

## PHARMACEUTICAL CARE

# (12) MOOD DISORDERS: DRUG TREATMENT OF DEPRESSION

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*In this, the second part of our mood disorder feature, the drug treatment of depression is discussed. The first part (PJ, February 24, p259) covered the clinical presentation and public health implications of mood disorders. The final part of this feature, to be published at a later date, will focus on the drug treatment of bipolar disorders*

Depression is managed by addressing the signs and symptoms of the depressive syndrome, by restoring the patient's social and working capacity, and by reducing the risk of relapse and recurrence. Medication is central to the management of major depressive disorders. An agent that suits an individual patient must be selected and prescribed at an effective dose, and treatment must be maintained for a period well beyond the resolution of symptoms.

Mental health problems affect one in six of the population at any one time. Panel 1 provides a profile of affective disorders in the population of a pharmacy serving 5,000 patients.

Expansion in the number and types of agents available to treat depression means that there are a wide range of issues to consider in the provision of pharmaceutical care. The complexities of actions and interactions of antidepressants require the promotion of guidelines to improve effective use. Guidelines encourage caution in use of drug combinations (both with other drugs and, perhaps, other antidepressants) so that patients can be monitored for previously undocumented effects while clinical experience is gathered.

## EVIDENCE BASE AND CLINICAL GUIDELINES

The British Association for Psychopharmacology recently published evidence-based

guidelines for treating depressive disorders following a comprehensive review of the available evidence and a consensus meeting of specialists.<sup>10</sup>

The evidence does not support the use of antidepressants for acute mild depression at first presentation. Alternative strategies such as support and education, such as teaching patients simple problem-solving techniques, are recommended. Published evidence is available on a number of other non-drug treatments in the management of depression. For example, in mild to moderate major depression, effective interventions include specific psychological treatments such as cognitive behaviour therapy (CBT)<sup>28</sup> and problem-solving therapies.<sup>29</sup> Specific psychological treatments, antidepressants or a combination of the two appear to be equally effective in mild to moderate major depression, although the relative merits of psychological treatments in severe major depression compared with drug treatment are uncertain.<sup>30</sup> The effectiveness of non-directive (patient-led) counselling is uncertain in major depression, although a recent study has indicated that it is more effective in the short term in patients with depression or mixed anxiety and depression than usual general practitioner care.<sup>31</sup>

The choice of antidepressant has become more difficult because of an in-

## Panel 1: Profile of affective disorders in the population of a pharmacy serving 5,000 patients<sup>1,2,17,23-27</sup>

### 750 people with mental health problems (500 women, 250 men)

130 with symptoms of generalised anxiety disorder (70 women, 60 men)  
300 with symptoms of mixed anxiety and depression (200 women, 100 men)  
500 with symptoms of depression (300 women, 200 men)  
250 with undiagnosed symptoms of depression  
8 attempted suicides annually  
1 suicide every two years

### 1,000 general practitioner consultations annually specifically relating to depression 325 patients with depression and/or anxiety being treated (225 women, 100 men)

90 are aged over 64 years, 70 women, 20 men

### 200 patients diagnosed with a depressive disorder (130 women, 70 men)

60 with chronic mild depression (dysthymia)  
60 with recurrent brief depression  
25 aged over 64 years receiving home care

### 90 patients suffering a major depressive episode (60 women, 30 men)

25 will have a single episode without recurrence  
25 will recur within a year  
30 patients have a severe depressive episode  
20 patients have combined major depression/dysthymia  
20 patients treated by psychiatrist  
5 cases are directly induced by physical disease or drugs  
5 hospital admissions with major depressive episode (1 recurrent episode)

### 20 patients have bipolar disorder

1 hospital admission with bipolar disorder

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creasing number of classes of antidepressant as well as the number of agents within each class (see Figure 1, Panel 2 and Table 1).<sup>32</sup> A guiding principle is to match choice of antidepressant to individual patient requirements. According to systematic reviews and meta-analyses of studies undertaken in primary care and outpatient settings, the antidepressants have similar effectiveness in the majority of patients with major depression.<sup>33-37</sup>

Newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are better tolerated than older tricyclic antidepressants (TCAs), are safer in overdose and are more likely to be prescribed at recommended doses for an adequate period.<sup>35,36,38,39</sup> However, in severely ill patients in hospital, evidence suggests that older TCAs or venlafaxine (at daily doses of 150mg or greater) may be more effective than SSRIs. Therefore, these drugs are recommended in such situations where it is of prime importance to achieve maximum efficacy.<sup>35,36,40,41</sup> Although the side effect profile of newer antidepressants would seem to make them preferable in older patients, there is little demonstrable evidence of clinical advantage.<sup>42</sup> A summary of clinical guidelines for use of antidepressants is given in Table 2.

There has been much publicity surrounding the use of St John's wort (in which the active ingredient is believed to be hypericum) for the treatment of depression. Although studies have generally involved poorly defined groups of people with mild depressive disorders, a

