>
<td>MAOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Classic MAOI food and drink restrictions</td>
</tr>
<tr>
<td>Reboxetine (Edronax)</td>
<td>8–12 mg</td>
<td>NaRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good in fatigue</td>
</tr>
<tr>
<td>Sertraline (Lustral)</td>
<td>50–200 mg</td>
<td>SSRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTSD in women</td>
</tr>
<tr>
<td>Tranylcypromine (Parnate)</td>
<td>10–30 mg</td>
<td>MAOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Classic MAOI food and drink restrictions</td>
</tr>
<tr>
<td>Trazodone (Molipaxin)</td>
<td>100–600 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low CVS risk</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>75–375 mg</td>
<td>SNRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Possibly more effective than other antidepressants</td>
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CVS, cardiovascular system; EMS, eosinophilia myalgia syndrome; NaRI, noradrenaline reuptake inhibitor; MAOI, monoamine oxidase inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; OCD, obsessive compulsive disorder; PMT, premenstrual tension; PTSD, post-traumatic stress disorder; RIMA, reversible inhibitor of monoamine oxidase-A; SNRI, selective serotonin–noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. *Hospital specialist use only.
compliance and the ability to reach the therapeutic dose early. I know there is a disagreement between GPs and psychiatrists over what constitutes an effective dose of a tricyclic.

The cost–benefit analysis of these relative advantages is more difficult to calculate, depending on who is doing the arithmetic and how much different components of the equation are valued. Some would say that money is saved by:

- better compliance, leading to greater efficacy
- less need for treatment in intensive care units following overdoses
- greater savings in getting patients back to work sooner

but a lot depends on which budget the money comes out of and how you do your arithmetic. Drug budgets are highly visible on a balance sheet, but we are doctors not accountants.

8.3 If an antidepressant does not appear to be working after a couple of months’ treatment, what should I do?

The first question is whether the patient has the sort of depression that is likely to benefit from antidepressants. Sadly, antidepressants do not cure sadness, social adversity or personality disorders. You should consider whether the patient has the sort of depression that ought to benefit, namely of sufficient severity with the presence of ‘biological symptoms’, or is it more an ‘existential depression’ for which there may be no medical cure? Another common reason for therapeutic failure is a lack of compliance. Patients are often reluctant to take medication, and when they do they take it irregularly. Some GPs are often reluctant to prescribe the maximum dose of medication, whereas psychiatrists are keen to do so. It is always worth increasing the dose to the next dosage increment or even more before giving up the particular drug as ineffective. I would advocate a dosage increase before changing to another drug providing there are no side-effects. The question then is should one change to a drug of another class for example SSRI to a tricyclic or SNRI, or will another SSRI do equally well? The evidence at present is that it does not matter what antidepressant to change to, a change in medication generally confers some therapeutic benefit (10–20% chance of success) if one antidepressant does not work. Further strategies for treatment resistance (see Box 8.1), such as augmentation therapies with lithium, combined antidepressants, the addition of tryptophan, thyroxine or ECT, are best left in the hands of specialists, unless you feel confident in doing so yourself. (See also Chapter 11.)

8.4 How long should treatment last, and how should it be stopped?

Patients are unlikely to get the full benefit of an antidepressant in less than 3–4 weeks, and it sometimes takes up to 6 weeks to get the maximum
benefit. If the patient has benefited from treatment, the evidence is that there is a 50% risk of relapsing in the following weeks if the antidepressant is stopped. If they continue on the medication the risk of relapse drops to about 20%. The risk of relapse generally drops to about 20% on stopping medication after 6 months – much the same as if the patient stayed on the medication. On that basis the general advice is to continue the medication for about 6 months if it has been of benefit and the side-effects are tolerable, before gradually cutting down the medication. As with everything there is a value judgement necessary, depending upon the benefit that the patient gets from the medication, whether or not they are happy to continue with it, whether they get side-effects, and the consequences of relapsing. If the patient is severely ill and has derived considerable benefit from the medication then he or she would be advised to continue the medication for longer, whereas if the therapeutic response has been marginal and the side-effects troublesome then continuing with medication may be less justified. As a rule of thumb, continue the medication for 6 months after the depression has receded.

8.5 Will some patients need to stay on medication for a longer period?

Patients with unstable conditions, where the impact of relapse is substantial, would be advised to stay on medication longer and possibly indefinitely. The evidence is that the longer patients stay on medication the less chance of relapsing. Prophylactic antidepressants appear to be of benefit in

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**BOX 8.1 Treatment for resistant depression**

- Addition of lithium
- ECT
- High doses of non-tricyclic antidepressant
- Addition of tri-iodothyronine (T3)
- Addition of amitriptyline
- Addition of pindolol
- Addition of dexamethasone
- Addition of lamotrigine
- High-dose tricyclics
- MAOIs and tricyclics
- Addition of buspirone
- Addition of clonazepam
- Mirtazapine
- Addition of olanzapine
- Addition of folic acid
preventing recurrences, and if patients are prone to frequent relapses then they may well be happy to stay on medication indefinitely to reduce the chances of relapse. This has to be balanced against the cost in financial and personal terms of taking long-term treatment.

8.6 What are the desirable properties of an antidepressant drug?

The main requirement is that it is effective, not only in treating the acute episode but also in preventing relapse. Sadly, modern antidepressants are only about 70% effective, and we need something that is more effective than the standard preparations. Also there is a delay in establishing a full effect; a treatment that became effective in the first few days would be highly desirable. The treatment has to be safe. Fortunately modern antidepressants have side-effect profiles very similar to placebo, although every now and then something untoward occurs. Importantly, they are generally safe in overdose. The treatment should be simple to administer, ideally with a once-daily dosage. There should be no potential for abuse and no withdrawal problems. They should be free of drug interactions and should be safe not only in uncomplicated cases but also in those where there is concomitant physical illness, especially in the elderly who have cardiovascular disease and other physical ailments. Ideally of course the antidepressants should be curative, as opposed to simply suppressing symptoms, but that may be a search for the Holy Grail.

8.7 How does alcohol interact with antidepressants, and should all patients be advised not to drink at all while on treatment?

The warning about drinking alcohol while taking antidepressants is a generic one related to all categories of antidepressants. The real danger is with sedative antidepressants, where the antihistamine component of the antidepressant has an additive effect on the sedative effects of the alcohol; this can result in sedation and possible disinhibition over and above what would be expected with either compound on its own. This is a particular problem with the tricyclics and, for example, mirtazapine. The SSRIs and other more-modern compounds tend not to interact with alcohol to any significant degree, so therefore there is theoretically no harm in a patient drinking modest amounts of alcohol. Excessive amounts of alcohol or high doses of antidepressants may well be ill advised in combination, especially in emotionally unstable individuals. Patients should be advised to be careful, but there is probably no harm in a small amount of alcohol in combination with an antidepressant. The important thing is they should try it out under conditions of relative safety such as in their own home with a partner present, rather than going to a social gathering and drinking to excess and risking loss of control and social embarrassment. The answer to
the issue of whether patients who are well but remain on long-term antidepressants can indulge in social drinking is probably yes.

The very specific contraindication of Chianti for patients on MAOI therapy is dealt with in Qs 6.5 and 6.6.

Drug abuse is best avoided, although its effects in combination with antidepressants are generally unknown. Some SSRIs appear to reduce craving for cocaine, but this is generally an area for specialist involvement. Many depressed patients self-medicate with drugs, and many drug-abusing patients become depressed. Dual diagnosis, as it is known, where patients have a drug and psychiatric problem at the same time, is an expanding area. I am increasingly asked to see patients who have blamed aggressive or violent behaviour on their antidepressants, but in whom the likely cause is actually the effects of substantial amounts of alcohol taken at the same time by an individual with an unstable personality.

8.8 Is it better to give sedatives or antidepressants for anxiety?

Sedatives are probably contraindicated, but anxiolytics are effective in the treatment of anxiety, especially in the short term, possibly while the antidepressants begin to work. Anxiolytics such as benzodiazepines are highly effective in dealing with acute short-term crises, allowing patients the opportunity to deal with the psychological trauma and recover their composure over a few days. So, if the anxiety symptoms are likely to last for only a week or so, then probably a brief course of anxiolytics is all that is indicated. A brief course of a sedative or hypnotic may deal with a brief crisis-induced sleep problem.

If the problem is likely to be more related to a depressive illness of longer duration then the case for giving an antidepressant is stronger, but of course they take time to work and are not necessarily more effective than anxiolytics. The case for giving an antidepressant is that they do not cause dependency and are better at treating the depressive symptoms. Patients are then better able to discontinue their antidepressant medication because of the lack of withdrawal problems, whereas if they took anxiolytics they may have some withdrawal symptoms and may continue taking them in the longer term. Nevertheless benzodiazepine anxiolytics are pleasant to take and patients generally prefer taking them to taking antidepressants. There is currently still a large amount of excessive prejudice against benzodiazepines, and therefore few people would recommend prescribing them long-term to patients who are not already dependent on them. Anxiolytics are often victims of their own success.

There may be a case for prescribing benzodiazepines to cover the first few days and weeks of treatment with an antidepressant before the antidepressant effect kicks in, whereupon the aim is to tail off the benzodiazepine. In my experience patients prefer taking the
8.9 Does nicotine interact with antidepressants or have an antidepressant effect of its own?

CASE STUDY 8.1

A 26-year-old female patient with recurrent depression who was doing well on nefazodone became increasingly depressed when she gave up smoking. She improved when her treatment was changed to paroxetine.

