

# Management of Clinical depression

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Antidepressants are the mainstay of treatment for clinical depression, but which one suits which circumstances? The second part of this special feature looks at the options

The National Service Framework (NSF) for Mental Health states that patients should be offered effective treatments for depression.<sup>1</sup> Despite the fact that such treatments are available, there remains a significant burden of disease.<sup>2</sup> Choosing the appropriate drug therapy and enhancing concordance by providing appropriate support can help to improve patient outcomes.

Before reaching a diagnosis of depression and initiating treatment, it is important to eliminate other possible causes such as disease processes (eg, hypothyroidism), drug-induced effects (eg, calcium channel blockers, levodopa and cimetidine) and substance abuse (eg, excess alcohol use, withdrawal from amphetamines).

Depression is a common mental illness and the majority of patients are treated in the primary care setting. Referral to secondary care is necessary if the patient has any of the following characteristics:

- | Presents with psychotic features
- | Is actively contemplating suicide
- | Suffers from a bipolar disorder
- | Has not responded to adequate therapy with at least two classes of antidepressants

## ANTIDEPRESSANTS

Antidepressants are the mainstay of drug treatment. Symptoms of depression are believed to occur because of a lack of monoamines within the brain. Most antidepressants increase the availability of such monoamines. (see below and Table 1, p224) Despite the development of newer agents, the importance of each neurotransmitter on outcome for individual patients is not known.

**Tricyclic antidepressants** The first tricyclics imipramine and amitriptyline were developed in the 1950s and are well established in therapy. Since then, more agents in this class have been introduced. Tricyclic antidepressants inhibit the reuptake of

noradrenaline and serotonin (5-hydroxytryptamine, 5HT) to varying degrees. For example, clomipramine acts predominantly by inhibiting the reuptake of 5HT while the principal action of lofepramine is to inhibit the reuptake of noradrenaline.

The need for dose titration and patients' inability to tolerate side effects can limit the usefulness of tricyclics. Newer compounds have been developed with the aim of producing drugs with fewer side effects. Sedation, anticholinergic effects and cardiotoxicity are common with older drugs whereas lofepramine, a more recent addition to the class, has fewer of these side effects. Trazodone and maprotiline are related to the tricyclics, as is the tetracyclic compound mianserin.

**Selective serotonin reuptake inhibitors** Selective serotonin reuptake inhibitors (SSRIs) are considered safer drugs to use than the older antidepressant drugs because they exhibit fewer anticholinergic, sedative and cardiotoxic effects. However, they are not devoid of side effects (eg, nausea and vomiting). The choice of a particular drug within the class is influenced by variations in both the potential for interactions and the effects of withdrawal. Some of the SSRIs are also licensed for other conditions such as panic disorder (eg, citalopram and paroxetine) and obsessive-compulsive disorder (fluoxetine, paroxetine, fluvoxamine and sertraline).

**Monoamine oxidase inhibitors** Monoamine oxidase inhibitors (MAOIs) include phenelzine and tranylcypromine. These drugs irreversibly block the enzymes monoamine oxidase A (MAO-A) and MAO-B, thus increasing the availability of monoamines in the synaptic cleft. The effect remains for two weeks after the drug is stopped. MAOIs are not widely prescribed due to their potential for interactions with food and drugs, which can precipitate a hypertensive crisis. They can, however, be useful in atypical depression.

Reversible inhibitor of monoamine oxidase  
The only reversible inhibitor of monoamine

oxidase (RIMA) licensed in the UK is moclobemide. Due to the reversible nature of MAO inhibition, the risk of interactions is a lot less than with the MAOIs and it is a safer drug to prescribe.

**Newer drugs** There have been a number of new antidepressants developed in recent years. These generally have fewer side effects than the older tricyclics.

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI) which also has dopaminergic activity. At low doses (75–150mg), its predominant action is on 5HT, with the noradrenergic activity increasing at higher doses. At low doses, it has fewer sedative and anticholinergic effects compared with tricyclics.

Reboxetine is a noradrenaline reuptake inhibitor (NARI); nefazodone inhibits the reuptake of serotonin and also selectively blocks serotonin receptors, and mirtazapine is a noradrenergic and specific serotonin antidepressant (NaSSA).