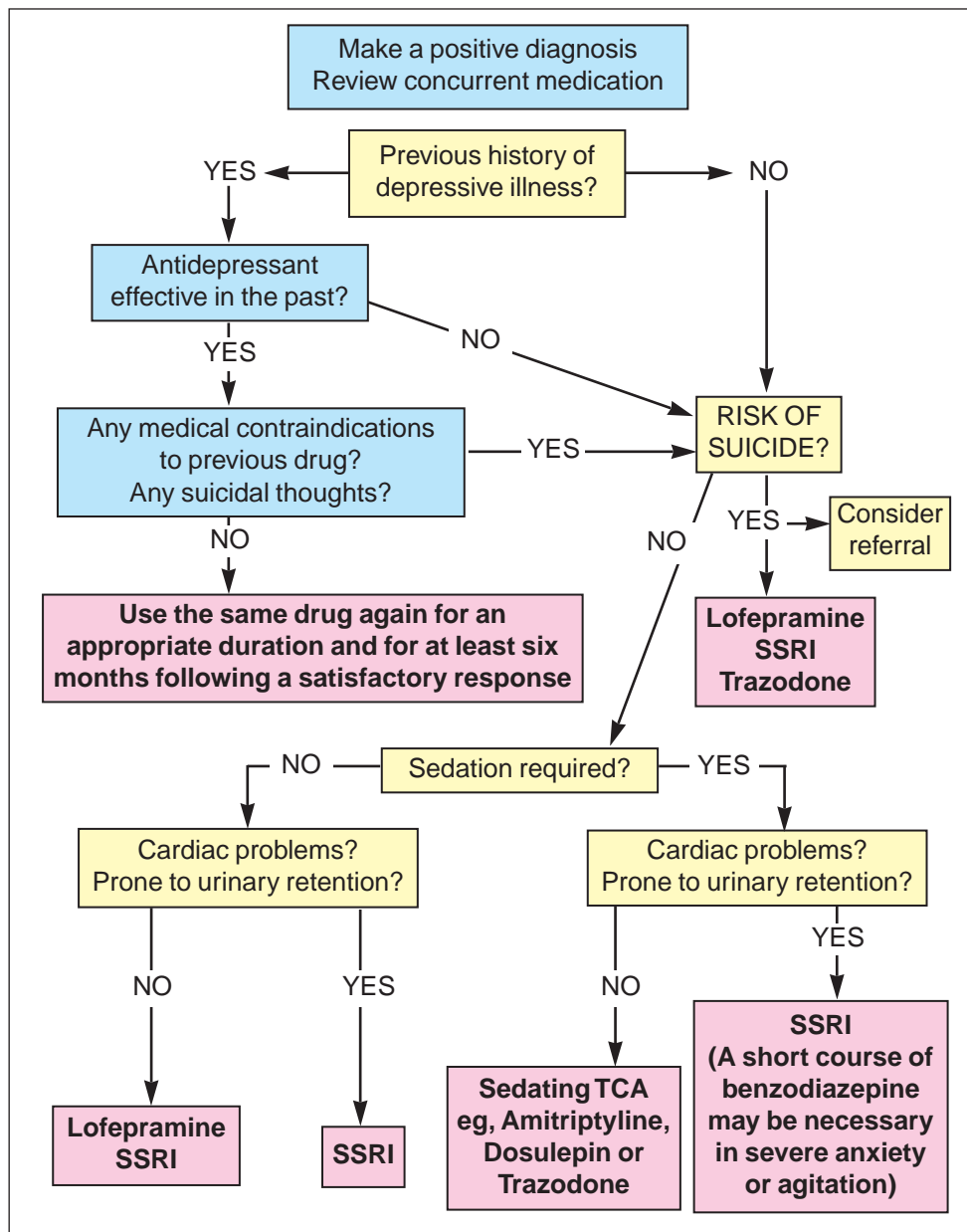


Figure 1: Depression drug choices (from Depression management guidelines, Greater Glasgow Health Board<sup>51</sup>)

TABLE 1: ACTION OF ANTIDEPRESSANT DRUGS <sup>32,43,44</sup>		
Drug group	Main agents	Pharmacological action
<b>Tricyclic and related drugs</b>		
Tricyclic antidepressants (TCAs)	Amitriptyline, amoxapine, clomipramine, dosulepin/dothiepin, doxepin, imipramine, lofepramine, nortriptyline, protriptyline, trimipramine	Inhibition of the reuptake of predominately serotonin (clomipramine), noradrenaline (nortriptyline), with most agents affecting both neurotransmitters
TCA-related antidepressants	Maprotiline, mianserin, trazodone	As above
<b>Monoamine-oxidase inhibitors</b>		
Monoamine-oxidase inhibitors (MAOIs)	Isocarboxazid, phenelzine, tranylcypromine	Irreversible monoamine oxidase inhibition
Reversible inhibitors of monoamine oxidase A (RIMA)	Moclobemide	Reversible (competitive) presynaptic monoamine-oxidase A inhibition
<b>Selective serotonin reuptake inhibitors</b>		
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Inhibition of the reuptake of serotonin
<b>Other antidepressant drugs</b>		
Newer reuptake inhibitors	Reboxetine Venlafaxine	Noradrenaline reuptake inhibitor (NARI) Serotonin and noradrenaline reuptake inhibitor (SNRI)
Mixed action drugs	Mirtazapine  Nefazodone	Complex action on serotonin and noradrenaline via presynaptic $\alpha$ -antagonism (NaSSA) Inhibition of the reuptake of serotonin and selective postsynaptic serotonin blockade

## Panel 2: Factors to consider when choosing an antidepressant

- Class of previously given antidepressants
- Tolerability and adverse effects of previously given antidepressants
- Previous response to treatment
- Likely side effect profile
- Effects of antidepressants on co-morbidity
- Lethality of antidepressant if history of, or likelihood of, overdose
- Concurrent physical illness or condition that may make the antidepressant more noxious or less well tolerated
- Associated psychiatric disorder that may specifically respond to a particular class of antidepressant (eg, obsessive compulsive disorder and serotonin reuptake inhibitors)
- Patient preference

meta-analysis of 27 studies concluded that St John's wort was more effective than placebo and equal to antidepressant drugs.<sup>48</sup> However, there are concerns about potential drug interactions, especially with warfarin,<sup>49</sup> along with uncertainties about dosing, standardisation of active ingredients and a lack of long-term safety and efficacy data.<sup>50</sup>

**Side effects** TCA-induced side effects include anticholinergic effects such as dry mouth, blurred vision and constipation. Cardiovascular adverse effects including ECG changes, tachycardia and postural hypotension have also been associated with TCAs. Other adverse effects with this group of antidepressants are weight gain (and occasionally weight loss) and sexual dysfunction. Although SSRIs are more commonly associated with anorexia and weight loss, weight gain has been reported with citalopram.<sup>43</sup>

SSRIs may be associated with sexual dysfunction, such as male impotence. Nefazodone has little effect on sexual function and may be used as an alternative if SSRI-induced sexual dysfunction occurs. It also may be beneficial for patients who suffer from significant sleep disturbance. Moclobemide is well-tolerated, relatively free from dietary tyramine interactions associated with irreversible MAOIs (although patients taking the drug should avoid consuming large amounts of tyramine-rich foods) and comparatively safe in overdose. With mirtazapine, weight gain tends to occur early and is less likely to appear with prolonged treatment than with TCAs. Evidence of safety of antidepressants in pregnancy is limited, but most experience has been with the more long-standing TCAs and fluoxetine.<sup>12</sup>

