Diagnosing and treating depression in general hospitals

Chris Hawley

Depressive conditions are common in general hospital patients but if recognized can be treated by both pharmacotherapeutic and psychotherapeutic means. Although hospital doctors cannot be expected to be masters of the intricacies of treating depression, they can make the diagnosis and prescribe first-line antidepressants to the benefit of most cases.

This article is written with the needs of general hospital specialists in mind and promotes the view that all doctors can have the skills to recognize depression and supervise simple, effective treatment. While not diminishing the importance of psychotherapeutic approaches this article will focus principally on the pharmacotherapeutic treatment of depression: antidepressant therapy being the option most immediately at a doctor's disposal.

A sceptic might reasonably ask how good antidepressants are at treating depression. If the treatment available to the clinician for a given medical condition is powerfully effective and efficacious, e.g. with a number needed to treat (NNT) tending towards 1, then there is an imperative to identify the condition and administer the beneficial treatment. However, with treatments of lesser benefit, e.g. NNTs of 10, 50 or 100, the imperative to diagnose and treat is proportionately less. One could say that the effort involved in recognizing and diagnosing depression is only worthwhile if something can be done in response.

Antidepressant drugs are unequivocally efficacious in the treatment of depression. There have been many dozens of studies in which antidepressants have been shown to be superior to placebo (Joffe et al, 1996). This represents an unassailable body of data, but still leaves the question: by how much are antidepressants superior to placebo?

The answer to this question is illustrated in *Figure 1*. As a rule of thumb, about one third of patients will improve significantly with placebo, and two thirds will improve with active antidepressant. This represents an NNT of approximately 3 and a substantial level of efficacy, although the corollary of this is worth noting: that one third of depressed patients will improve substantially without treatment and of those treated with antidepressant one third will fail to improve despite the treatment.

Although the usefulness of antidepressant treatment is beyond doubt, there is a qualification: this impression of NNT derives from the conditions of randomized controlled trials, and a full understanding of the prognosis for depression must take into account observational studies as well. This will be covered later in this article.

THE DIAGNOSIS OF DEPRESSION

For those who feel that the diagnosis of depression is imprecise and largely subjective, help is at hand in the shape of the American Psychiatric Association's (2000) *Diagnostic and Statistical Manual* IVth edition (DSM-IV). The DSM-IV sets out practical rules to guide diagnosis of the various forms of depression. Of these, the diagnosis of major depression is of the greatest importance. The diagnostic criteria for major depression are summarized in *Table 1*. In essence there are nine characterizing features of major depression, and if the depressed person exhibits five or more of these nine continuously for 2 weeks or more, then the diagnosis can be said to be present. However, *Table 1* is only a summary of key symptoms and the full defini-

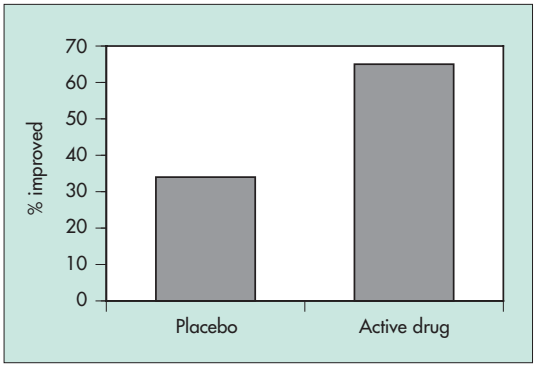

Figure 1. Percentage of major depressed cases with more than 50% improvement in symptoms over 6 weeks of treatment: typical clinical trial data.

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tion in DSM-IV adds some qualifications. The most important of these qualifications for hospital doctors is that the symptoms are not directly caused by a general medical condition, the use of substances, or prescription medications. What does constitute direct causation is a matter of clinical judgment and is not further defined.

Major depression is not to be equated with 'severe depression'. Major depression itself may be graded as mild, moderate or severe. The mildest case (e.g. with just five of the nine features) may not appear to be depressed upon casual inspection or superficial conversation. However, the great value of the major depression diagnosis (at any level of severity) is that it identifies patients most needing of antidepressant therapy – and most likely to benefit. DSM criteria can be used as a checklist of questions by the clinician, which may take 5–10 minutes.

In general practice or psychiatric settings, identifying major depression is often easy because the patient's main presenting complaint, such as insomnia, lassitude or depressed mood itself, readily raises the possibility in the clinician's mind. Matters may be a little less easy in hospital settings. The patient is likely to be under clinical attention for a somatic disorder and major depression is an additional disorder to the main reason for attendance. Furthermore, the patient may not see the physician or surgeon as the appropriate person to whom to report psychological symptoms. Thus a fairly active index of suspicion should apply, given that the prevalence of depression in general medical populations is often as high as 20% (Anderson et al, 2000).