Anxiolytics and hypnotics may have a short-term role, particularly if a non-sedating antidepressant has been prescribed. However, it is essential to review such anxiolytics and hypnotics regularly and not to exceed the two to four weeks maximum duration of treatment, as recommended by the British National Formulary (BNF). As the underlying depression resolves, the symptoms of anxiety and insomnia are likely to decrease.

Combination products of antidepressants with anxiolytics or other agents such as antipsychotics are not recommended as it is not possible to review the doses of each drug independently.

Due to the limited evidence available about St John's wort, and the lack of standardisation of preparations, it is not a treatment of choice.<sup>3,4</sup>

## TREATMENT CONSIDERATIONS

Before treatment begins, the prescriber must consider whether or not antidepressants are needed, and if so, which one. The dose and length of treatment are also impor-

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**Table 1: Mode of action of antidepressants**

Class or drug	Effect
Tricyclic	Inhibition of noradrenaline and serotonin (5HT) Dopamine antagonism
Tetracyclic	5HT <sub>2a</sub> and 5HT <sub>2c</sub> antagonism
SSRI	Selective 5HT reuptake inhibition varying within the class
MAOI	Irreversible blockade of MAO-A and MAO-B
RIMA	Reversible inhibition of MAO-A
NaSSA	Pre-synaptic alpha <sub>2</sub> adrenoreceptors (increases noradrenaline transmission) and indirectly enhances serotonergic transmission, with additional 5HT <sub>2</sub> and 5HT <sub>3</sub> receptor blockade
NARI	Selective inhibition of noradrenaline reuptake Weak 5HT reuptake
SNRI	5HT and noradrenaline reuptake inhibition Weak dopaminergic. Low doses possibly act predominantly on 5HT; effect on noradrenaline increases at higher doses
Nefazodone	5HT <sub>2</sub> blockade Inhibits serotonin reuptake

know more about their medicines, the context of the treatment, as well as the relative severity of side effects and what to do about them.<sup>26</sup> Providing this information can help to overcome the negative view of medicines and allay patient fears.

Dose and length of treatment Vigorous treatment of the index episode of depression, as well as the use of appropriate prophylactic therapy, are some of the measures recommended to counteract the potential long-term nature of depression.<sup>27</sup>

The majority of drug trials define response to mean at least a 50 per cent reduction in depression score from baseline, when measured on a rating scale. But such a response may still leave patients with symptoms. The ultimate aim is for remission to a pre-morbid state.<sup>28</sup> In order to achieve this, an adequate dose of antidepressant should be prescribed. For the older tricyclic antidepressants, consensus guidelines recommend a dose of 125–150mg but this is not always adhered to in practice.<sup>29,30</sup> Opinion about whether the use of suboptimal doses affects outcome is mixed,<sup>31,32</sup> but the aim should be to put a patient on doses that have been shown to be clinically effective. This is achieved more easily with SSRIs, which do not require dose titration.<sup>33</sup> Increasing the dose of SSRIs above the recommended maximum dose is unlikely to increase effectiveness.

If antidepressant treatment is continued for six months after remission, the rate of relapse is halved.<sup>4,34</sup> This practice is becoming increasingly common.<sup>35</sup>

Maintenance therapy at the recommended dose reduces the recurrence rate in patients who have had three or more episodes of major depression in five years.<sup>36</sup> For patients with major depression, antidepressant therapy also increases the time to relapse or recurrence and reduces the severity of residual depressive symptoms.<sup>37</sup> It is important to review patients so as to maximise the benefits of therapy, especially as one study found that only a third of patients on long-term antidepressant therapy were in remission and one-fifth of the patients experienced persistent symptoms.<sup>38</sup>

Onset of action Antidepressants take a minimum of two weeks to

tant.

Place of antidepressants in treatment The strategy for treating depression has been described as “watchful waiting for minor depression, full dose treatment for major depression”.<sup>5</sup>

In mild depression, education, support and problem-solving are recommended. The efficacy of non-directive counselling when patients meet with a trained counsellor and talk through the issues, with the objective of coming to terms with them, is uncertain. In moderate depression, specific psychotherapy treatments, including cognitive behavioural therapy, interpersonal therapy and problem-solving therapy have benefits. Drug therapy is effective in moderate depression and is the treatment of choice in severe depression.<sup>6</sup>