TABLE 2: SUMMARY OF CLINICAL GUIDELINES FOR USE OF ANTIDEPRESSANTS<sup>10</sup>

Evidence-based findings	Evidence-based recommendations
Antidepressants are effective in both moderate and severe acute major depression, including depression associated with physical illness <sup>45</sup>	Prior life events do not influence response in major depression but do make response to placebo more likely. In most patients with milder forms of major depression or symptoms not meeting major depression criteria, effects of antidepressant are hard to distinguish from placebo <sup>46,47</sup>
Antidepressants are an effective first line acute treatment in chronic persistent depressive symptoms of greater than two years duration (dysthymia)	Treat dysthymia with the same principles as major depression
Older TCAs are more effective in doses of 125–150mg than doses of 75mg	TCAs are often prescribed in too low a dose and for too short a course. Doses below 75mg are probably no more effective than placebo. However, side effects from antidepressant medication are related to dose. Introduce TCAs using a gradual increase in dose every three to seven days
There are few proven generalisable distinctions affecting the choice of agent	Venlafaxine (>150mg/day) may be more effective than SSRIs for moderate/severe major depression in patients in hospital. MAOIs are less effective than TCAs in inpatients but more effective in outpatients with atypical depression symptoms
Compliance problems with antidepressants may be a cause of apparent non-response and is improved by counselling	Ensure non-response is not because of non-compliance or failure to use a therapeutic dose. Consider other social factors that may be associated with non-response. Partial response at four weeks requires continuation with same antidepressant for another two weeks (or up to five weeks in older patients)
Response is unlikely if no improvement is evident after four weeks of treatment, except in elderly patients who may take longer (six to nine weeks) to respond	If response is unsatisfactory, the options are to increase the dose or switch to another agent. Follow precautions when switching agents to avoid adverse drug interactions. In failure to respond to a second antidepressant, the options are to add an augmenting agent, add psychotherapy or treat with electro-convulsive therapy
Continuation of antidepressant medication for at least six months halves the relapse rate and benefits patients with recurrent major depression and, probably, elderly patients	Continue antidepressant treatment for at least six months after remission of major depression and 12 months in the elderly. Patients with residual depressive symptoms and other factors increasing the risk of relapse should continue longer
Maintenance antidepressant drug treatment reduces the recurrence rate in patients who have had more than two episodes of major depression in the previous five years or more than five episodes altogether	Patients with recurrent major depression should receive maintenance antidepressant drug treatment. Maintenance treatment is indicated for patient with three or more episodes of major depression in the previous five years or more than five episodes altogether
Patients should be maintained on a therapeutic dose. This is more effective than maintenance on half the therapeutic dose	The same dose used for acute treatment should be used for maintenance therapy
Lithium is an alternative second-line agent for maintenance therapy	Lithium is an effective, alternative, second-line maintenance agent
Discontinuation symptoms may occur on stopping an antidepressant abruptly	Patients should be warned about the possibility of discontinuation reactions. Non-compliance should be suspected if unexplained symptoms occur after a few weeks of treatment. Symptoms are usually mild (balance and sensory disturbance, gastrointestinal effects, insomnia and mood abnormalities in a pattern different from re-emergence of the original depressive disorder). They resolve soon after reinstatement of antidepressant or slowly after discontinuation (up to several weeks). Reactions can be avoided by tapering the dose over at least four weeks. In those who have been on long-term maintenance treatment, the dose should be tapered over six months

### ADJUNCTIVE THERAPY

l-Tryptophan is no longer marketed as an antidepressant because of an association with an eosinophilia-myalgia syndrome.<sup>52</sup>

Use of l-tryptophan is restricted to patients specially registered to be prescribed it under hospital specialist care. It is only used as adjunctive therapy in severe depression.

Although lithium is principally used in prophylaxis and treatment of bipolar disorder, it is also used as adjunctive therapy, particularly to augment TCAs in the prophylaxis of recurrent depression under specialist advice.

Other adjunctive agents that may be used to accelerate response to antidepressants, and also for treating refractory depression, include tri-iodothyronine, pindolol, dexamethasone, carbamazepine and lamotrigine but clear guidance for their use is lacking from clinical trial evidence.<sup>53,54</sup> Electro-convulsive therapy is also used but is outside the scope of this article.<sup>30</sup>

#### IMPLICATIONS OF STOPPING AND SWITCHING ANTIDEPRESSANTS

**Drug discontinuation syndrome** Antidepressants are not drugs of dependence but a drug discontinuation syndrome can occur as a consequence of abrupt withdrawal. It has been reported after patients have received treatment for eight weeks or longer and may involve somatic and/or psychiatric symptoms including general malaise, headache

and nausea through to agitation/irritability, movement disorders, cognitive impairment and vivid dreams.<sup>55,56</sup> In some cases, the discontinuation effects have been confused with a relapse of the original psychiatric disorder.

Generally, withdrawal from an antidepressant should be done slowly over at least four weeks. Patients should be educated about these effects and reassured that they do not mean that their medication produces dependence or addiction. Gradual withdrawal and lower starting dose of the second drug are preferred when switching certain agents requiring precautions (see Figure 2).

**Drug interactions** The potential for drug interactions with antidepressants is high. Interactions between MAOIs and tyramine sources in food, and between MAOIs and other drugs are well documented.

The number of possible interactions has been expanded by the use of SSRIs which are potential inhibitors of the cytochrome P450 isoenzymes. This enzyme inhibition can affect a number of drugs including an-

tippsychotics, antiepileptics, many other antidepressants and anticoagulants (see Table 3).<sup>43,57</sup> Conversely, antidepressants can be susceptible to enzyme induction, for example by phenytoin, carbamazepine and rifampicin. For many new antidepressants, these enzymic interactions remain to be evaluated, so precautionary monitoring of concurrent anticoagulants and antiepileptics is generally advisable. Lithium interactions will be considered in a future article. The potential for interactions between antidepressants further complicates prescribing decisions.