The antidepressant effects of nicotine are probably a learned and short-term effect. Patients develop tolerance and then become dysphoric without nicotine. Some antidepressants can counteract nicotine withdrawal effects. Bupropion, an antidepressant that facilitates dopaminergic transmission, acts in this way. Others such as the SSRIs appear to be less effective in this respect. Clinical experience shows that, in patients who become depressed when they give up cigarette smoking and who can benefit from an antidepressant for their depressive symptoms, bupropion would be the obvious choice, although the treatment of depression is not a licensed indication. I have seen patients who have been helped in dealing with nicotine withdrawal by taking an antidepressant, and it is certainly worth a try.

8.10 Do patients become dependent on antidepressants in the same way that they may become dependent on benzodiazepines?

No. Antidepressants have a different mechanism of action from benzodiazepines and do not act on the alcohol–GABA–benzodiazepine receptor complex. They are not associated with the classic tolerance and withdrawal syndrome associated with sedative hypnotic compounds. Patients can become clinically reliant on antidepressants to prevent recurrences and relapses. There may be some level of psychological habituation. The suggestion that long-term antidepressant consumption can make patients more liable to relapse on stopping antidepressants is an interesting notion and one without real evidence to support it. The Committee on Safety of Medicines tells us there is little evidence, from spontaneous reporting, of dependency. Other published literature and usage data suggest that SSRIs and related drugs are not drugs of dependence.

Withdrawal reactions have been reported with SSRIs. These commonly include symptoms of dizziness, paraesthesia, headaches, anxiety and nausea. These symptoms are distinct from a recurrence of depression. They tend to last a few days only. Because of this, abrupt discontinuation of treatment with antidepressants should be avoided. It is best to cut down the medication over a matter of days to minimize any withdrawal symptoms.
8.11 Is there any point in switching a patient from one SSRI to another SSRI and, if so, what precautions should I take?

Ideally you should withdraw the first SSRI and then start the replacement. The reduction should be over 2–4 weeks. An alternative strategy would be to halve the dose of one SSRI and substitute it for the half dose of the other, thereby cross tapering. There should not be any problem. There are two reasons for switching from one SSRI to another. The first would be because of side-effects. Providing the side-effects are not general to SSRIs as a class (headaches and nausea) but specific to a particular drug, then that might be a reason for changing. The alternative reason would be lack of efficacy, and it is as valid to change to another SSRI as it is to change to an entirely different type of antidepressant.

8.12 If I decide to switch a patient from an SSRI to an NaSSA or vice versa, what precautions should I take?

This is best done by cautious cross tapering, increasing the dose of one while cautiously reducing the other. The same applies whichever way you go. There is logic in switching to a different class of antidepressant if the switch is instigated because of an inadequate therapeutic response or side-effects. Noradrenergic and specific serotonergic antidepressants (NaSSAs) theoretically have an additional mode of action, by inhibiting the uptake of noradrenaline (norepinephrine), compared with an SSRI and therefore might work when the latter has not, but definitive evidence for this is lacking.

Similar considerations apply when switching between an SSRI and an SNRI.

8.13 If I decide to switch a patient from an MAOI to an SSRI or vice versa, what precautions should I take?

Combining SSRIs and traditional MAOIs is extremely dangerous and can result in fatal reactions. Great caution needs to be exercised if a switch is contemplated. Two weeks have to be left after stopping MAOIs before introducing any other antidepressant. Two weeks have to be left after stopping an SSRI (5 weeks for fluoxetine) before starting an MAOI. This is a procedure best left in the hands of a specialist. It usually entails gradually tapering down one antidepressant in someone who is not responding, and giving a 2-week drug holiday before starting on another antidepressant, which may take several weeks to work. This means that the patient will be without effective treatment for several weeks and will need support during this time.

8.14 If I decide to switch a patient from an MAOI to a tricyclic or vice versa, what precautions should I take?

This can also be hazardous, and great caution needs to be exercised. Adding a tricyclic antidepressant in a patient already on an MAOI can result in a
fatal interaction, with the dramatic ‘serotonin syndrome’ of hyperpyrexia, fits, elevated blood pressure and death. Adding a tricyclic thus to an MAOI is absolutely contraindicated. Adding an MAOI to a tricyclic is acceptable under some circumstances. If the tricyclic is one of the secondary amines such as dosulepin (dothiepin), amitriptyline or trimipramine, then it may be clinically appropriate to add phenelzine carefully, one of the older treatments for resistant depression. If, however, the patient is taking imipramine the procedure may be hazardous. Phenelzine is the MAOI to use. It is best to avoid tranylcypromine. Again this is a procedure best left in the hands of the dwindling number of psychiatrists experienced in these matters.

8.15 If I decide to switch a patient from a tricyclic to an SSRI or vice versa, what precautions should I take?
This should not pose a problem. Ideally, cross-tapering cautiously with a low dose of tricyclic added to the SSRI or vice versa and then gradually increasing the dose would be the best way forward. Appendix 5 gives, for a variety of antidepressants, details of precautions to take when switching or stopping the drugs.

8.16 What is the serotonin syndrome, and how may it be avoided?
This condition is characterized by restlessness, sweating, tremor, shivering, muscle spasms, confusion, convulsions and ultimately death (Box 8.2). It classically occurs with the combination of MAOIs and SSRIs. It can occur to a lesser degree if for example the dose of an SSRI is too high or if it is combined with lithium or L-tryptophan, both drugs that increase the functional amounts of serotonin in the system. In its milder form it is treated by drug discontinuation; in its more severe forms it is a medical emergency and needs symptomatic treatment often in an intensive-care unit.

8.17 What are cholinergic rebound effects?
These are symptoms of mild anxiety, restlessness, possible insomnia with nightmares, tiredness, dizziness and headaches. There might be nausea and vomiting. These symptoms are generally short lived and, when caused by the withdrawal of antidepressants, are at the mild end of the spectrum.

**BOX 8.2 The serotonin syndrome**

**Neurological symptoms:** myoclonus, nystagmus, headache, tremor, rigidity, seizures

**Mental state changes:** irritability, confusion, agitation, coma

**Other symptoms:** hyperpyrexia, cardiac arrhythmias, death
8.18 Do some drugs cause symptoms even after they have been discontinued?

Once a drug has left the body, and the body has readjusted by homeostasis, then all effects caused by the antidepressant should be over. The obvious exception is when some permanent damage is done by a side-effect, such as agranulocytosis or hepatic necrosis or some other dramatic drug-specific effect. Some patients complain of long-term withdrawal effects lasting several months and years, especially following the use of benzodiazepine tranquillizers. In my experience this is more a function of a return of the underlying illness rather than a prolonged withdrawal reaction or specific side-effect caused by a drug.

8.19 Can bupropion, the anti-smoking drug, be prescribed to a patient who is already taking antidepressants?

This should only be done cautiously, because of the risk of causing epileptiform convulsions. Antidepressants lower the threshold for seizures, and two will do so more than one. It is a rare problem. On the other hand adding bupropion to another antidepressant is a known treatment for resistant depression and may actually enhance the therapeutic effect.

8.20 How can I help patients deal with the stigma of taking antidepressants?

Sadly there is a stigma both about being depressed and having mental illness in general and secondly about the consequential need for antidepressant medication. The first stigma to deal with is that of mental illness. The Royal College of Psychiatrists is currently running a 5-year campaign entitled ‘Changing Minds: Every Family in the Land’ dealing with precisely this issue. Information is available from them and of course their website (www.rcpsych.ac.uk). It is helpful for patients to know that they are not alone in their affliction. An explanation that maybe one in ten people will suffer depression at some time in their lives goes some way to make patients realize they are not unique. Getting in touch with self-help groups and providing patients with helpful user-friendly information sheets is a useful route. The most helpful factor is allowing the patients to realize that someone close to them, possibly at work, has also suffered from depression and recovered. Helping patients realize that their depression is not a sign of weakness, failure or inadequacy is important, although these are precisely the emotions that their depression will conjure up.

Some patients feel that it is the taking of the antidepressant itself that is in some way stigmatizing. Having to stand in a pharmacy and admit to yourself and to others that you are depressed and in some way inadequate is something people do not like doing. Patients then translate their anxiety
about taking antidepressants into fears of addiction, dependency and the belief that they have no willpower and need to resort to external means to overcome their problem. Ultimately, reassurance, patience and encouragement constitute the essential support needed in helping people deal with their anxieties.

**TRICYCLIC ANTIDEPRESSANTS (TCAS)**

### 8.21 How do TCAs work, and are they effective?

The leading theory to explain the biological basis of depression has been the monoamine hypothesis. According to this, depression is due to or mediated by a deficiency in one or another of three biogenic monoamine neurotransmitters: serotonin, noradrenaline (norepinephrine) or dopamine. Tricyclic antidepressants act by increasing the functional amount of these monoamines in the synaptic cleft by blocking their reuptake once they have
been released (see Fig. 8.1). There may then be a postsynaptic down-regulation, which is probably the next step in antidepressant action.

Tricyclics are the traditional antidepressants and are as effective as any other, giving an overall efficacy of about 70% as opposed to about 30% for placebo (by whatever means this is measured).

