

Gavel

Evidence-Based Medicine *in practice*

Managing depression in general practice

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- Most cases of depression are treated in primary care. At least one patient with depressive symptoms will present at each GP surgery session.
- The natural history of depressive illness, including its response to treatment in a general practice population, is not fully understood.
- Psychiatric definitions of depression (both major and minor) are rarely used by GPs in making decisions on treatment but are an essential aspect of clinical trials.
- Tricyclic antidepressants (TCAs) and selective serotonin reuptake-inhibitors (SSRIs) show similar clinical efficacy but have different side-effect profiles.
- Treatment decisions are often based on side-effect patterns. However, the influence of these side-effects on patient compliance is often difficult to estimate.
- Newer classes of antidepressant drugs have recently emerged. They may show advantages for some patient groups, but their impact on overall prescribing patterns is so far limited.
- No clear-cut economic advantages have been demonstrated for the use of different classes of antidepressant or for individual drug agents.
- Clinical guidelines based on a more detailed study of depressed patients in primary care are urgently required.

Depressed patients in general practice

Depression is among the most common psychiatric presentations seen in general practice.¹ Of more than 2,000 consecutive GP attenders presenting in a year, over a third (35.3%) had a psychiatric disorder.¹ Of these, almost 5% met the criteria for major depression and slightly fewer had a minor depressive disorder.¹ Only stress/adjustment disorders were more common.¹

These figures reflect the widespread occurrence of depressive complaints. Community studies suggest a lifetime prevalence of major depression as high as 5–12% for men and 10–25% for women (Table 1).^{2,3} By far the majority of these cases will be treated in general practice. However, approximately half of these cases will not be recognised at the first consultation, and around 20% will remain unrecognised six months later.⁴

The joint initiative by the Royal College of General Practitioners and the Royal College of Physicians to 'defeat depression' in the early 1990s produced estimates for the burden of depression in general practice. These figures are easily remembered and are widely quoted (Table 2, opposite).⁴ The consensus was that 5% of a GP's patients have major depression; another 5% of patients show milder episodes and a further 10% have 'some depressive symptoms'.⁴ Translated into a GP list of 2,000 patients, this means that 100 patients will have major depression and a further 100 patients will have minor depression. Another 200 patients will have some

symptoms. The joint colleges expressed the GP's problem in very practical terms: 'at least one patient with mild depression or worse is likely to present at each surgery session'.⁴

Questions of definition

But such figures mean very little until these different levels of depression are defined. The criteria for what actually constitutes major and minor depression have been laid down by the American Psychiatric Association in its *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV,⁵ Box 1, opposite) and in the European *International Classification of Disease 10*.⁴ The two systems provide a largely similar list of symptoms.

To qualify for major depression, patients must exhibit at least two weeks of depressed mood or loss of interest or pleasure *together with at least four of symptoms a–g in Box 1* (opposite).⁵ For a diagnosis of minor depression, they must exhibit 1–3 of them.

Many psychiatrists also recognise the condition of *dysthymia*. This is a chronic mood disorder, said to be present in 3–6% of the population.^{6,7} To qualify for dysthymia, depressed mood must occur on most days during a two-year period and two other criteria for major depression (apart from psychomotor disturbances) must also be present.⁷

Although they define the condition, few GPs will consult these lists of symptoms when deciding which of their patients are depressed or are likely to injure themselves. The lists are, however, used to select patients for clinical

Table 1. Prevalence (%) of major depressive disorders in the community

Men			Women			Total	
Lifetime	12-month	Point prevalence	Lifetime	12-month	Point prevalence	Lifetime	12-month
12.7	7.7	–	21.3	12.9	–	17.1	10.03
5–12	–	2–3	10–25	–	5–9	–	–

Data from Kessler et al,² and Gumnick and Nemeroff³

trials. They are the benchmark used to interpret efficacy studies of antidepressive agents. Such studies show, for example, that 60% of patients with major depression respond to initial medical treatment and that 30% respond to placebo.⁵ Many patients with dysthymia also respond to treatment but most of those with minor depression do not.⁵ Randomised controlled trials are the essential first step in evaluating any new drug therapy. But such studies of *efficacy* (using selected patients in idealised conditions) do not necessarily reflect the GP's experience of a drug's *effectiveness* when used by patients in the real world.

These criteria also portray depression as an episodic, remitting condition. However, it is better regarded as a chronic or recurrent illness.^{8,9} Unfortunately, studies of its long-term natural history among GP patients are rare. Up to a third of those treated with apparent success for major depression may relapse in one to two years, but the patient's response after three months of treatment is a strong predictor of the probability of relapse over two years.⁹

GP management of depression

The recognition that depressed patients in primary care present particular problems has generated a large volume of literature on the management of depression in general practice, covering a range of differing viewpoints. Some authors place emphasis, for example, on the use of assessment instruments like the General Health Questionnaire (GHQ) for patient screening.¹⁰ Others discuss the value of psychotherapies, such as structured problem-solving, for trying

Table 2. Prevalence (%) of depressive disorders among GP consulters

	% of GP consultations
Major depression	5
Milder episodes	5
Some depressive symptoms	10

Data from Paykel and Priest⁴

to reduce long-term vulnerability factors and hence the probability of relapse.