Although the efficacy of antidepressant drugs has been questioned, systematic reviews show that they are effective in the acute treatment of all grades of depressive disorders.<sup>6,7</sup> This finding relates to younger adults, and there are no specific data for older adults.<sup>8</sup> Most benefits are to be seen in moderate to severe depression; in acute mild depression, the evidence is less conclusive. Antidepressant therapy should be considered for depressed patients with physical illness<sup>9</sup> and in the treatment of low grade chronic depression of two or more years duration.<sup>10</sup>

Relative efficacy Meta-analyses and systematic reviews have not found any significant difference in effectiveness between SSRIs and tricyclics,<sup>11,12</sup> but older tricyclics may be more effective in hospitalised patients with more severe symptoms.<sup>13,14</sup> Newer drugs have shown similar efficacy to established drugs in short-term studies.<sup>15,16</sup> There is a comparable degree of effectiveness among SSRIs.<sup>17,18</sup>

There is evidence that venlafaxine is more effective than SSRIs (but not tricyclics), particularly at doses over 150mg. The clinical significance of this is yet to be determined.<sup>19,20</sup>

Patient preference Drug therapy with antidepressants is part of a holistic approach required to treat depression. A good therapeutic relationship between prescriber and patient is essential, and patients need to be involved in their treatment. Unfortunately, many people have a negative view of antidepressants, including the fear of addiction and concern about observable side effects or effects on functioning.<sup>21–23</sup> Patients often prefer counselling, although evidence for its effectiveness is lacking. Some studies have shown that when patients have been able to choose between drug treatment and psychotherapy, the latter has not produced better outcomes.<sup>24,25</sup>

Qualitative research has highlighted the fact that patients want to

exert their effect but may take longer, particularly in the elderly. Some studies have claimed faster onsets of action for mirtazapine and venlafaxine.<sup>32</sup> The side effects of the drugs can appear before any benefits, and patients need to be made aware of these so that they do not stop taking their drugs too soon. A trial period of four to six weeks is advocated to assess the full effect before considering a switch to another drug.

**— SIDE EFFECTS**

There are marked differences between the side effect profiles of SSRIs and tricyclics. Nevertheless, no significant differences in compliance were seen in systematic reviews.<sup>39</sup> Only slightly lower discontinuation rates have been seen for newer agents compared with older tricyclics.<sup>40-43</sup> Despite the lack of strong evidence, SSRIs are more likely to be acceptable to patients.<sup>44</sup> Table 2 shows the main side effects of selected antidepressants.

**Drowsiness and sedation** Central antihistaminergic activity is responsible for the sedative properties of mirtazapine, and this is particularly pronounced at the 15mg initiation dose. In combination with central anticholinergic activity, it causes the sedation and drowsiness seen with older tricyclics. Lofepamine causes far less sedation and SSRIs have minimal sedative effects.

**Anticholinergic effects** The central anticholinergic effects of tricyclics have a marked effect on cognitive dysfunction, a particularly problematic side effect for the elderly and those who drive. Patients taking tricyclics are more likely to have road traffic accidents than those

not taking them.<sup>45</sup> Peripheral anticholinergic effects include dry mouth, blurred vision, urinary retention and constipation.

**Sexual dysfunction** Since sexual dysfunction, such as loss of libido, is symptomatic of depression it is often difficult to determine whether the dysfunction is due to drug treatment or a manifestation of the underlying illness. Antidepressants affect all aspects of sexual function through central and peripheral actions. Tricyclics, SSRIs and venlafaxine can all cause sexual dysfunction and it is worth considering a switch to nefazodone or mirtazapine if this persists. Trazodone may increase libido, and has been reported to cause priapism.

**Gastrointestinal disturbances** Nausea and gastrointestinal upset are common side effects of SSRIs, with fluvoxamine showing the highest incidence.<sup>16</sup> Peripherally, tricyclics can cause this effect by antagonism at serotonergic sites.

**Cardiovascular effects** Postural hypotension seen with tricyclics can result in falls in the elderly although this has not been proved in practice.<sup>46,47</sup> Venlafaxine, at doses over 200mg a day, can exacerbate hypertension, and the blood pressure of patients taking the drug should be monitored.

Prolongation of the QT<sub>c</sub> interval is the main cause of toxicity in overdose. The majority of fatal toxicities due to antidepressants are seen with amitriptyline and dothiepin.<sup>48</sup> SSRIs are less likely to cause this effect; moclobemide and mirtazapine also have low cardiotoxicity. Patients have survived large overdoses of SSRIs, but there has

been concern over a report of six deaths with citalopram.