Patients using MAOIs should be issued with a warning card to advise them about the avoidance of tyramine-containing foods and the possibility of drug interactions.

**Serotonin syndrome** A serotonin syndrome has emerged as a potential adverse effect of antidepressant drugs and drug combinations. It is thought to be related to a net increase in central serotonergic neurotransmission.<sup>58</sup> Although its cause is unknown, it is often confused with neuroleptic malignant syndrome which is a hyperthermia

**TABLE 3: DRUG INTERACTIONS ASSOCIATED WITH ANTIDEPRESSANTS<sup>43</sup>**

Antidepressant*	Mechanism and effect	Drugs implicated
TCAs	Additive pharmacological effects and enzyme inhibition  Lowering of seizure threshold Enzyme induction affecting TCA Enhanced antidepressant toxicity	Alcohol, antiepileptics, antihistamines, sympathomimetics, antihypertensives, antipsychotics including phenothiazines, hypnotics/anxiolytics, certain analgesics, baclofen, certain antivirals Antiepileptics Rifampicin, phenytoin Certain other antidepressants (see Figure 2)
Tricyclic-related agents	Antagonism of anticonvulsant effect Enhanced sedative effect Enhanced antidepressant toxicity	Antiepileptics Alcohol, hypnotics/anxiolytics Certain other antidepressants (see Figure 2)
MAOIs	Effects of tyramine as a noradrenaline precursor and hypertensive crisis Enhanced effects on the interacting drug  Antagonised effect on interacting drug (ie, lowered seizure threshold) Mutually enhanced toxicity	Tyramine containing foods, antihypertensives, levodopa, sympathomimetics Anaesthetic agents, antidiabetic agents including insulin, sumatriptan, opioids and nefopam, antiepileptics, antihistamines, antipsychotics Antiepileptics  Other antidepressants (see Figure 2)
RIMA (moclobemide)	Enhanced antidepressant toxicity Other effects of MAOIs	Other antidepressants except MAOIs See above, but less marked and tyramine effects depending on quality of tyramine ingested
SSRIs	Enzyme inhibition by SSRI  Lowering of seizure threshold Potential loss of antidepressant effect (selective effect requires inquiry) Enhanced antidepressant toxicity	Enhanced effects of anticoagulants, MAOIs, alcohol, selegiline, antipsychotics, lithium, sumatriptan, theophylline, antiepileptics (especially phenytoin), propranolol, some anxiolytics/hypnotics, omeprazole, cisapride Undermining effect of antiepileptics Enzyme inducers (selectively) such as phenytoin  Certain other antidepressants (see Figure 2)
NARI (reboxetine)	Enhanced reboxetine toxicity  Enhanced antidepressant toxicity	Enzyme inhibiting anti-infectives (eg, macrolides, imidazoles and triazoles) MAOIs, TCAs (see Figure 2)
SNRI (venlafaxine)	Enhanced antidepressant toxicity	MAOIs, TCAs (see Figure 2)
NaSSA (mirtazapine)	Enhanced sedative effects Enhanced antidepressant toxicity	Anxiolytic/hypnotics, alcohol MAOIs, TCAs, reboxetine (see Figure 2)
Nefazodone	Enhanced antidepressant toxicity Increased risk of myopathy Increase in plasma concentration of tacrolimus	MAOIs, TCAs (see Figure 2) Simvastatin toxicity enhanced Tacrolimus toxicity enhanced

\* Note there are differences between agents within each class. Citalopram and sertraline have narrower and more limited P450 isoenzyme inhibitory effects than other SSRIs. Refer to manufacturers' Summary of Product Characteristics for more complete list of interactions.

CHANGE TO ► FROM ▼	SSRI	Trazodone Nefazodone	Venlafaxine	Moclobemide	MAOI	Reboxetine	TCAs	Mirtazapine
SSRI	Lower starting dose	Lower starting dose	Lower starting dose	Wash-out period*	Wash-out period*	Lower starting dose	Wash-out period/lower starting dose	
Trazodone Nefazodone	Lower starting dose	Lower starting dose	Lower starting dose	Wash-out period one week	Wash-out period one week	Lower starting dose	Lower starting dose	
Venlafaxine	Lower starting dose	Lower starting dose		Wash-out period one week	Wash-out period one week		Lower starting dose	
Moclobemide	Wait 24 hours	Wait 24 hours	Wait 24 hours			Wait 24 hours	Wait 24 hours	Wait 24 hours
MAOI	Wash-out period two weeks	Wash-out period two weeks	Wash-out period two weeks	Continue diet for two weeks		Wash-out period two weeks	Wash-out period two weeks	Wash-out period two weeks
Reboxetine				Wash-out period one week	Wash-out period one week			
TCAs				Wash-out period one week	Wash-out period one week			
Mirtazapine				Wash-out period two weeks	Wash-out period two weeks			

Figure 2: Summary of precautions needed when switching antidepressants (adapted, with permission, from Oxleas NHS Trust pharmacy department<sup>57</sup>)

Key:  Washout required, risk of interaction  Care required  No specific precaution

\*Washout period depends on SSRI half-life and varies between one and five weeks (citalopram one week, paroxetine/sertraline two weeks, fluoxetine five weeks)

reaction associated with muscular rigidity. Diagnosis of serotonin syndrome requires a switch of serotonergic agent, or a change in dosage, associated with at least three of the following symptoms: agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhoea, inco-ordination and fever. Hyperthermia is a sign of severe serotonin syndrome. Various drug combinations can be implicated but most cases involve MAOIs, SSRIs, l-tryptophan and lithium. Therefore, precautions are required when switching or adding antidepressant drugs to minimise adverse reactions and interactions.<sup>57</sup>

The sequential use of antidepressants requires careful consideration of overlapping effects. Specific guidance on switching from a first agent to a second should be sought from manufacturers' recommendations and psychiatric drug prescribing guidelines (Figure 2 provides a summary).