8.22 Are they more or less effective than other antidepressants, particularly the SSRIs?

In general in head-to-head clinical trials they are as effective as SSRIs. There are some suggestions that clomipramine may perhaps be slightly more powerful, but this is not a consistent finding. How this then translates into everyday clinical practice is a more complicated question. Because some of the older antidepressants have side-effects and need dosage titration and multiple dosings, they are more complicated to give and there is greater room for patients to have subtherapeutic doses or to manifest poor compliance. On that basis they may ultimately be less effective than the more palatable, easier to administer, newer antidepressants.

8.23 Why are TCAs so dangerous in overdose?

Tricyclics are for the most part ‘dirty drugs’, having actions on many different neuronal systems and pathways beyond the primary amine-reuptake-blocking action. In overdose, these secondary pharmacological actions become important, the most important being the quinidine-like action upon the heart that can result in ventricular arrhythmias and other cardiac complications. The anticholinergic action can be excitatory to the heart, there is some alpha-blockade resulting in hypotension, and the antihistamine action can potentiate other sedatives, especially alcohol, resulting in deeper comas and complications associated with that. Some antidepressants are epileptogenic, and this can result in fits especially in susceptible individuals.

8.24 Are TCAs effective in treating both depression and anxiety?

Yes. To what degree this is a function of the sedative actions or their specific neurotransmitter profile is uncertain. The antidepressants which markedly block serotonin reuptake, such as clomipramine, have demonstrated efficacy in the treatment of obsessive compulsive disorder. They also appear to be effective in phobic states and bulimia. Imipramine has been demonstrated to be effective in panic disorders, although the dosage necessary can be quite low. Tricyclic antidepressants and the newer classes
of antidepressants are effective in treating a broad spectrum of mood disorders and allied conditions.

8.25 What are the major side-effects encountered by the patient taking TCAs?

The common anticholinergic side-effects are a dry mouth, constipation, urinary retention and impotence. Sweating, blurred vision, confusion, problems with narrow-angle glaucoma, and cardiovascular side-effects – tachycardia, arrhythmias, postural hypotension and syncope, cardiomyopathy, cardiac failure and ECG changes – are rare but serious. Other side-effects include seizures, tremor, weight gain and, rarely, agranulocytosis.

The side-effects are primarily the result of unwanted actions on physiological systems unrelated to the treatment of depression, namely anticholinergic actions, alpha-blocking actions, quinidine-like actions and antihistamine effects (Box 8.3). In addition there are the idiosyncratic effects.

8.26 What are the toxic effects encountered in overdose?

Toxic effects are cardiac arrhythmias, cardiac arrest, ECG changes (Fig. 8.2), prolongation of QT interval, postural hypotension, epileptic seizures, hyperreflexia, mydriasis, coma and death.

The major effects in overdose are caused by the atropine-like effects, neurological effects and cardiovascular effects. In addition there is the sedation caused by the antihistamine function.

The important features and potentially fatal effects are cardiac arrhythmias and conduction defects – an important diagnostic feature distinguishing tricyclic overdoses from others. This can lead to ventricular fibrillation and cardiac arrest. There can be hypertension followed by hypotension. Epileptic seizures and hyperpyrexia can occur. Sedation and seizures can result in inhalation pneumonitis, another potential cause of death. There is often a delay of some days before the fatal arrhythmias

**BOX 8.3 Unwanted effects of TCAs at secondary sites of pharmacological action**

- **Antihistamine H1** – weight gain, drowsiness
- **Anticholinergic** – constipation, blurred vision, dry mouth, drowsiness, urinary retention, glaucoma, confusion – especially in the elderly, potency problems
- **Quinidine** – cardiac arrhythmias
- **Alpha-1** – hypotension, dizziness, drowsiness
- **Non-specific** – epileptiform convulsions, agranulocytosis (rare)
become manifest, so it may be dangerous to discharge the patient too soon following an overdose.

8.27 How many deaths are caused by TCA overdoses per year in the UK?
Before the widespread introduction of the more modern and safer antidepressants, approximately one person per day on average died of antidepressant overdose (350 per year). This has to be seen in the context of about 1330 deaths annually as a result of self-poisoning and approximately 6000 suicides annually. Nevertheless the National Suicide Prevention Strategy for England recommends the promotion of safer prescribing of antidepressants to help combat the current epidemic of suicide. About 5% of suicides were caused by tricyclic antidepressants, a notable figure in an identifiable high-risk group (see Fig. 8.3). Tricyclic overdoses are of course often taken in combination with other drugs which complicate the picture considerably.

8.28 Why are TCAs used to treat neuralgia and chronic pain in the absence of depression?
Tricyclic antidepressants have an enhancing effect on the descending bulbo-spinal 5HT-mediated analgesic pathway to the dorsal horn. Thus theoretically they have an analgesic action independent of any antidepressant effect. An analgesic effect of amitriptyline has been shown...
convincingly in some neuropathic pains, notably post-herpetic neuralgia. The SSRIs are less effective. The doses of amitriptyline used are usually far below what would be an effective antidepressant dose. There may be some benefit from the mild sedation or anxiolytic action also. There may also be a strong placebo effect. Antidepressants also have an effect on migraine headaches by blocking the uptake of 5HT into the cerebral blood vessels, which is so important in the causation of migraine, as well as the specific action on the 5HT_{1D} receptor.

8.29 I believe that dosulepin is the most widely prescribed TCA. Why is this?

SSRIs are certainly the most widely prescribed antidepressants when initiating new treatment, but tricyclics remain widely prescribed in patients who are established on long-term treatment and who are happy with it. Indeed patients should not be switched from one medication to another if there is no problem. ‘If it ain’t bust, don’t fix it’. Tricyclics are also widely used by pain specialists.

8.30 Is trazodone different from other TCAs, and when is it most useful?

Trazodone is not a tricyclic. It has a ‘unique structure’ and mode of action, being mainly a 5HT_{2} antagonist as well as performing as an uptake inhibitor.
It is low in cardiotoxicity and anticholinergic side-effects, but produces a higher incidence of drowsiness because of its antihistamine properties and causes nausea. On that basis it is useful for agitated depression and also in patients with insomnia because of its sedative qualities.

8.31 Are the second-generation TCAs, e.g. lofepramine and dosulepin, any different from amitriptyline?

Lofepramine is a tricyclic similar to imipramine but with a more favourable side-effect profile. It appears to be uniquely safe in overdose and has less in the way of cholinergic cardiovascular side-effects. It is mainly a noradrenergic reuptake inhibitor and therefore is categorized as an SNRI (selective serotonin–noradrenergic reuptake inhibitor). Dosulepin (dothiepin) is an analogue of amitriptyline. It is generally lower on side-effects but reputed to be more lethal in overdose.

8.32 Is lofepramine recommended for any particular type of depression?

Yes, it is particularly useful in the elderly where cardiac side-effects and hypotension may be an issue, and also in potentially suicidal patients. It is less good for agitated patients. It has a slightly stimulating action. The advantages are that it can be titrated upwards from 70 mg to the full dose of 210 mg or even more if necessary.

8.33 For whom is mianserin suitable, and are any special precautions necessary?

Mianserin was generally safe in overdose and somewhat sedative, but the need for a full blood count every month made it too cumbersome to give, and it has been withdrawn. Mirtazapine is effectively a newer, safer version which has superseded mianserin.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

8.34 How do MAOIs work?

The classical MAOIs phenelzine, tranylcypromine and iproniazid work by inhibiting the enzyme inside neurones that breaks down amine neurotransmitters after they have been reabsorbed from the synapse (see Fig. 8.1). By doing this they increase the amount of other antidepressants available for release. This action is generally different from that of tricyclics, which block the reuptake of neurotransmitters from the synapse or block the presynaptic receptors which stimulate the release of neurotransmitters. MAOIs tend to work on all of the amine neurotransmitters: serotonin, noradrenaline and dopamine. The newer, reversible inhibitors of monoamine oxidase-A (RIMAs), supposedly act in a similar way, but do
not have the same risk of drug interaction and the cheese effect, since they
do not inhibit the MAO in the bowel and are reversible.

8.35 Are they effective antidepressants, and when should they be used?
In general MAOIs are seen as less effective than the standard tricyclic-type
reuptake inhibitors. The view is that they are more suitable for ‘atypical
depression’ where anxiety and phobic anxiety, obsessional and hysterical
symptoms are more prominent. They can be used in resistant depression
when other antidepressants have been tried and failed. They are often useful
in chronic anxiety disorders where depression is a lesser feature. There was
a vogue for combining phenelzine with amitriptyline, trimipramine or
dosulepin (dothiepin) as a treatment for resistant depression. In general,
however, partly because they are no longer being marketed and partly
because of the almost unacceptable side-effect profile, mostly to do with the
highly dangerous ‘cheese reaction’ or hypertensive crisis in combination
with other drugs, they have virtually stopped being used outside of the
hands of specialists experienced in their use.

The newer generation of RIMAs would appear to be very much safer,
but sadly in my experience moclobemide, the only commercially available
RIMA, is not very effective, despite the published evidence to the contrary.

8.36 What are the main drug and food interactions with this group?
The main drug interaction is with tyramine, which is present in protein and
is released when the protein decomposes. This is found in cheese
(decomposed milk), hung game (decomposed meat), Marmite
(decomposed yeast), and a whole host of other exotic foods (see Box 8.4).
Although the list is exhaustive and frightening, most patients find it
relatively easy to deal with the dietary restrictions, which are really quite
straightforward. Sympathomimetic amines are also to be discouraged, as
should other amines such as phenylethylamine (present in chocolate).
MAOIs interfere with the metabolism of pethidine, and on that basis this
drug should not be given. There is a dramatic and highly dangerous
interaction with antidepressants, especially SSRIs, which are quite likely to
result in the fatal hypertensive and hyperpyrexial ‘serotonin syndrome’
(see Q. 8.16).