A special case is the patient with persistent physical symptoms which remain medically unexplained despite adequate investigation. Diagnoses that may become attached to such patients include chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome. Although different specialists tend to attach different 'functional' diagnoses, such patients themselves have rather similar and wide-ranging somatic symptoms. The diagnoses differ by speciality because specialists are inclined to ask about symptoms that most relate to their speciality area. Although the management of cases with medically unexplained symptoms is both complex and uncertain a proportion will have treatable depressive disorder. Thus routine enquiry into the psychological state is recommended (Bass et al, 2001).

TABLE 1.
Summary of DSM-IV diagnostic criteria for major depression

Depressed mood by self report of appearance
Lack of interest in most or all usual activities
Appetite change (decreased or increased) or corresponding weight change
Insomnia or hypersomnia
Agitation or retardation
Lack of energy
Feelings of worthlessness
Diminished concentration
Thoughts of death/suicidal thoughts

DSM-IV = *Diagnostic and Statistical Manual* IVth edition. From American Psychiatric Association (2000)

TABLE 2.
Standard and maximum doses of some commonly used antidepressants

Drug	Brand name	Standard daily dose	Maximum daily dose
Paroxetine	Seroxat	20 mg	50 mg
Fluoxetine	Prozac	20 mg	20 mg
Sertraline	Lustral	50 mg	200 mg
Citalopram	Cipramil	20 mg	60 mg
Escitalopram	Cipralex	10 mg	20 mg
Fluvoxamine	Faverin	50 mg	300 mg
Venlafaxine	Efexor XL	75 mg	225 mg

Treatment choices

There are some thirty antidepressants available in the UK; a somewhat bewildering array. However, matters can be simplified. Except in the hands of psychiatrists the tricyclic and related antidepressant drugs (British National Formulary (BNF) section 4.3.1; British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003) can be largely disregarded. So too can the monoamine oxidase inhibitors (BNF sections 4.3.2). Although tricyclic antidepressants and monoamine oxidase inhibitors do have a place, it is a limited one and the physician or surgeon does well to use only those antidepressants which are the most simple and most safe.

Suggestions for the 'simplest and safest' treatments are listed in *Table 2*. The standard doses mentioned are the basic daily doses known to be efficacious. All these agents are presynaptic serotonin reuptake inhibitors. Venlafaxine has an additional effect of noradrenaline reuptake at doses toward 225 mg/day.

Any of these agents at the basic daily dose would be a suitable prescribing option for the hospital practitioner. However, there are some finer points of preference between them. Fluvoxamine, although sound pharmacologically, is hardly used in the UK and may have poor dispensing or formulary availability. Fluoxetine has an active metabolite with a very

long half-life (norfluoxetine, 120 hours) and causes marked inhibition of hepatic CYP450 enzymes. Paroxetine is associated with withdrawal effects which although not medically serious can be a significant inconvenience.

It has been an historical dictum that all antidepressants have the same efficacy and that the only differences between them are the side-effect profile and other peripheral pharmacological considerations. However, this is no longer tenable: data for at least three agents (clomipramine, escitalopram and venlafaxine) indicate a greater degree of antidepressant efficacy than other antidepressants. Clomipramine is a particularly toxic tricyclic drug and is not suitable for general medical populations. The evidence for the superior efficacy of venlafaxine is substantial although this is at higher doses with reduced tolerability (Thase et al, 2001). Generic citalopram is a racemic mixture of s- and r-enantiomers and does not have greater than standard efficacy. Escitalopram solely contains the s-enantiomer and there is credible evidence that the mono-enantiomer has superior efficacy to the mixture without any reduction in tolerability (Waugh and Goa, 2003).

Timeframes for treatment

In the introduction to this article it was asserted that antidepressants have a NNT of about 3. But the short-term, randomized controlled studies from which this figure derives give only a partial insight into the prognosis for major depression. This is an important matter for it begs the question 'how long does one have to treat before expecting improvement?'

A number of naturalistic studies have examined the time course to recovery in major depression (Keller et al, 1992; Spijker et al, 2002). The time taken for half of patients to achieve full remission has been estimated between 12 and 26 weeks (*Figure 2*). However, precise figures are less important than the general implication: that even with treatment improvements accrue slowly over months rather than weeks. Clinicians should not expect early improvement, e.g. after 2–4 weeks of antidepressant therapy. If the patient is unimproved for too long the generalist may wish to enlist psychiatric help but what constitutes 'too long' is virtually impossible to define absolutely given the heterogeneous nature of major depression. For example, if the patient is profoundly ill with depression one might wish to elicit psychiatric help from the outset whereas for a mildly ill case it is not unreasonable to wait several months before becoming concerned about insufficient improvement.