#### INDIVIDUAL PATIENT CARE

The treatment of depressive symptoms is a routine part of the delivery of primary care. Depression has an impact on other physical complaints<sup>11</sup> to the extent of affecting life expectancy, for instance, by increasing the prevalence and worsening the outcomes of coronary heart disease.<sup>61</sup> Chronic depression in the elderly complicates the management of other diseases<sup>62</sup> and its physical consequences include a worsening of various chronic illnesses.<sup>63</sup> Specifically, it has been shown to reduce outcomes in hip fracture and residential care populations. Since

depression is generally recognised to be undertreated,<sup>64</sup> sub-optimal prescribing of antidepressants is likely to have a wide impact on individual quality of life and to be an important consideration in the public health of the community.

Treatment of depression aims to address signs and symptoms of the depressive syndrome, restore a patient's social and working capacity and reduce the risk of relapse and recurrence. Medication is central to the

management of major depressive disorders. Symptomatic improvement within the first two weeks of commencement is seen in trials of patients taking placebo as well as antidepressants. Short-term clinical improvement or relapse that occurs in the first few weeks of treatment may reflect loss of placebo effect.<sup>65,66</sup> Judgment of the effectiveness of medication on mood disorder, with the goal of effective monotherapy, requires a therapeutic trial in an individual patient for an

## Panel 3: Risk factors for relapse or recurrence of depression<sup>60</sup>

#### PHARMACEUTICAL FACTORS

- Antidepressants stopped too soon by general practitioner
- Complete or partial non-compliance with prescribed medication
- Failure to appreciate the need to continue to take medication
- Too low a dose of antidepressant prescribed for long-term therapy
- Treatment resistance
- Multiple prescribers making independent decisions in same patient
- Experience of distressing drug side effects and past adverse drug reactions
- High educational needs concerning medication (and demotivation by lack of provision of such information)

#### OTHER PATIENT FACTORS

- Severity of the illness
- Living alone and poor family support
- Patients' inability to care for themselves
- Outside agencies (eg, community psychiatric nurses, social workers) failing to live up to patients expectations

adequate duration (usually four to eight weeks).

The rational treatment of recurrent depression is facilitated by accurate past medical and drug histories to distinguish a patient's pattern of remissions and recoveries. Follow-up studies indicate that within two years of a first episode of major depression, 40 per cent of patients continue to be affected and over 50 per cent of those with dysthymia go on to require treatment for major depression.<sup>67</sup> There are few long-term studies of antidepressants other than

TCA's. Prophylactic maintenance is recommended for consideration only in recurrent major depression, after a third episode in middle-aged patients and after the first or second episode in older patients.<sup>68</sup> Risk factors for relapse or recurrence of depression are given in Panel 3.

Individualisation of treatment is based on experience from treatment of past episodes of depression, and it requires the securing of a sense of active participation by the patient in the management of their condition.<sup>69</sup> Individual selection of antide-

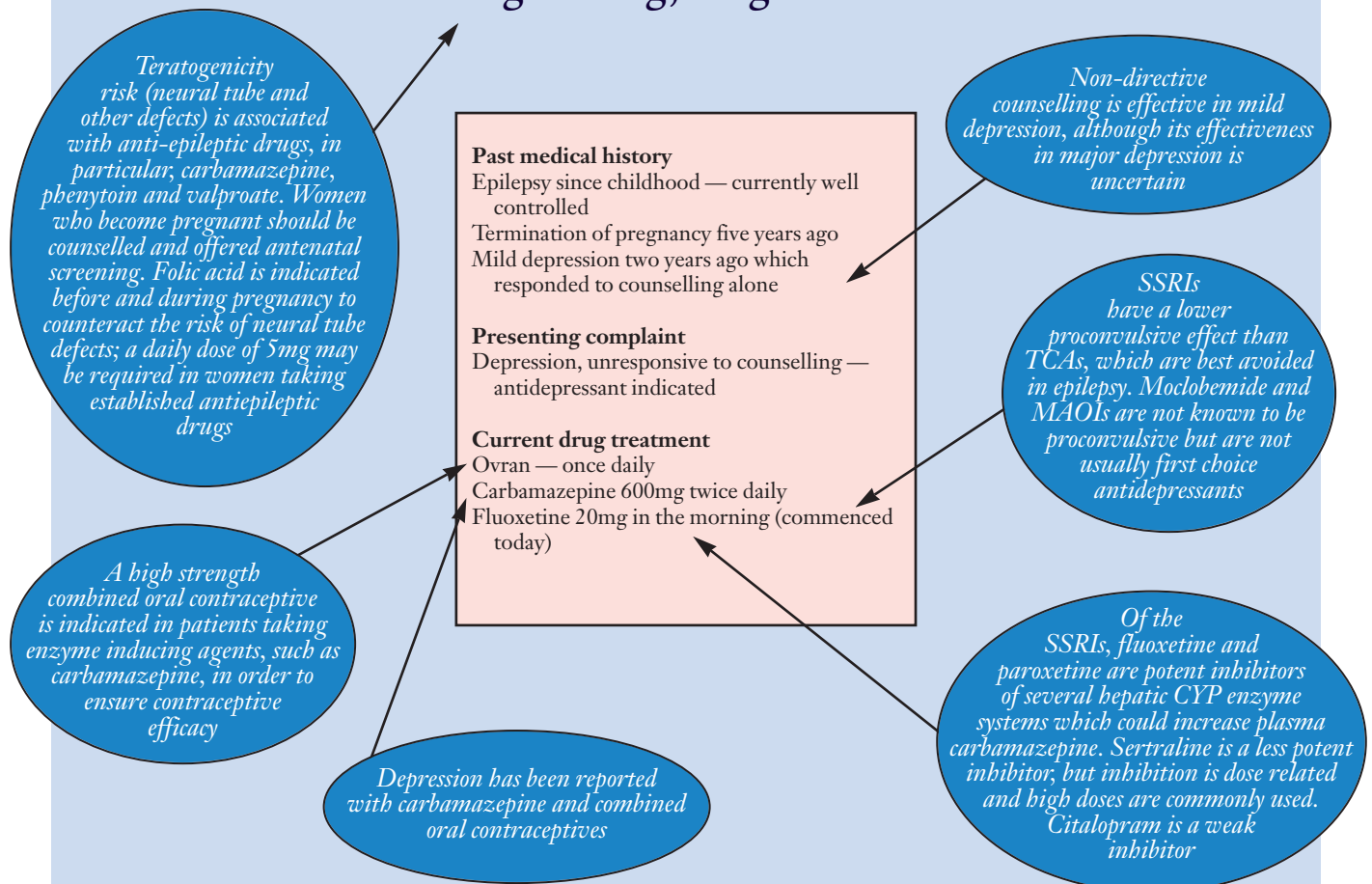
pressants includes consideration of co-morbidities, unwanted effects and overdose risk.