8.37 What advice should be given to patients starting MAOI
treatment?
Patients should be warned of the dietary restrictions in detail and given a
dietary warning card, which if not available immediately can be added to
the prescription and supplied by the pharmacist. The risks to patients are
very small providing they obey the dietary restrictions, which really come
down to avoiding cheese and Marmite. They are also a function of how much tyramine-containing food they eat, and not all patients get bad reactions. An occasional glass of white wine or two does not appear to be harmful, only heavy red wines (which are made from the whole grape, including the skin). Drug combinations should be avoided. If patients experience really bad headaches then they should go to the local casualty department or GP surgery immediately and have their blood pressure checked as a matter of urgency. Chlorpromazine 50 mg is a good alpha-blocker for immediate help in lowering the blood pressure, before giving more-intensive hypotensive treatments if needed.

8.38 I find the drug and food interactions with MAOIs rather daunting; hence should I prescribe them? Am I denying my patients a useful treatment or should this group of drugs only be initiated by psychiatrists?

They should only be initiated by doctors experienced in giving them. In experienced hands they are not a big problem. In my view they are often very effective in the properly selected patients where other treatments seem

**BOX 8.4 Monoamine oxidase inhibitors – important potential dietary and drug interactions**

**Dietary**
- Cheese
- Bovril/Oxo/Marmite
- Pickled herring
- Broad bean pods
- Food going 'off', e.g. offal/game/fish
- Alcohol, especially Chianti or fortified wines

**Drugs**
- Sympathomimetics (as in nasal decongestants)
- Tricyclics (e.g. clomipramine) and SSRIs
- Amphetamines
- Fenfluramine
- L-dopa/dopamine
- Pethidine
- Barbiturates

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*An early warning symptom is a throbbing headache indicating a potential, severe rise in blood pressure. The wide range of possible interactions means that practitioners should always check in the *British National Formulary* and warn patients as to what they eat and the risks of other medications (e.g. anaesthetics).*
not to work as well; some patients are probably being denied useful
treatment when other treatments have failed. Because of their side-effect
profile I would only see them as ‘third-line treatments’ after other avenues
have been exhausted. If they do prove effective, patients often need to stay
on them indefinitely, and sometimes tolerance occurs and the dose needs to
be increased in time. Occasional drug holidays are needed to let the
tolerance wear off and the patient to start at a more modest dose again.

8.39 What are the problems encountered when changing a patient’s
medication from an MAOI to another antidepressant or vice versa?

Important considerations in this regard are discussed in Qs 8.13
and 8.14.

8.40 I have come across patients who have been prescribed MAOIs
as well as TCAs – surely this is rather dangerous?

This treatment – starting a patient on a TCA and an MAOI together and
slowly increasing the dose – in experienced hands is regarded by some as
more effective than either treatment on its own. If anything, combining
tricyclics with MAOIs protects against the cheese reaction. Provided that a
sedative tricyclic and not an SSRI or imipramine is used, and ideally
phenelzine is the MAOI, then the risks are relatively low. NB: Adding a
TCA in a patient who is already on an MAOI is potentially fatal.

8.41 What are RIMAs and how do they differ from conventional
MAOIs?

There is only one commercially available RIMA: moclobemide. RIMAs
differ from traditional MAOIs in being selective for MAO(A) and also being
immediately reversible and competitive with tyramine; by contrast,
traditional MAOIs inhibit MAO(A) and MAO(B) for a period of weeks,
and, when the drug is stopped, the enzyme levels take time to be restored.
MAO(A) is the enzyme involved in the breakdown of neurotransmitters in
the neurones and the one important for the treatment of depression.
MAO(B) is found in the liver and gut wall, where it normally is protective
and prevents the influx of tyramine into the systemic circulation where it
can cause hypertensive problems. RIMAs do not affect the gut and liver
MAO(B), which can still act in its protective function against the tyramine,
but inhibit the neuronal MAO(A).

In addition the action of MAO(A) on the enzymes that metabolize
neurotransmitters is competitive. And so if a competitor is present it stops
the action of moclobemide immediately. Selegiline is a selective MAO(B) inhibitor used in the treatment of parkinsonism.

8.42 When should RIMAs be used, and are they as effective as conventional MAOIs?
RIMAs are generally not to be compared directly with conventional MAOIs but to antidepressants generally (according to the manufacturers). Although the research data suggest they are as effective as standard antidepressants, the overall impression is that they are not. They appear to be very low in side-effects, and on that basis can be used in patients who are intolerant to other antidepressants. Generally the dose needs to be increased to the upper limit of the range before any real efficacy is noted. Moclobemide is indicated for the treatment of social phobia. It is also useful in the elderly who are less able to tolerate side-effects of other antidepressants. RIMAs would appear to be less powerful as anxiolytics than conventional MAOIs.

8.43 Are RIMAs any safer in overdose or in interaction with conventional MAOIs?
The answer is yes. They are relatively safe in overdose and because they are displaced by tyramine and other amines from the enzyme systems, when challenged by hazardous amines they are removed from the system and therefore tend not to interact with other drugs.

8.44 Is it easier to change a patient’s treatment from or to a RIMA than from or to an MAOI?
Yes, although the same cautions should apply. It should not be necessary, as it is for a conventional MAOI, to wait for 2 weeks after stopping a RIMA to allow the enzymes to recover – a few days should be sufficient. Adding a tricyclic to a RIMA needs 24 hours free of the RIMA. Adding a RIMA to a tricyclic is probably not hazardous, but caution dictates a gap of about 48 hours before gradually introducing the RIMA.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

8.45 How does this group of antidepressants work?
They work in the same way that other antidepressants work: by increasing functional amounts of serotonin (5HT), one of the principal neurotransmitters involved in mood regulation, in the brain. They differ from other antidepressants in effectively only boosting levels of serotonin and not other neurotransmitters, many of which are responsible for side-effects. They are therefore ‘cleaner’ and more specific than other antidepressants.
8.46 When should they be used?

They are currently the medication of first choice in the treatment of depression. They have superseded the tricyclic antidepressants because of their greater tolerability and therefore ease of administration, enabling patients to get to a therapeutic dose without the need to titrate it upwards. They are generally not sedative, which can be troublesome for some patients. They lack the quinidine-like and anticholinergic effects of tricyclics, which can cause problems in those with cardiovascular disease, glaucoma and bladder problems, especially in the elderly. They are safer in overdose. Like tricyclics, many have a broad spectrum of therapeutic activity, including diagnoses such as panic disorder, OCD, bulimia and prevention of relapse of depression. They also have efficacy in the premenstrual syndrome – where they appear to have a different mode of action, as they work within a few days of being taken. Not all SSRIs have the same spectrum of licensed indications.

The suggestion that some TCAs, such as clomipramine, may be more effective than SSRIs is a possibility but relatively unimportant in normal clinical practice.

8.47 Are they (a) more effective and (b) safer in overdose than the older TCAs?

Although SSRIs are no more effective than TCAs in clinical trials, in clinical practice it is easier to get patients onto full therapeutic doses of an SSRI because there is no need to titrate the dose up, or if titration is desirable then there are fewer steps necessary to achieve a full therapeutic dose. Also patients are more likely to comply with the full dose because of a relative lack of side-effects, and on that basis they should prove more effective because patients are more likely to take them appropriately. SSRIs are of course much safer than tricyclics in overdose because they lack the sedative and quinidine-like adrenergic stimulating effects which can be cardiotoxic.

8.48 What are the main side-effects of this group of drugs?

Headaches, GI side-effects and sexual dysfunction are the main adverse effects. Although they lack the sedative and anticholinergic side-effects of tricyclics, the most prominent and troublesome side-effects are headache and nausea, which can occur in the first few days of treatment. They may occasionally be so severe as to result in discontinuation of treatment. Another troublesome side-effect occurring in the first 24 hours of treatment is an increase in anxiety symptoms, which again can stop treatment. This is best overcome by a gradual upward titration of the dose, warning the patient it may occur, and possibly covering the first day or so of treatment
with a few benzodiazepine tablets. Sexual dysfunction is a problem in prolonged use. Whereas this may not be an issue while treating an acute depressive episode, it becomes a serious issue while keeping people well long-term on prophylactic treatment. Sexual dysfunction (anorgasmia, reduced arousal and lack of libido) is a dose-related effect and can be minimized by titrating the dose down. It appears to be a specific SSRI effect and may be less of a problem with non-SSRI antidepressants. (See also Chapter 7.)

8.49 What was the first SSRI to be used in the UK, and did it have any particular beneficial or adverse effects?

Zimeledine (Zelmid) was the first SSRI, introduced in 1981. It was withdrawn shortly after its introduction because of a rare but serious Guillain–Barré type syndrome. The next to be introduced was fluoxetine (Prozac) in the late 1980s. At the time it was revolutionary in its selectivity and specificity. One of its characteristics was its very long half-life. It is possible that the dose at which it was introduced was too high. On that basis it probably resulted in effective doses even if the patient missed one or two capsules every week, thus improving compliance and efficacy. The problem was that, if one wanted to switch from Prozac to another antidepressant, there had to be a long washout period. It turns out, however, that the long half-life appears to be protective against withdrawal reactions. Prozac was the legendary forerunner of the other SSRIs, primarily because it caught the public imagination in America, which had been very much behind the UK in the introduction of more-modern antidepressants. With the Americans’ love of new things and with skilful marketing, it achieved a phenomenal breakthrough and cult status early on.