There are clear data indicating the value of continuation of antidepressant therapy. Once the symptoms of depression have fully resolved it should be the clinician's standard recommendation to continue the full dose of antidepressant for a further 6 months. Such continuation treatment approximately halves the relapse rate although a quarter or so of patients will still relapse over the 6-month period.

There is also compelling evidence for use of maintenance treatment where depression has been a recurring problem for the patient over many years. For such cases maintenance treatment for 3, or maybe 5, years can reduce the recurrence rate substantially. However, very long-term treatments are probably best referred to a psychiatrist.

DRUG INTERACTIONS

Many antidepressants inhibit cytochrome P450 hepatic enzymes. The coadministration of an enzyme inhibitor (e.g. an antidepressant) with a drug that is a substrate for the same enzyme can result in the levels of that substrate drug being greater than would otherwise have been the case. Medically serious complications can result.

However, it is unrealistic to expect all doctors to have an encyclopaedic knowledge of all potential CYP450 interactions. Two general rules substantially minimize the risks. First, when prescribing an antidepressant reflect on whether there is the potential for interaction with another drug already being prescribed and take advice when in doubt. Second, chose a drug with the least general propensity for causing interactions (*Table 3*) as there is then less prospect of making an error in oversight.

Side effects

Table 4 lists the most commonly occurring adverse effects with serotonin reuptake antidepressants. The exact figures are less important than the overall impression of nature and frequency. Many adverse effects of antidepressants reported by patients also arise frequently under

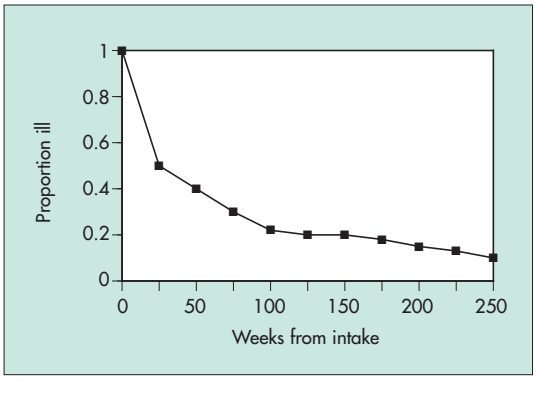

Figure 2. Naturalistic remission rates. Remission defined as the first week of 8 weeks with a psychiatric status rating score of 1 or 2. From Keller et al (1992).

placebo treatment, e.g. headache is just as common with placebo as it is with active treatment.

Although antidepressants are generally well tolerated about 15% of patients discontinue treatment because of adverse effects. However, a patient who is intolerant of one serotonin reuptake inhibitor may well tolerate another. If the patient is intolerant of two agents, and the clinician feels that antidepressant treatment is important, the advice of a psychiatrist might be obtained.

Although most adverse effects of antidepressants subside over the first few weeks of treatment, sexual side effects are often persistent. Although estimates vary, about one third of patients treated with serotonin reuptake inhibitors experience significant impairment of sexual function (Montejo et al, 2001). Impotence and ejaculatory failure in males are particularly notable but the sexual function (loss of libido and anorgasmia) of females is also affected. In the author's experience, patients accept sexual side effects early in treatment but less so when the depression has improved – which may result in premature treatment discontinuation, with risk of relapse. Although it may not always be appropriate for the clinician to probe for sexual side effects (e.g. if the patient is so medically ill that sexual activity is not felt to be an option) a simple question of the patient regarding the presence of sexual side effects is usually rewarded with a straightforward response. Where sexual side effects are an obstacle to compliance a psychiatrist's opinion can be sought. The only truly reliable remedy for sexual side effects is to discontinue the offending agent although sildenafil minimizes antidepressant-associated impotence in most cases (Nurnberg et al, 2003).

NON-PHARMACOLOGICAL APPROACHES TO DEPRESSION

The high prevalence of major depression in general medical populations allows the implication that medical disorders themselves increase the propensity to depression. Mediating factors may include the features of the medical disorder itself, the treatment, and social impairments incurred by the condition. Pain and insomnia arising from general medical disorders are commonly cited as increasing the propensity to depression in general medical populations. If pain and insomnia can be better controlled through the optimal use of analgesics, or the judicious use of hypnotics, then that is desirable.

In the BNF many drugs for general medical disorders are said to have 'depression' as a side effect. In the author's experience, instances where the patient's depression can be directly attributed to a drug are rather uncommon. However, in circumstances where there appears to be a plausible (as opposed to merely tenuous) relationship between a medicine and the onset of depression a dechallenge can be considered.