The TCAs are associated with higher incidences of anticholinergic side effects, sedation, weight gain and cardiovascular complications, such as postural hypotension. Most carry a relatively high fatality risk in overdose.<sup>32</sup> Given the relatively long half lives of TCAs (except lofepramine) there is no rationale for using divided doses and single bed-time doses of TCAs may minimise the effects of certain side effects, particularly sedation. Patients should be alerted to the

TABLE 4: PHARMACEUTICAL CARE IN DEPRESSION

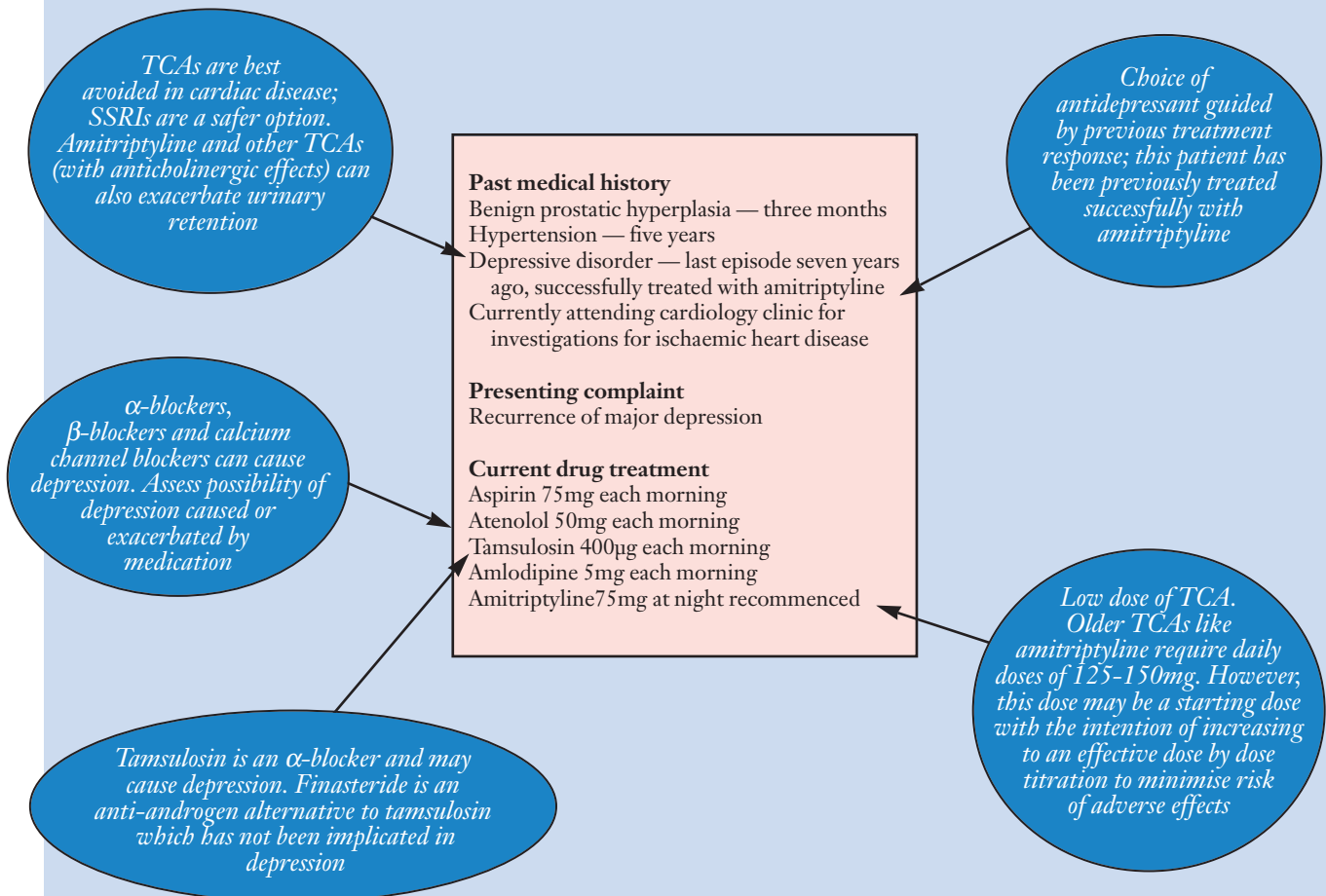
Stage of treatment	Actions	Points to consider at each stage
<p><i>Treatment plan</i></p> <ul style="list-style-type: none"> <li>● Patient comprehension/active participation</li> <li>● Patient's characteristics</li> <li>● Indication (the need for each drug)</li> <li>● Drug history</li> <li>● Choice of medication</li> <li>● Contraindication/interaction</li> <li>● Conformity to guidelines</li> <li>● Continuity of care</li> </ul>	<p><i>Verify the plan in respect of</i></p> <ul style="list-style-type: none"> <li>● Patient's characteristics</li> <li>● Medication suitability</li> <li>● Patient's needs for education</li> <li>● Concordance and agreed expectations</li> </ul> <p><i>Modify the plan to address</i></p> <ul style="list-style-type: none"> <li>● Specific educational needs</li> <li>● Need for individualisation of treatment plan</li> </ul>	<ul style="list-style-type: none"> <li>● Seek and refer cases of suspected undiagnosed depression among patients with physical illness on chronic medication, especially among those on drugs acting on musculoskeletal system and/or central nervous system</li> <li>● Concomitant physical disorders that are associated with, or which complicate, depression</li> <li>● In patients started on antidepressant medication, establish what patients have been told and how they are interpreting their condition</li> <li>● Assess patients' understanding of depression, the non-addictive nature of antidepressants and the delay in onset of antidepressant activity</li> <li>● Characterise somatic complaints and patients' interpretation of them</li> <li>● Social circumstances, family environment, family stigma and support</li> <li>● Alert patients to common side effects and the fact that they are not normally persistent</li> <li>● Identify other medication that can cause or aggravate depression</li> <li>● Choice of medication to avoid/utilise particular side effects, eg, sedative, postural hypotension, anticholinergic side effects, other CNS effects</li> <li>● Co-morbid states that complicate treatment and its evaluation, eg, Parkinson's disease and thyroid disorders</li> <li>● Accurate and comprehensive drug history, especially past psychiatric medication and self medication</li> <li>● Flag certain identified patients as an overdose risk</li> <li>● Provide advice on request about non-drug treatments and patient support groups</li> </ul>
<p><i>Implementation</i></p> <ul style="list-style-type: none"> <li>● Dose</li> <li>● Frequency</li> <li>● Timing</li> <li>● Compliance</li> <li>● Clinical signs</li> <li>● Laboratory markers</li> </ul>	<p><i>Monitor the patient for</i></p> <ul style="list-style-type: none"> <li>● Continuing suitability of drug/dose regimen</li> <li>● Signs/symptoms of effectiveness and toxicity</li> </ul> <p><i>Adjust the process by</i></p> <ul style="list-style-type: none"> <li>● Further individualisation in response to monitoring</li> </ul>	<ul style="list-style-type: none"> <li>● Identification of underdosing or failure to allow adequate duration of therapeutic trial</li> <li>● Monitoring to ensure individualisation of dose. Especially important for gradual introduction of TCAs using low doses and when switching SSRIs</li> <li>● Adjust regimen with particular agents to minimise side effects (morning dose to avoid insomnia and evening doses to avoid daytime sedation)</li> <li>● Checks of compliance and maintenance of concordance</li> <li>● Checks of handling of medicines and safety of storage</li> <li>● Monitoring and recording of effects of medication (eg, body weight, blood pressure)</li> <li>● Specific monitoring for blood dyscrasias (eg, routinely for mianserin, and, if suspected, for mirtazapine), liver function tests (eg, for lofepramine), renal function tests for lithium in conjunction with therapeutic drug monitoring</li> <li>● Specific drug induced syndromes, eg, syndrome of inappropriate antidiuretic hormone (SIADH), reported with various antidepressants, and serotonin syndrome</li> <li>● Specific checks for interactions, including drug-food interactions with MAOIs</li> </ul>
<p><i>Clinical outcome</i></p> <ul style="list-style-type: none"> <li>● Therapeutic benefit</li> <li>● Safety</li> <li>● Unwanted symptoms</li> <li>● Recorded adverse drug reactions</li> </ul>	<p><i>Confirm evidence of treatment success</i></p> <ul style="list-style-type: none"> <li>● Reassure patient in relation to agreed expectations</li> </ul> <p><i>Prompt a review from</i></p> <ul style="list-style-type: none"> <li>● Identification of treatment failure</li> <li>● Newly identified patient needs</li> <li>● Sharing information and discussion of implications with the prescriber and other team members</li> </ul>	<ul style="list-style-type: none"> <li>● Reduction in severity and range of somatic symptoms as a sign of effectiveness</li> <li>● Check for inadequate symptom control during expected delay in onset of antidepressant medication (eg insomnia, agitation)</li> <li>● Check for any noted reduction in mental state and exclude/identify possible drug side effects</li> <li>● Recognition of persistent side effects requiring clinical review of the therapeutic plan</li> <li>● Duration of course of treatment — continue well beyond resolution of symptoms and encourage the patient accordingly</li> <li>● Confirm reasons for reviewing choice of antidepressant to ensure switching agents is not done prematurely and the process is well documented</li> <li>● Identify potential candidates for maintenance medication among those with recurrence and especially among older patients</li> <li>● Recognise symptom changes to allow early referral for a clinical review of the patient's needs</li> </ul>