**Risk of suicide** Some patients develop akathisia (motor restlessness) or increased anxiety when taking SSRIs. However, there is no convincing evidence that links SSRIs with violence and suicide.<sup>49,50</sup> The risk of suicide is identical with new and old antidepressants. This risk may increase in the early stages of treatment with any anti-depressant, therefore patients with suicidal thoughts or plans should be monitored.

**Hyponatraemia** Hyponatraemia is associated with all antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions when taking an antidepressant.<sup>51</sup> If hyponatraemia occurs, the antidepressant should be withdrawn immediately. Plasma sodium levels lower than 125mmol/L should prompt immediate referral for specialist medical care.<sup>52</sup>

**Other side effects** Other side effects include sweating (a noradrenergic effect seen with tricyclics and venlafaxine), blood dyscrasias (mirtazapine) and extrapyramidal effects (seen predominantly with paroxetine).

SSRIs often cause headache and, less commonly, gastrointestinal bleeds.<sup>53</sup> Serotonin syndrome, which is characterised by agitation, restlessness, fever, lack of coordination, confusion, myoclonus, and shivering tremor may also be seen, particularly at high doses or with concomitant medication affecting serotonin levels.

**— INTERACTIONS**

Antidepressants are known to react with other drugs. In addition, the use of alcohol while on antidepressants is not recommended due to increased sedation and the propensity of alcohol to cause or exacerbate depressive symptoms.

**Tricyclics** Tricyclics are metabolised by a range of P450 enzymes (CYP1A2, CYP2D6, CYP3A3 and CYP3A4) and can interact with a number of drugs metabolised by the same enzymes.

Barbiturates and carbamazepine reduce plasma levels of tricyclics, and cimetidine and haloperidol increase the levels. Concomitant use of drugs with similar side effects can increase sedation, anticholinergic effects and ventricular arrhythmias.

**SSRIs** SSRIs are also metabolised by a range of P450 enzymes, with CYP2D6 being the most common. This is pronounced with fluoxetine but minimal with sertraline and citalopram. Thus, fluoxetine may cause a significant increase in the levels of clozapine, phenytoin, metoprolol and clarithromycin.<sup>32</sup> SSRIs may enhance the effects of warfarin.

**MAOIs** The potential for highly significant

**Table 2: Comparison of the side effects of antidepressants<sup>32,51</sup>**

Drug	Usual therapeutic dose	Relative side effects at usual doses			
		Anticholinergic	Cardiac	Nausea	Sedation
<b>Tricyclics</b>					
Amitriptyline	150mg	+++	+++	++	+++
Dothiepin	150mg	++	++	0	+++
Lofepamine	140mg	++	+	+	+
<b>SSRIs</b>					
Fluoxetine	20mg	+	+	++	0
Citalopram	20mg	0	0	++	0
Paroxetine	20-30mg	0	0	++	0
Sertraline	100mg	0	0	++	0
<b>RIMA</b>					
Moclobemide	300mg (150mg twice daily)	+	0	+	0
<b>NaSSA</b>					
Mirtazapine	30mg	0	0	0	++
<b>SNRI</b>					
Venlafaxine	75-150mg	0	++	++	+
Nefazodone	400mg	+	0	++	+

**Key:** 0, little or minimal effect; +, mild effect; ++, moderate effect; +++, marked effect

interactions with foods and drugs has made MAOIs unpopular in recent years. Hypertensive crisis may occur in conjunction with sympathomimetic amines, which are widely available in cough and cold remedies. Food and drink restrictions also limit their use in patients. The concomitant use of an MAOI and another antidepressant can produce serious toxicity and therefore care is required if switching from one to the other.

RIMAs have fewer interactions with food when compared with MAOIs, although problems may arise if large quantities of tyramine-containing foods are consumed.

### CHOICE OF DRUG

For the majority of patients, antidepressants are likely to be equally effective. The choice of treatment should be based on symptoms, age, weight, lifestyle, patient acceptability, toxicity and cost.<sup>9</sup> Previous response to antidepressants can predict future response. In addition, concurrent illness and medication, as well as likely compliance, should be considered.