There is a broad range of psychotherapeutic approaches applicable to the treatment of depression. However, judging whether a patient is a suitable candidate for psychotherapy, and if so which sort, is a matter of considerable subtlety. Where it strikes the hospital practitioner that a psychotherapy might be suitable (or, as is often the case, the patient expresses a preference for psychotherapeutic treatment) it is best to refer to a psychologist or psychiatrist for an opinion.

DEPRESSION AND SPECIAL CIRCUMSTANCES

Depression and the elderly

Old age is not in itself a cause of depression but the many illnesses, privations and losses that attend old age are significant risk factors. Although a full exposition of depression in old age is outside the scope of this article, three issues deserve to be highlighted.

First, depression is common, but often covert. Even on direct interrogation the elderly person

TABLE 3.
P450 enzymes inhibited by antidepressants

Drug	P450 enzymes inhibited to a minor or moderate degree	P450 enzymes inhibited to a major degree
Citalopram	2D6	none
Escitalopram	2D6	none
Fluoxetine	1A2, 2B6, 2C9, 3A4	2C19, 2D6
Fluvoxamine	2B6, 2C9, 2D6, 3A4	1A2, 2C19
Sertraline	1A2, 2B6, 2D6, 3A4	none
Paroxetine	1A2, 2C9, 2C19, 3A4	2B6, 2D6
Venlafaxine	2D6	none

From Cozza et al (2003)

TABLE 4.
Most common adverse events with serotonin reuptake antidepressants

Adverse event	Frequency
Nausea	22%
Dry mouth	21%
Headache	17%
Agitation	14%
Dizziness	13%
Diarrhoea	13%
Anxiety	13%
Insomnia	12%
Constipation	10%

may not articulate the prime symptom of major depression – the depressed mood. The clinician may have to infer the depressed state from other cues, e.g. lethargy, insomnia, weight loss or otherwise unexplained decline in cognitive function.

Second, the more advanced elderly have limited 'functional reserve' and comparatively minor degrees of depression may cause a precipitous decline in daily living skills. Supportive and social measures are likely to be required, and a low threshold for referral to a social worker or community nurse is recommended.

Third, the elderly tolerate antidepressants poorly. Depending on age and infirmity one will commence antidepressant therapy at between a quarter and one tenth of the standard daily dose. The dose is then increased, according to tolerability, towards the standard dose over a month or so. The finely graded dose increments are best undertaken using an antidepressant available as a liquid presentation. Options are Cipramil (citalopram, 40 mg/ml; Lundbeck, Milton Keynes), Prozac (fluoxetine, 20 mg/5 ml; Eli Lilly, Basingstoke) and Seroxat (paroxetine, 10 mg/5 ml; Glaxo Smith Kline, Uxbridge).

Repeated self harm

One special group seen is hospital settings are patients who engage in repetitive self harm, most usually by recurrent overdose or self laceration. Although superficially presenting as 'depressed and suicidal' the most common psychiatric diagnosis for such patients is borderline personality disorder. Changeable mood, poor frustration tolerance, anger and impulsivity also characterize such persons. These cases require a quite different approach to management than cases of major depression, The hospital practitioner is well advised not to intervene, but rather refer for a psychiatrist's diagnosis and opinion.

Depression in terminal illness

Sadness and grief naturally accompany the knowledge that one has a terminal illness. However, if major depression supervenes in the terminal phase attempts can be made to address this. Fisch et al (2003) conducted a placebo-controlled study of fluoxetine in terminal cancer patients with depression and found the active drug provided worthwhile control of the depressive symptoms as well as superiority on quality of life measures. Of course, the psychological care of the dying person involves considerably more than prescribing an antidepressant but this study emphasizes that the treatment of depression should not be neglected – even under the unpromising conditions of the impending end-of-life.

CONCLUSION

Depression is a ubiquitous condition, but has a particularly high prevalence in general medical populations. It is well within the competence of the general hospital practitioner to diagnose straightforward cases of major depression and instigate simple antidepressant treatment where needed. Although more complex cases will require psychiatric attention the benefits of simple antidepressant treatment for the non-complex majority of cases can be substantial. **HM**

Figure 2 *is reproduced by kind permission of the American Medical Association and* Table 3 *is reproduced by kind permission of the American Psychiatric Association.*
Conflict of interest: Professor Hawley has received research funding from governmental, charitable and industry sources, and been a paid lecturer by a number of pharmaceutical companies, the NHS and higher education sectors.

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KEY POINTS

- Major depression is the diagnosis of greatest importance: the *Diagnostic and Statistical Manual* provides simple rules for making this diagnosis.
- Antidepressant therapy is effective in reducing depressive symptomatology in the majority of cases.
- Even in cases where depression accompanies serious medical illness antidepressant therapy can still be of assistance.
- Modern antidepressants are simple and safe although the clinician should be aware of the potential for cytochrome P450-mediated drug–drug interactions.