8.50 Introduced in the UK in 1989, fluoxetine (Prozac) is the best-known drug in this group. What are its main advantages and disadvantages?

Fluoxetine is simple to take. One capsule a day should suffice, and missing the odd dose may not affect the therapeutic outcome. It is relatively low on side-effects and is generally not sedating. It may even have a mild stimulating effect due to an amphetamine-like action. The main disadvantage is that some patients experience GI side-effects.

Prozac has become a victim of its own success, and this success has brought claims of harm made by the ‘Victims of Prozac’ who allege that fluoxetine can drive them into violent, suicidal and homicidal acts. I do not believe these claims to be founded in reality, but they have entered into popular mythology. The myth has now spread to paroxetine.
8.51 Some people have been on Prozac for many years – indeed someone has written a book about their experiences on the drug. Does this mean that we should be wary of prescribing it because it is hard to come off, or do some people need lifelong treatment for their depression?

Several books have been written about Prozac (see Box 8.5). Prozac reached cult status not only as a lifestyle-enhancing drug and happiness pill, but also as an example of how pharmaceutical companies would manipulate our minds and beliefs for profit. The general view is that depressive illnesses are relatively long-term conditions with an average duration of about 18 months per cycle (Fig. 8.4). Therefore treating a single episode for a few weeks and then stopping the drug is associated with a strong risk of early relapse. From a psychiatric point of view we usually encourage patients to take the antidepressant for as long as possible. Beyond the statistical risk that long-term antidepressant consumption reduces the risk of relapse by about five-fold, there is also the less clear issue of ‘kindling’, where every depressive relapse makes it more likely that there will be further episodes. If this is true then there is a strong case for treating depression vigorously and long term rather than the somewhat haphazard approach we adopt today. Also there is a lot to be said for allowing patients to get used to the experience of feeling well rather than being right on the edge of a recurrence of depressive symptoms. This has a psychological benefit. Being well also allows patients to deal with the therapeutic issues surrounding their illnesses either through formal therapy or through living a healthy lifestyle. On that basis I take the view that it is good to take antidepressants for somewhat longer than is absolutely necessary rather than for too short a time.

BOX 8.5 Some books written about Prozac
- Prozac Nation
- Potatoes not Prozac
- Listening to Prozac
- Plato not Prozac
- Better than Prozac
- Prozac Backlash
- Prozac Diary
- Prozac: Panacea or Pandora
- Prozac on the Couch
- Natural Prozac
- Beyond Prozac
The issue of whether SSRIs are ‘addictive’ has recently been raised. Addiction is a dramatic word used when people take substances against medical advice and to their ultimate detriment. This is not the case with antidepressants. Some patients may experience withdrawal symptoms, and there may be some small element of physiological dependency. This can be overcome by gradually tailing off the dose over a couple of weeks. Some patients become dependent upon the idea of feeling well. Some patients need lifelong treatment for their depression, others become reliant upon the use of a pill, which is probably not therapeutically indicated. As with all powerful treatments, the risks and benefits need to be evaluated, especially if consigning someone to a long-term treatment that has cost and health implications. There may be a case for seeking a specialist opinion if there are concerns about long-term use.

8.52 Some SSRIs are easier to stop than others. Why is this so? How should SSRIs be withdrawn at the end of the treatment period?

SSRIs with short half-lives appear to cause more withdrawal reactions than do longer-acting ones. Most notably paroxetine has been tarred with the withdrawal reaction label. Fluoxetine, with its long half-life, seems not to have this problem. The way to overcome withdrawal problems is to cut down the dose gradually, by reducing the dose to half a tablet daily and thereafter half on alternate days over a 2-week period. If withdrawal reactions are really a problem there may be a case for switching to fluoxetine first (because of its long half-life) and then gradually
withdrawing, or switching to the liquid form of the SSRI and titrating the
dose downwards in more gradual steps. The patient should be warned that
any symptoms experienced will be transient and will be at their maximum
in the day or two after stopping medication. They are not an indication that
the patient is about to relapse.

8.53 What are the main advantages and disadvantages of sertraline?
Sertraline came in 50 mg tablets, and the initial recommendation was not to
increase the dose beyond 150 mg. More recently dose increases have been
allowed up to 200 mg. As well as being indicated for the treatment of
depression, including associated anxiety, it has the additional licensed
indication for the treatment of OCD in adults and children. It is also
licensed for the treatment of PTSD in women but, interestingly, not men. It
is generally well tolerated by patients, low on side-effects and suitable for
patients who have had recent cardiac disease or strokes. There is little
interaction with other drugs. The disadvantage is an uncertain dose range.
There remains debate as to whether all the SSRIs are essentially the same, or
whether there are distinct differences between them. There is evidence that,
if one SSRI does not work, 20% of patients will respond to the prescription
of a different SSRI, and so they may not all be quite the same after all.
Whether this relates to differential effects on the subclass of serotonin
receptors or some other reason is unknown. (See also Table 8.1.)

8.54 I had a patient who only felt well on 200 mg of sertraline a day,
yet I believe that this dose is not licensed for long-term use.
Have you any comment to make on this?
It is well known that some patients only respond to higher doses of anti-
depressants. Sertraline was only licensed for short-term use at higher doses,
although that licence has now been changed and 200 mg is quite acceptable
even for long-term use if clinically indicated. It is very common for
treatments to be used outside their licensed indications in psychiatric
practice. Licensing is about commercial and regulatory issues, but many
patients do not fit into neat categories in their clinical needs and therapeutic
responses.

8.55 The most recent SSRI to be introduced has been citalopram.
Does it have any particular advantages over other, older SSRIs?
Citalopram is clean and effective and used in cases where there is the
potential for drug interactions. Citalopram is metabolized by a different set
of enzymes of the cytochrome system (the enzyme system involved in drug
metabolism). There is therefore less potential for drug interactions with
citalopram than with other antidepressants, which may saturate the
enzymes and impede their ability to deal with both drugs at the same
time. The more recent version of citalopram (escitalopram) has recently been launched. This is the L-form of the racemic mixture of citalopram, which is the pharmacologically active component of the mixture. On that basis it is a purified form of citalopram. Trials data suggest it is slightly more effective than the older citalopram, but this is probably of limited clinical relevance.

8.56 What are dual-action SSRIs, and how do they work?

Dual-action SSRIs work by not only blocking the reuptake of serotonin at the synaptic cleft but also by blocking presynaptic 5HT_2 receptors, thereby enhancing 5HT transmission. For example, mirtazapine blocks 5HT_2 and enhances 5HT transmission in that way. These drugs appear to have less in the way of the ‘fierce’ 5HT_2 side-effects such as nausea and headache (see Box 8.6). Whether this translates into any relevant clinical advantage or not is open to speculation.

**BOX 8.6 Effects of stimulation of key 5HT receptor subtypes**

**Presynaptic 5HT_{1A}**  
Classic SSRI antidepressant effects  
- anti-anxiety  
- anti-panic  
- anti-OCD  
- anti-appetite

**5HT_2**  
Classic SSRI side-effects  
- agitation  
- akathisia  
- anxiety  
- panic attacks  
- insomnia  
- sexual dysfunction

**5HT_{1D}**  
Anti-migraine

**5HT_3**  
Nausea  
Diarrhoea  
Headaches  
(Noradrenaline)  
Controls release of 5HT
8.57 Is there any advantage in prescribing nefazodone, a dual-action SSRI?
Nefazodone has recently been withdrawn in the UK, primarily because no one was prescribing it. Nefazodone had a presynaptic 5HT₂ blocking action, enhancing 5HT transmission, as well as being a 5HT reuptake inhibitor. Its reduced side-effect profile gave it unique qualities, namely a lack of sexual impairment and an enhancement of natural sleep. Unfortunately it was a relatively weak antidepressant requiring large doses for an effective therapeutic action, and the doses had to be titrated up. It was never a commercial success, probably because it was not a very good antidepressant despite its complex pharmacology.

8.58 What are SNRIs, and what are their advantages?
SNRIs are selective serotonin–noradrenergic reuptake inhibitors. They act on a different neurotransmitter system to the SSRIs. They boost levels of noradrenaline, as opposed to serotonin, in the synaptic cleft. They may therefore be effective in specific forms of depression where SSRIs are less effective, although the case for that is not very compelling. They do have a different spectrum of side-effects. Sexual impairment is less of an issue, and they appear to be more energizing.

8.59 What are NaSSAs, and when are they useful?
They are noradrenergic and specific serotonergic antidepressants. An example is mirtazapine, with its complex actions as an α₂ antagonist with potent HT₂-, HT₃- and antihistamine-antagonist properties. The main difference between this and other antidepressants is again in the side-effect profile. Mirtazapine is notably sedative and promotes a healthy appetite and weight gain. These effects may be advantages or disadvantages. It is otherwise an effective antidepressant.