## Case 1: Patient SF, female, 28 years weight 62kg, height 1.62m



PHARMACEUTICAL CARE PLAN	
CARE ISSUES	ACTION TAKEN AND FUTURE PLANS
1. Verify drug history to eliminate medication as causing or aggravating depression	Carbamazepine and contraceptive use established as pre-dating previous depressive symptoms
2. Modify choice of antidepressant drug	Moclobemide/MAOIs are least likely to be proconvulsive, but are not first-line agents. Tricyclic antidepressants lower the seizure threshold and are best avoided. Selective serotonin reuptake inhibitors are, therefore, a good first choice in a patient with epilepsy being treated for depression in primary care. However, SSRIs potentially interact with anti-epileptic drugs. Contact prescriber to discuss substitution of fluoxetine (which can increase carbamazepine levels via hepatic enzyme inhibition) for citalopram or sertraline (which have lower potential for interaction)
3. Verify treatment against guidelines	Response to treatment should be monitored and reviewed, with clear response expected within four weeks
4. Monitor procedures for switching antidepressants and adjust accordingly	Switching from one SSRI to another carries a theoretical risk of serotonin syndrome and a lower starting dose of the second agent may be required. Particular care is required when switching from fluoxetine because of its long half life and its active metabolite (five weeks required for complete washout). However, the need for caution is reduced in this patient because she has only just commenced fluoxetine treatment
5. Monitor carbamazepine plasma concentration	Advise additional monitoring of carbamazepine levels (range 4-12mg/L) to monitor for any effects of introducing SSRI
6. Monitor patient compliance with antidepressant	Check for continued adherence to medication during each stage of treatment initiation to reinforce patient confidence, even when it may seem not to be working. Maintain checks with patient to ensure continued adherence after apparent resolution of symptoms
7. Verify patient comprehension of SSRI side effects	Patient should be educated about possible SSRI side effects, such as gastrointestinal disturbance, and encouraged to report any problems. Ensure patient knows who to contact to report persistent side effects
8. Verify patient comprehension	Provide written and oral educational support on depression and on antidepressant treatment and seek to maintain concordance. As necessary, reinforce education on depression through direct patient contact