There is a lower risk of relapse and recurrence when antidepressant therapy is stable and this is why it is important to make the right choice at the outset.<sup>54</sup> For most patients, either fluoxetine (the cheapest SSRI available) or lofepramine, will be the preferred choice. In hospital inpatients who can tolerate them, the older tricyclics may be indicated. Clomipramine and SSRIs are more useful if there are obsessional components. MAOIs and moclobemide are useful in atypical or phobic depressions.

In pregnancy and breast feeding, there has to be a balance between maintaining mental state and the risk of exacerbation of side effects such as constipation or foetal abnormalities. There is considerable experience with the use of tricyclics in pregnancy but these should be withdrawn over three to four weeks before delivery to avoid withdrawal effects in the neonate. All antidepressants pass into breast milk although the effects of tricyclics are more widely known. Table 3 contains information on the use of anti-depressants in other special cases.

Any antidepressant taken for six weeks or more should be withdrawn slowly over a

minimum of four weeks to avoid withdrawal symptoms. These include gastrointestinal disturbances, headaches, chills, insomnia, anxiety, agitation and motor restlessness.<sup>55,56</sup> Paroxetine is associated with the highest number of reports of withdrawal effects.<sup>50</sup> If these symptoms occur, the withdrawal period should be extended and the patient reassured. Symptoms rarely last more than one to two weeks but if symptoms are severe or prolonged, the antidepressant can be restarted at a dose that is effective but devoid of the effects of withdrawal and then the dose can be tapered gradually. If these effects occur during treatment, the possibility of non-compliance should be considered.

### WHEN MONOTHERAPY FAILS

If a patient has not responded to an appropriate dose of antidepressant after a period of four to six weeks, then the patient's compliance should be investigated. It would be wise to find out if there is a particularly troublesome side effect. Also, it would be worthwhile confirming the validity of the diagnosis. If these investigations do not reveal any problem, then other strategies that can be pursued include switching to a different class of drugs, augmentation, combining antidepressants and electroconvulsive therapy.

Care is needed when switching patients from one class of drugs to another. Some factors to consider when switching include:

- The dose and half-life of the initial drug
- Potential interactions
- Cholinergic rebound or antidepressant withdrawal effects of the initial drug (which could be erroneously interpreted as side effects of the second)

The speed of the switch depends on the severity of the depression, but the patient may need more careful monitoring if it is done quickly. In general, it is best to taper the dose of the initial drug before discontinuing it and then slowly introducing the new drug.

Washout periods vary. Switching from a tricyclic antidepressant to another drug is usually less problematic as, in general, the former have shorter half-lives, although 7–14 days should be allowed if switching from a tricyclic to an MAOI.

Switching from an MAOI requires a two-week wash out, while for a RIMA, one day will suffice. SSRIs vary in half-life: citalopram (about one week), paroxetine and sertraline (two weeks), and fluoxetine (four to five

weeks). Therefore, when switching from an SSRI to a tricyclic, it is necessary to wait several days for peak levels of these drugs to fall before adding a tricyclic cautiously at low dose and then slowly building up. Care is needed while the first drug remains in circulation (up to five weeks for fluoxetine), as the potential for interaction also remains. Side effects should be monitored, as there may be increased tricyclic side effects or serotonin syndrome depending on the drug used.

It is believed that 66 per cent of patients respond to tricyclics or SSRIs.<sup>57</sup> If there is no response after an adequate trial of two classes of antidepressants, and non-compliance and wrong diagnosis have been ruled out as possible causes of such a lack of response, the patient can be considered treatment-resistant. Partial response after such a trial may also need further action as patients are at a higher risk of functional impairment, relapse and suicide.<sup>58</sup>

Venlafaxine, at a dose of 200–300mg daily has been shown to be slightly superior to paroxetine in treatment-resistant depression.<sup>59</sup> Blood pressure monitoring is required and patients may experience nausea, vomiting and sweating.

Augmentation Augmentation refers to the practice of adding a drug with no intrinsic antidepressant activity to an antidepressant already being taken by a patient; this has the aim of increasing antidepressant effect. The resulting enhancement of antidepressive effect could be due to a separate mechanism from the original antidepressant or it could be due to an increase in plasma levels of the existing antidepressant. In the latter case, there can be an increase in the incidence of adverse effects. Augmentation should only be initiated and monitored by specialists.