8.60 Reboxetine is a noradrenaline reuptake inhibitor. What advantage does that offer over the older SSRIs?
The main difference is that it boosts noradrenaline in preference to other neurotransmitters. This may then translate into a different spectrum of activity for different subclasses of depression. Sadly, despite 30 years of research, there is little to suggest that particular types of depression are responsive to different types of antidepressant, and, on that basis, finding the right antidepressant for the individual patient remains a matter of trial and error. There is some evidence that reboxetine is more effective than other antidepressants, but again whether this is clinically relevant or not is open to speculation. Overall it is good to have a spectrum of pharmacological activities that at least allows the clinician to try a different class of
antidepressant if there is a lack of response to the drug of first choice. For example, if an SSRI does not work there is a strong case for switching to a different class of antidepressant. Some patients are particularly intolerant to the SSRI side-effects such as sexual dysfunction, anxiety or GI side-effects, in which case switching to a different class of antidepressant would be a sensible strategy, as these side-effects appear to be specific SSRI effects.

8.61 I have found paroxetine to be a very effective drug to use, though a few patients have been unable to tolerate its side-effects. One woman, in particular, had severe night sweats. Is that common?

Paroxetine was a market leader for SSRIs in the UK for many years and as widely used as fluoxetine. All drugs have side-effects, and the sweating you describe (in which the patient had to change the sheets and her nightdress in the middle of the night) would appear to be an unusual side-effect although well documented. Some 5% of patients will complain of some lesser but unacceptable side-effects to any of the SSRIs.

8.62 Some patients have found paroxetine rather difficult to stop taking. Why is this, and how can the problem be avoided?

The issue of SSRI withdrawal effects is something that has been highlighted in the media, although withdrawal symptoms have been reported on stopping most antidepressants. Interestingly, withdrawal effects have supplanted the issue of suicidality and aggression with fluoxetine, and we now talk about withdrawal effects and dependency on paroxetine. Whereas withdrawal effects do undoubtedly occur, their true clinical impact is less certain. Like all powerful drugs, they should not be stopped suddenly but tailed off gradually over a matter of a few days to minimize withdrawal effects. If that fails the liquid form of paroxetine could be used and the patient could then titrate themselves down gradually over a matter of a few weeks using a syringe to measure out doses decreasing by, say, 1 mg per day.

8.63 I believe that paroxetine is no longer recommended for the treatment of depressive illness in children and adolescents. Why is that?

New data have shown no benefit in the treatment of depression compared with placebo in those aged less than 18 years and an increase in the rate of reporting of suicidal thoughts and behaviour while on treatment. On that basis it should not be prescribed as new therapy for under-18-year-olds. For patients successfully being treated with paroxetine, completion of the course is acceptable. If the treatment is not effective it should be changed.
8.64 **Is paroxetine the only drug to cease to be recommended for treatment of depression in this age group?**

No, venlafaxine is also no longer recommended for the treatment of depression in children and adolescents. No other SSRI or SNRI is licensed for the treatment of children or adolescents aged less than 18 years.

8.65 **Which antidepressants are licensed for the treatment of depression in children and adolescents?**

No antidepressant is currently licensed for this use. Having said that, major depression is a very serious illness in children, and doctors may prescribe an antidepressant because it is the necessary treatment. They may prescribe a medicine off-licence if it is considered to be in the best interests of the patient. Non-licensed prescribing is quite widespread in psychiatric practice, as licensing requirements and clinical trials are increasingly becoming divorced from the practical realities of clinical practice. The Committee on Safety of Medicines (CSM) have set up an expert group to review the situation.

8.66 **How many people receive paroxetine treatment?**

Approximately 4 million prescriptions were issued for paroxetine in the UK in 2002, of which possibly 7–8000 were for patients under the age of 18. It was the market leader, with annual sales of about £100M. Venlafaxine will soon overtake it as the market leader.

8.67 **What is the problem with paroxetine?**

Paroxetine is a highly effective antidepressant that is used in many countries worldwide. Concern has recently been voiced over any possible association between SSRIs and suicidal behaviour, and some anecdotal evidence was screened in a TV documentary. The CSM formally reviewed this question in December 2001 and found that there was insufficient evidence to confirm a causal association between SSRIs and suicidal behaviour, though an effect in a small high-risk population could not be ruled out.

Despite the scare stories in the press, there have been no court cases where paroxetine or other antidepressants have been shown to cause or release aggression. The more obvious answer is that depression is a condition associated with a high risk of suicide. Many depressed patients are given an antidepressant and then make a suicide attempt which they would have made anyway. Alcohol, a drug well known to disinhibit people, is often taken concurrently.
8.68 Lithium is best known as a treatment for bipolar affective disorder. Does it have a role in the treatment of depression?

Lithium is not in itself an antidepressant but does have the recognized action of ‘boosting’ the effects of other antidepressants when patients fail to respond to standard antidepressant treatments. As a treatment for resistant depression, there is a good case for adding a modest dose of lithium (Priadel 400 mg daily) to an antidepressant. This is likely to give a further 10–20% improvement in patients who have not responded properly and will make a few patients respond completely who have not previously responded. Lithium enhancement is probably one of the first-line treatments for resistant depression (see Chapter 11). The risk is that patients will develop the serotonin syndrome and become overstimulated, with anxiety, movement disorders and other strange symptoms. If this occurs the lithium should be stopped as a matter of urgency.

The other major use for lithium is as a prophylactic against relapse in both bipolar and unipolar depression, although antidepressants are probably more widely used for relapse prevention for unipolar depression (Table 8.2). The third use for lithium is in depressed patients who are at risk of being triggered into a manic episode by antidepressants but who need treatment because of their depression. Giving lithium at the same time as an antidepressant will reduce the risk of triggering a ‘high’ in these patients.

### TABLE 8.2 Long-term prophylaxis against relapse of depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclics</td>
<td>Tried and tested</td>
<td>Side-effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May precipitate mania</td>
</tr>
<tr>
<td>Modern anti-</td>
<td>Efficacy and long-term</td>
<td>Cost</td>
</tr>
<tr>
<td>depressants</td>
<td>safety data available</td>
<td>May precipitate mania</td>
</tr>
<tr>
<td></td>
<td>Greater tolerability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often one tablet per day</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Tried and tested formula</td>
<td>Not antidepressant</td>
</tr>
<tr>
<td></td>
<td>Effective</td>
<td>Side-effects can occur</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needs monitoring of blood level</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Efficacy data emerging</td>
<td>Toxic to thyroid and kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side-effects may be a problem</td>
</tr>
</tbody>
</table>
8.69 How does lithium work?

It works by stabilizing the cell membranes and enhancing 5HT effects on the brain. It competes with sodium for a cell membrane carrier site. It reduces the supersensitivity of dopamine receptors and increases the turnover and reuptake of noradrenaline into cells. In truth, we do not really know how lithium works.

8.70 What are its adverse effects?

Lithium side-effects are listed in Box 8.7. Lithium gives rise to GI effects, tremor, feelings of muscle weakness, and polyuria and polydipsia (nephrogenic diabetes insipidus). Lithium is pharmacologically a ‘bad drug’ insofar as the effective dose is not far removed from the toxic dose, and it therefore needs careful blood level monitoring to maintain a plasma concentration of 0.5–0.8 mmol/L. At doses in excess of 2 mmol/L, there is the risk of serious toxicity, with neurological side-effects, coma and convulsions.

The one common serious side-effect is hypothyroidism, which can develop after a modest exposure in a significant proportion of patients (say 10%). Once it has developed, stopping lithium treatment does not necessarily result in recovery, although the first line of treatment would be to stop the lithium if clinically possible. It may be necessary to give replacement thyroxine long-term. It is therefore important to monitor thyroid function before treatment starts and at regular, say 6-monthly, reviews because hypothyroidism develops gradually and the first sign of abnormality may be an increasing level of thyroid-stimulating hormone. It may be possible to stop the process before it becomes too advanced. A different mood stabilizer might be indicated.

The other issue of concern is renal damage. Whereas polydipsia and polyuria are common occurrences, they are not in themselves dangerous. Interstitial nephritis, which could lead to renal failure, was something that caused concern in the past but is probably no more likely on lithium than without it. Again, it is usual to test for renal function every 6 months.

8.71 What precautions should be taken when prescribing and monitoring lithium treatment?

Lithium is generally contraindicated in pregnancy because of a risk of significant harm to the fetus (mainly cardiac effects), although again the risks and benefits of treatment need to be balanced. Ideally the patient should be assessed and advised by someone with experience in these matters since overall the risks are small but the impact is great if problems occur. Lithium should be prescribed cautiously in
BOX 8.7 Main side-effects of lithium

**Gastrointestinal tract**
- Anorexia
- Nausea
- Vomiting
- Diarrhoea
- Thirst
- Incontinence

**Neuromuscular changes**
- General muscle weakness
- Ataxia
- Tremor
- Fasciculation and twitching
- Choreaathetoid movements
- Hyperactive tendon reflexes

**Central nervous system**
- Slurred speech
- Blurring of vision
- Dizziness
- Vertigo
- Epileptiform seizures
- Somnolence
- Confusion
- Restlessness
- Stupor
- Coma

**Cardiovascular system**
- Hypotension
- Pulse irregularities
- ECG changes
- Circulatory collapse

**Other effects**
- Polyuria
- Glycosuria
- General fatigues and lethargy
- Dehydration

\[a\] Side-effects usually associated with the toxic effects of lithium.
patients with renal impairment and advice sought from a nephrologist. Patients on long-term lithium should ideally be seen in a lithium clinic where their condition can be monitored on a routine basis. Once the patient is established on maintenance treatment, the lithium level should be checked every 6 months. A ‘trough level’ of the plasma concentration (12 hours after the last dose) should be measured in the morning when the morning dose is omitted. The plasma concentration should be in the range 0.5–0.8 mmol/L. Electrolytes, creatinine and thyroid function should be measured approximately every 6 months, or annually if the patient is well stabilized. Lithium should not usually interact significantly with other drugs, although there have been concerns about lithium and haloperidol causing long-term neurological damage if given together in high doses. Lithium may also cause a serotonergic syndrome when given with antidepressants.