## Case 2: Patient HS, male, 59 years weight 82kg, height 1.82m



### PHARMACEUTICAL CARE PLAN

CARE ISSUES	ACTION TAKEN AND FUTURE PLANS
1. Verify drug history to eliminate medication as causing or aggravating depression	Depression has been reported with α-blockers, β-blockers and calcium channel blockers. However, on considering time sequence, only tamsulosin, which was started three months ago, seems likely to be implicated
2. Confirm depression as a possible adverse drug reaction	Contact doctor to consider depression as caused or exacerbated by α-blocker, tamsulosin. However, this patient does have a long-standing history of depressive disorder. Finasteride is an anti-androgen alternative for benign prostatic hypertrophy that has not been implicated in causing depression. Change from α-blocker to anti-androgen will require specialist referral after which reconsideration of the requirement for an antidepressant may be necessary
3. Verify choice of antidepressant	Check that prescriber is aware that TCAs such as amitriptyline should be used with caution in cardiac disease and in patients with a history of urinary retention
4. Verify patient comprehension of side effects of TCAs	If amitriptyline is continued, patient should be encouraged to report any worsening in symptoms of urinary retention
5. Monitor any switch from TCA to SSRI	If a decision is made to switch from amitriptyline to an SSRI, then care must be taken. General advice is to taper the TCA dose to around 50mg/day, then introduce the SSRI at the usual starting dose and discontinue the TCA over the next five to seven days with careful observation. The potential problems are serotonin syndrome, raised TCA levels resulting from hepatic enzyme inhibition, cholinergic rebound or TCA withdrawal symptoms*
6. Monitor to ensure adequate duration of antidepressant medication	If antidepressant therapy is indicated, then there is evidence that continuing treatment for a minimum of six months approximately halves the relapse risk (minimum 12 months in the elderly)

\* For more information, see Bazire S. Psychotropic Drug Directory 2000. Quay Books Division, Mark Allen Publishing Ltd, Jesses Farm.

possibility of side effects and reassured that unwanted symptoms are likely to diminish over the first weeks of starting treatment.

The SSRIs require less individualisation

## Panel 4: Drugs that can cause depression<sup>59</sup>

### CARDIOVASCULAR DRUGS

- $\beta$ -blockers
- Calcium channel blockers
- Digoxin
- Methyldopa
- Statins

### HORMONES

- Corticosteroids
- Oestrogens
- Progestogens

### DRUGS ACTING ON THE CNS

- Alcohol
- Amphetamines (withdrawal)
- Amantadine
- Benzodiazepines
- Carbamazepine
- Levodopa
- Phenothiazines

### ANTIBACTERIALS

- Sulphonamides
- Ciprofloxacin

### MISCELLANEOUS

- Disulfiram
- Interferon- $\alpha$
- Isotretinoin
- Mefloquine
- Metoclopramide
- NSAIDs
- $\alpha$ -blockers

because they are effective in a narrower range of doses and are generally better tolerated when used as monotherapy (although see section on serotonin syndrome). SSRIs are now prescribed in more than 50 per cent of patients with depressive symptoms.<sup>13</sup> Treatment with an SSRI might cause restlessness or insomnia early in treatment and therefore administration as a morning dose is usual.

Antidepressants should be prescribed in adequate doses; TCAs in particular are likely to be prescribed at less than recommended doses.<sup>70</sup> The older TCAs appear to be more effective at daily doses of 125–150mg, and probably lack antidepressant efficacy at doses of less than 75mg. Although lower doses of antidepressants are usually recommended in the elderly,<sup>43</sup> this is not based on clear evidence.<sup>10</sup> The risk of side effects increases with dose<sup>71</sup> and doses of TCAs are usually titrated upwards whereas newer antidepressants are, in general, initiated at doses at, or close to, the therapeutic dose.

Drugs that can cause depression are listed in Panel 4. Depression is common among hospital inpatients. Inpatients may start treatment while in hospital with the need for follow-up in the community; failure to follow-up in the community may affect individualisation of medication and result in underdosing and non-compliance. Table 4 summarises examples of pharmaceutical care issues at different stages of treatment of the patient with depression.

There is a problem of adherence to guideline recommendations by general practitioners in the United Kingdom.<sup>39</sup> Primary care prescribers' knowledge and understanding of guidelines can be improved by educational interventions. However, an effect on diagnosis and treatment of depression in practice is limited by constraints on guideline implementation, particularly consultation times.<sup>72,73</sup> Drug counselling by the primary care team, designed to provide education about depression, can increase the likelihood of patients continuing with antidepressant

treatment beyond 12 weeks. In contrast, the provision of information leaflets alone has had no impact on compliance.<sup>74</sup> It is clear that patient education should include information about depression itself, as well as about the benefits and side effects of treatment.<sup>75,76</sup>

Specific guidance on frequency of patient monitoring is lacking, but weekly review of patients in the initial stages of treatment has been suggested. Assessment of patient response, compliance, side effects and suicide risk should be undertaken at each clinical review.<sup>10</sup> Systems devised to issue only small amounts of medication at a time, by instalment dispensing, can be used for vulnerable patients to help to reduce the risk of the medication being used in suicide attempts.

Individualisation of care and follow-up are important in the management of mood disorder, requiring the same kind of organised primary care team effort that increasingly is proving to be necessary for the management of other common primary care illnesses.<sup>5,69,77</sup> Although educational programmes to implement clinical guidelines are well received, they have not translated into effects on outcomes in depression.<sup>73</sup> Studies have indicated the benefits of organised multidisciplinary primary care team efforts.<sup>78</sup> Systematic patient follow-up and care management by telephone contact improves outcomes in acute depression.<sup>79</sup> The management of depression is becoming the subject of greater public awareness and of local primary care team strategies. Public education and improved pharmacological treatment of common mood disorders are important public health goals to which pharmacists can contribute.

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