Lithium Although adding lithium to both tricyclics and SSRIs has been shown to be effective, the evidence base is stronger for tricyclics than for SSRIs. Lithium is well tolerated in patients taking tricyclics and adverse effects are a combination of those of the two classes of drugs. An increase in central nervous system effects and lithium toxicity has been reported when lithium is combined with an SSRI. Evidence is limited with the use of lithium and a MAOI, but no serious adverse events have been reported.<sup>32</sup> Care is needed when prescribing lithium in the elderly as impaired renal function can increase lithium levels and potentially cause toxic effects.

Tryptophan Tryptophan, available as Optimax in the UK, is a precursor of 5HT that is used in combination with tricyclics and other antidepressants. The risk of eosinophilia-myalgia syndrome means that it is only licensed for use by hospital specialists as a treatment for resistant depression in patients with severe depression of more than two

**Table 3: Choice of antidepressant in special cases**

Special cases	Avoid/higher risk	Lower risk
Epilepsy	Tricyclics Venlafaxine	SSRIs Reboxetine
Cardiovascular disease	Tricyclics Tricyclics	SSRIs Lofepramine
Elderly		SSRIs (particularly sertraline and citalopram)
Liver damage	Lofepramine	Paroxetine

years' continuous duration after adequate trials of standard drug treatment, and only as an adjunct to other treatments. Patient and prescriber must be registered with the Opti-max Information and Clinical Support (OPTICS) unit.<sup>51</sup> There is a risk of developing serotonin syndrome if tryptophan is taken with serotonergic drugs.

**Antidepressant combinations** If antidepressant combinations are used at all, it should be under specialist supervision. SSRIs and tricyclics given in combination increase the plasma levels of tricyclics.<sup>60</sup> Some newer drug combinations are currently being tried, but they are based on predicted pharmacological effects rather than clinical trials. These should be discussed with the patient and informed consent obtained.<sup>52</sup>

**Electroconvulsive therapy** Electroconvulsive therapy should normally be reserved for people who cannot tolerate, or who have not responded to, drug therapy. It can be useful in life-threatening situations if a patient has stopped eating or drinking or when a rapid response is required.<sup>61</sup>

**Other strategies** Other treatments have also been tried in treatment-resistant depression. Some of these treatments (eg, levothyroxine and tri-iodothyronine) are supported by published evaluations, while others (eg, pindolol and lamotrigine) have limited published information on their effectiveness. These treatments should be reserved for specialist use.

#### IMPROVING OUTCOMES

**A** number of approaches have been used to improve treatment outcomes in depression.

**Education** Educating patients can help them cope with symptoms but it does not necessarily improve outcomes.<sup>62,63</sup> Leaflets on their own have not been effective but could be useful as part of a package.<sup>64</sup>

**Psychological therapies** As mentioned earlier, combining problem-solving with antidepressant treatment is not effective in major depression.<sup>65</sup> Combining antidepressants and psychotherapy may be effective in chronic severe depression or for those with a partial response to antidepressants alone.<sup>66</sup>

**Systems of care** Even though effective treatments for depression exist, the literature is full of studies showing undertreatment and poor outcome in primary care.<sup>67</sup> A more systematic approach to the treatment of depression, in which patients are actively followed up on a regular basis using an agreed protocol, has been suggested.<sup>68</sup> The type of treatment is probably not as important as ensuring that any treatment is carried out

properly and that there is follow-up.<sup>69</sup>

Intensive follow-up can produce benefits but these may be purely psychosocial.<sup>70,71</sup> Interventions increasing adherence to drug therapy have improved outcomes but only in moderate to severe depression at full therapeutic doses,<sup>64,72-74</sup> or in patients who had not responded at six to eight weeks.<sup>75</sup> Practical and cost-effective ways of delivering this approach in the UK can be considered but it is probably most beneficial to target patients suitable for such follow-up.

A clinic approach has been suggested<sup>76</sup> and a chronic disease management model proposed to encourage compliance, monitoring and support.<sup>77</sup> Depression clinics managed by nurses already exist<sup>78</sup> but benefits have yet to be proved.<sup>79,80</sup> As optimisation of drug therapy is an integral part of treatment, a role for pharmacists exists and has shown some success, although further work is currently being carried out.<sup>23,81</sup> This is worth pursuing as even modest improvements could result in considerable benefit to those who suffer under the burden of depression.<sup>82</sup>

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