**CARBAMAZEPINE**

**8.72 Carbamazepine is best known to most doctors as an anti-epileptic. How does it work in the treatment of depression?**

Carbamazepine is structurally similar to the tricyclic antidepressants, although pharmacologically distinct. It has complex actions. It inhibits sodium channels, and decreases the release of noradrenaline and noradrenaline activity. It interacts with GABA receptors among other actions. How this translates into an understanding of its mode of action in depressive disorders is not clear.

**8.73 When is carbamazepine most likely to be useful?**

As a second-line treatment when there are problems in using lithium. It may be better in rapid-cycling mood disorders when the mood swings quite rapidly from highs to lows, often several times during the day. It is also useful as an adjunctive treatment, acting as a booster to antidepressants and increasing their effectiveness in resistant cases.

**8.74 Are there any serious side-effects?**

The two problems to watch out for are blood dyscrasias (agranulocytosis and aplastic anaemia). The early onset of these is characterized by fevers, sore throat, a rash, bruising and mouth ulcers. The Stevens–Johnson syndrome is also a serious side-effect necessitating immediate cessation of treatment. Skin rashes are quite common.
8.75 What special precautions should be taken when prescribing and monitoring long-term treatment?

White cell and blood count and liver function tests should be carried out at the outset of treatment and after 2 weeks and then 3-monthly in order to guard against the emergence of blood dyscrasias and the Stevens–Johnson syndrome. Although this is recommended it is not a substitute for clinical vigilance, as the condition develops quite quickly and is unlikely to be picked up first on routine monitoring. Blood concentrations of the drug should be monitored to ensure it is given at the appropriate therapeutic dose. The ideal plasma concentration is in the range 7–12 mg/L, somewhat higher than the doses used in the control of epilepsy.

**SODIUM VALPROATE**

8.76 Sodium valproate is another drug that is known as an anticonvulsant. When is it used in psychiatry?

It is emerging as the first line treatment to replace lithium in the prophylactic treatment of bipolar mood disorders. Its position in preventing relapses in unipolar depression is less well established.

8.77 Does it have any severe adverse effects?

It is relatively free of cognitive side-effects, though alopecia and weight-gain occur frequently. The most serious side-effect is an idiosyncratic hepatotoxicity and pancreatitis.

8.78 How should treatment be monitored?

Blood levels should be checked and should be in the range 50–100 mg/L. Liver function tests should be done before treatment and at 6-monthly intervals, although raised values of LFT parameters are not uncommon and may require no specific intervention providing the prothrombin time is normal. Monitoring the overall clinical condition is the most important thing.

**DIAZEPAM**

8.79 Does diazepam have any antidepressant effects at all, or does it just subdue symptoms of anxiety?

Most benzodiazepine effects on depression are as a direct consequence of their action on the associated anxiety symptoms. Alprazolam is claimed to have antidepressant effects on the core symptoms of depression, but, while this may be true, they are not sufficient to justify its use as an antidepressant. The drug also causes dependency and withdrawal symptoms, and the treatment of depression may need to be continued long-
term. The inappropriate use of benzodiazepines to treat depression in the past, in the mistaken belief that they were safer than antidepressants, has in my view resulted in considerable under-treatment of mood disorders, leading to chronic depression and unnecessary benzodiazepine dependence.

8.80 Where I work, patients with symptoms of depression may already have been treated with diazepam (either by their doctors or by well-meaning friends who share their pills). Presumably it is best to start treatment with an appropriate antidepressant and to try to withdraw the diazepam at a later stage. How would you tackle this problem?

Diazepam remains the most effective of all drugs in psychiatry, giving rise to substantial symptomatic relief mainly of anxiety symptoms at least in the short term. Its efficacy in long-term treatment is more controversial although it probably still remains effective, despite causing dependency and withdrawal symptoms, at least to some degree. Many patients in general practice who complain of depression also have significant or even predominant anxiety symptoms. Theoretically, patients should be treated with antidepressants and benzodiazepines and then have their benzodiazepines withdrawn gradually when the antidepressant effect becomes apparent. In my experience this rarely works, and, once patients have become dependent on the benefits of benzodiazepines, they do not improve a great deal when given antidepressants. The therapeutic dilemma then is whether to stop their benzodiazepines, which the patients like, are cheap and give some benefit, in favour of continuing with expensive modern antidepressants, which are probably not as effective as the benzodiazepines.

8.81 I found that patients who have received diazepam for their symptoms are reluctant to try antidepressants, and when they do they invariably encounter side-effects and discontinue treatment saying, ‘Valium is the only thing that works for me and lets me live a normal life’. It is a very difficult problem to handle, and I wonder if you have any advice?

Benzodiazepines are unfashionable, but patients, especially those with long-term anxiety-type symptoms, do prefer benzodiazepines to antidepressants. The prevailing view is that benzodiazepines are not all that bad really, although the matter is still highly controversial.

Ultimately, each patient needs to be assessed on his or her own merits. If depressive symptoms are prevalent or if the therapeutic response is inadequate then the trial of an antidepressant should be considered. If the
patients really are functioning well on a modest dose of diazepam, then there is a strong case for leaving well alone. There are still some authorities that adhere to what I take to be the outmoded dictum that ‘benzodiazepines should not be prescribed long-term’. Counter to that is a strong body of general practitioner opinion that continues to prescribe long-term, presumably in the interest of their patients. The benzodiazepine debate is by no means dead, but is sadly fuelled more by prejudice than by solid scientific data.

About four million prescriptions are currently issued annually for daytime benzodiazepine anxiolytics. Alternative treatments exist; they do not cause dependency but are not without their own problems and risks.

**FLUPENTIXOL**

8.82 How does flupentixol work as an antidepressant?

Flupentixol is primarily an antipsychotic that acts by blockade of the D₂ receptor. Thus it has an anxiolytic action as well as an antipsychotic action by reducing dopamine activity.

At low doses, say 0.5 mg b.d., it has a paradoxical effect of blocking presynaptic dopamine autoreceptors, thereby stimulating the transmission of dopamine and acting as an antidepressant and energizer.

8.83 I sometimes use flupentixol to treat patients with mild depression coupled with anxiety. I would not use it to treat severe depression, and I think of it as a ‘gentle’ antidepressant. Am I right in my thinking?

Yes, it seems to be better in mild depression with prominent anxiety symptoms. It sometimes works in resistant depression where other antidepressants have failed. Whereas flupentixol often works quickly and with low side-effect problems, it does have the small risk of causing tardive dyskinesia and other extrapyramidal symptoms on occasions.

**ANTIPSYCHOTICS**

8.84 Do some of the newer antipsychotic drugs have mood-elevating properties?

There is no direct evidence of antidepressant activity by themselves. They would appear to be sedative and anxiolytic in the same way that traditional antipsychotics are. There is some evidence that olanzapine given in conjunction with antidepressants causes an enhanced antidepressant effect. Antipsychotics can be used for long-term prophylaxis, especially olanzapine.
8.85 Depression and schizophrenia may coexist. How would you treat this combination?

Depression may coexist with schizophrenia as one of the core symptoms of schizophrenia, in which case the correct treatment would be to manage the schizophrenic illness with full doses of antipsychotic drugs. Conversely, depression may be a function of either drug side-effects of the treatment for the schizophrenic illness or for psychological reasons associated with the illness. For example, as insight returns, patients may for very valid reasons be upset at the implications of having a long-term serious mental illness. Patients may suffer not so much depression but a ‘lack of mood’ as a function of the ‘negative symptoms of schizophrenia’. Depression is also a common condition and may coexist independently of the schizophrenic illness. Bearing in mind what a horrible condition schizophrenia is, I think an early trial of antidepressant medication is indicated if the patient is depressed, since whatever the reason it may help alleviate at least some of the symptoms that the patients have.

8.86 Does thyroxine have any mood-elevating properties?

Hypothyroidism is a well-known cause of tiredness and low mood, and correcting the condition with thyroxine is a gratifying therapeutic endeavour. Thyroxine by itself is not an antidepressant drug in depressive illnesses. Thyroxine is a potent adjunct treatment given in low doses to enhance the therapeutic effects of antidepressants in cases of resistant depression. Lithium, which is used in the control of mood disorders, can in some patients cause an insidious hypothyroidism, in which case of course this should be treated with thyroxine as well as by adjusting and potentially stopping lithium treatment. Hyperthyroidism and hypothyroidism can both give rise to symptoms that mimic mood disorders.

8.87 When is thyroxine used in the treatment of depression?

Thyroxine is added to an antidepressant in the treatment of resistant depression. The dose is 20–50 micrograms of tri-iodothyronine. Thyroid functioning needs to be monitored. It is also used in ‘subclinical hypothyroidism’, although this condition is more controversial as an entity which may be a function of a mood disorder. Hypothalamic instability may be associated with suicidal behaviour and associated depression, and so it is worth treating hypothyroidism in depressed patients vigorously.
ELECTROCONVULSIVE THERAPY (ECT)

8.88 How does ECT work in the treatment of depression?
ECT down-regulates beta-receptors and enhances central neurotransmission in a manner similar to antidepressants. It also affects GABA-B receptors and central muscarinic receptors, which may be the mechanism of the post-therapy memory deficits. The precise mode of action of ECT remains a matter of conjecture, but the benefits as the most effective treatment for severe depression are not in doubt.

8.89 Is ECT still used, and if so on whom?
ECT is primarily used for the treatment of severe depression that is not responsive to antidepressants. It is also used for patients who are in depressive stupors and unable to eat and drink, and is particularly indicated in patients with depressive delusions. It can also be used in acute mania and psychosis. It is the most effective treatment for severe depression, and probably the safest, and is generally under-used.

The superiority of ECT over antidepressants is most pronounced in the severely ill patient, and it is mainly kept in reserve as a treatment of last resort. In the milder cases the benefit is less marked, and treatment with antidepressants is probably more acceptable.

8.90 How is ECT administered, and do patients find it upsetting and painful or unpleasant?
Prior to the procedure, patients have the treatment explained to them. They should be reassured of its benefits. The treatment itself is administered after an anaesthetic and muscle relaxant has been administered. A current of about 150 milli-coulombs is passed either bilaterally between the patient’s temples or unilaterally between the frontal cortex and the mastoid bone on the non-dominant hemisphere. After the current has passed, the patient usually exhibits some minor twitching of the toes. The patient wakes up a few minutes later, with no memory of the actual treatment and remains dazed for an hour or so. Within an hour or so the patient makes a full recovery and can resume normal activities a few hours later and even go to work. The worst side-effect is a memory problem around the time of the treatment – this is usually not severe and tends to recover with time. The major problem is one of anxiety and prejudice about the procedure, rather than the procedure itself.
8.91 *What is the difference between unilateral and bilateral ECT?*

Bilateral ECT may be more effective. Unilateral ECT given to the non-dominant hemisphere appears to cause fewer memory problems.

8.92 *What are the side-effects of ECT, and do these eventually limit its use?*

The most troublesome side-effect is memory loss. Patients complain of strange gaps in their memory, especially for people’s names and details of events. It is maximal around the time of treatment and improves over the following weeks and months. This troublesome side-effect is not universal, and needs to be balanced against the harmful effects of severe, untreated depression and prolonged hospitalization. Side-effects can be minimized by giving unilateral ECT to the non-dominant hemisphere. In some cases if memory loss becomes troublesome, the course of ECT may be terminated prematurely. Otherwise, side-effects are rare and limited mainly to the hazard of anaesthetic or to musculoskeletal problems, both of which are extremely rare.

8.93 *Do patients have to consent to ECT?*

Patients have to consent to ECT and sign a consent form. There are interesting issues around consent for people who are severely depressed. The patient has to be able to give a ‘valid consent’. If patients are not willing or able to give consent, then ECT can be administered if the patient is detained under Section 3 of the Mental Health Act (a treatment order). A ‘second-opinion doctor’ from the Mental Health Act Commission is then required to certify that the treatment is appropriate, in which case treatment can proceed without the patient’s consent. In exceptional circumstances where a patient is severely suicidal or in a stupor, ECT can be given as an emergency procedure to save a patient’s life without consent. There are problems with patients who, because of their illness, are unable to consent although they do not refuse. For example, they may be in a depressive stupor and unable to communicate. In such cases they should be treated under the Mental Health Act. *(See also Chapter 13.)*

8.94 *Do patients have to consent to each individual treatment?*

Patients have to sign a consent form for the whole course of ECT. This should only happen after all the options available as alternatives to ECT have been discussed. The patient can always withdraw consent at any time, and the patient can refuse treatment even when some treatments have already been administered. Things have moved on a great deal from the days of *One Flew Over the Cuckoo’s Nest*. The rights and safeguards of patients are now paramount.
8.95 **Does consent still have to be sought when a patient is in hospital under a section of the Mental Health Act?**

If patients are detained under the Mental Health Act, they have to be able and willing to consent to the treatment for it to proceed. Just because they are sectioned does not mean they are unable to consent or do not have to consent. If they are unable or unwilling to consent then compulsory treatment can be given if a ‘second opinion doctor’ on behalf of the Mental Health Act Commission certifies that the treatment is appropriate (you don’t have to say it is the best treatment – only that it is appropriate).

8.96 **How dangerous is ECT?**

The danger of ECT is essentially that of the anaesthetic. There are about two deaths per hundred thousand treatments.

8.97 **What is RTMS and how does it work?**

Repetitive transcranial magnetic stimulation (RTMS) is a treatment in which the brain is stimulated using a hand-held magnetic coil focused onto selective brain regions. The patient remains awake during the treatment without needing an anaesthetic. The electromagnetic stimulation activates particularly the dorsolateral prefrontal cortex, increasing the activity in this area. Patients find the treatment less stigmatizing and safer than ECT. A typical treatment course involves daily brief outpatient sessions over 2–3 weeks. The treatment is still being evaluated, but it appears to be about as effective as antidepressants and less effective than ECT. It is still an experimental procedure.

8.98 **What advantages does it offer over traditional ECT?**

It does not require an anaesthetic, it is less stigmatizing with less drama attached to it. It is seen as more modern and acceptable. It appears to be low on side-effects. There is less memory impairment.
8.99 What types of treatment are available for depression?

There are two main types of treatment available: medication and psychological or ‘talking’ treatments. Medication in the form of antidepressants is probably the most effective treatment for moderate to severe depression. It works in most patients within a few weeks and gives reasonable relief of symptoms in most patients. Antidepressants make people feel better. Psychological treatments help people understand the roots of their symptoms and how their lifestyle and relationships have led to them feeling depressed. It helps people deal with the consequences of depression. Patients often want to talk about their symptoms. Talking treatments tend to take longer to work. They are often seen as more appropriate for milder depressions, especially those caused by lifestyle and relationship problems. Medication and psychological treatments in combination may well be the best option if available. Cognitive behaviour therapy (CBT) is a psychological treatment that helps people learn to do things and control their thoughts to make them feel better.

There are other treatments such as hypnosis and homeopathic remedies, social treatments, exercise and all manner of alternative approaches including St John’s Wort. These tend to be more appropriate for the milder forms of depression. Hospital admission and even ECT may on rare occasions be needed for the most severe forms where the depression may be life threatening or cause major problems for the individual. There is a broad range of treatment options available.

8.100 Will I become dependent on antidepressants?

Antidepressants are not addictive in the way that illicit drugs, alcohol or tranquillisers can be. Most patients take antidepressants for a brief period of time and then gradually stop taking them without any problems. Some patients develop mild withdrawal symptoms if they stop the antidepressant suddenly, and so patients are advised to cut down antidepressants gradually over a matter of weeks rather than stopping abruptly. Even then, withdrawal symptoms don’t always occur, and if they do they tend to be relatively mild and usually last only a few days, even if the antidepressants are stopped suddenly. Some patients become reliant upon antidepressants for keeping their symptoms under control. When they stop their medication they relapse. On that basis it becomes a choice of whether the benefits of staying on medication outweigh the disadvantages or whether the patients prefer to put up with their symptoms rather than take medication. Some patients may try alternative treatments rather than taking antidepressants long-term. This becomes a value judgement really for the patient to make in conjunction with their doctor, based on sound information from the doctor and informed choice by the patient.
8.101 Will it be difficult stopping antidepressant therapy?
The vast majority of patients stop antidepressant treatment, without seeking the advice of their doctors, simply because they want to. In doing so they have no problems at all. Most doctors spend a lot of time persuading patients to carry on taking antidepressants rather than persuading patients to stop them. Most patients have no trouble stopping antidepressants at all. If they are stopped suddenly, then some patients develop mild withdrawal symptoms lasting a day or two and these are generally tolerable. The symptoms may include dizziness, ‘electric shock’ feelings, anxiety and agitation, insomnia, flu-like symptoms, diarrhoea, nausea, tingling feelings and mood swings. If there are any problems, the antidepressant should be cut down over a number of days, either by reducing the dose gradually, or taking the tablets on alternate days, then every third day.

8.102 Do I have to inform the DVLA that I am taking antidepressants?
Straightforward anxiety and depression does not need to be notified to the DVLA. If there are problems relating to memory, agitation or suicidal thinking, then this needs to be notified. If the condition may make the driver dangerous, this must be notified, and the DVLA may then make enquiries to decide whether the licence should be withdrawn. There is no obligation to notify the DVLA if you are taking antidepressants, providing you are aware that all medication can impair alertness, concentration and driving performance especially within the first month of starting medication or increasing the dose. If you experience any problems then you should not drive. Sedative antidepressants are more likely to cause drowsiness, and antidepressants can interact with other drugs and tranquillizers as well as alcohol. In general, drivers with depression are safer when well and on regular antidepressant medication than when ill. If in doubt about your fitness to drive you should not drive and should notify the DVLA. It is the illness and the general condition that you suffer from that is the most important thing rather than the medication that you are taking.

8.103 Why do I have to go on taking tablets once I feel better?
Not everyone has to continue on tablets once they feel better. If you have had a severe depression, and were to stop taking the tablets, there is a risk that you will slip back and become depressed again. The longer you take the tablets the less the risk becomes, and after 6 months of feeling well, the risks of becoming depressed again when you stop the tablets are low, and so we generally recommend taking tablets for 6 months after you feel better to avoid relapsing too soon.

8.104 Should my child stop taking Seroxat immediately?
No. If your child is benefiting, it may well be appropriate to continue with the drug. If it is decided to stop the drug, it is important that it be tailed off gradually to avoid discontinuation or withdrawal symptoms. It is best to discuss this with your GP or psychiatrist.