Experience of treating depression in general practice shows the need for a high index of suspicion. It may often present in the form of somatic symptoms, frequently linked to problems in the patient's family or to apprehension about the future. Anecdotal evidence suggests that the practice nurse may be the first to spot depression. For any treatment (including drugs or counselling) to succeed, the patient also has to acknowledge that they have the illness. They also have to accept that the treatment package is appropriate for them. The therapeutic alliance therefore assumes a major importance.^{5,10}

The last decade has produced a wide range of clinical guidelines. These have appeared in the wake of the 1992 joint initiative by the Royal Colleges⁴ and the subsequent 1993 report from the NHS Centre for Reviews and Dissemination.¹¹ This report, cited by Littlejohns *et al* in their review of clinical practice guidelines,¹² called for the use of *evidence-based* guidelines for the detection and management of depression in primary care to provide a 'national template' to guide local management strategies.

Box 1. Diagnostic criteria for major depressive episode⁵

At least two weeks of depressed mood or loss of interest/pleasure, plus at least four of the following symptoms:

- (a) Significant weight loss or gain/appetite disturbance
- (b) Insomnia/hypersomnia
- (c) Psychomotor agitation/retardation
- (d) Fatigue/loss of energy
- (e) Feelings of worthlessness/excessive or inappropriate guilt

- (f) Diminished ability to think or concentrate/indecisiveness
- (g) Recurrent thoughts of death/suicidal ideation, attempt or plan.

Symptoms must cause significant distress or impairment of functioning; they must not be due to substance abuse or a medical condition, and must not be better accounted for by bereavement.

The guidelines also lead to the production of flow charts for drug choices. Ideally these can be updated to accommodate new agents as they appear. Such guidelines all tend to emphasise the following.

- Drug treatment should be used for moderate to severe depression, irrespective of its cause.
- TCAs at doses of 125–150 mg/day are effective for the treatment of major (but not mild) depression. There is no benefit from doses <75 mg/day and adequate doses should always be used. Upward titration may be required to counter side-effects.
- Antidepressants may take up to four weeks before any effect is evident. Avoid switching to another drug until the first drug has been tried at an effective dose for 4–6 weeks.
- If the patient does not respond, check compliance and reconsider the diagnosis.
- Following a response, treatment should be continued for at least 4–6 months.
- A minority of patients at high risk of recurrence may benefit from prophylactic treatment for 1–5 years in an attempt to prevent relapse.¹³
- There is a tendency for both patients or their doctors to stop or reduce medication too soon. Withdrawal of antidepressants should be gradual, to avoid the re-emergence of symptoms or a discontinuation syndrome which can occur with any type of antidepressant, regardless of class.¹³

Littlejohns *et al*¹² identified 45 sets of clinical guidelines for the management of depression, produced over a five-year period. They produced a detailed critique of nine of them (six national and three local).¹² Although the guidelines are described as evidence-based, Littlejohns *et al* emphasise that clinical trials do not necessarily reflect the population of patients in primary care. They also warn that such guidelines 'are intended to be a practical guide for clinicians managing real patients and should not detract from the need to tailor care to the individual patient's needs'.¹²

The value of educational programmes

The use of clinical practice guidelines is starting to be tested. A guideline-based educational programme for GPs was conducted in 60 primary care practices in Hampshire.¹⁴ An attempt was made to improve the recognition of depressed patients using a

rating scale. Once recognised, the trial also attempted to improve patient outcome.

Of 21,000 patients screened, 4,000 were classified as depressed. However, the clinicians' ability to detect depression among their patients was not improved by the programme, nor was the clinical outcome of patients improved at six weeks or six months.¹⁴ This led the authors to question the extent to which guideline data, based on controlled clinical trials, can be applied to the 'skill mix in management ... needed to improve the outcome of depression in primary care'.¹⁴

Why can't GPs follow guidelines on depression?

The difficulty of applying clinical guidelines to the GP management of depression was featured in a recent *BMJ* editorial¹⁵ which identified three separate problems.

First, the diagnosis of depression in primary care is not easy. GPs differ in the threshold at which they label patients as 'cases' needing treatment. Secondly, many GPs also emphasise the effect of the patient's life situation on the continuation or remission of their symptoms. They doubt the effectiveness of simple drug therapy in the face of major social problems. Finally, patients themselves are often reluctant to accept the use of drugs. Many take sub-therapeutic doses of tricyclics and discontinue them after a few weeks. GPs may also collude in this and be tempted to prescribe safe, rather than effective, doses. This may help to explain why, in an analysis of more than 16,000 patients with new episodes of depression followed for six months, only 6% of those initially given TCAs and 33% of those given SSRIs were prescribed treatment consistent with the guidelines.¹⁶

The implication of these findings is important. Significant improvements in treatment (particularly drug treatment) may not occur until the natural history of the disease and the evidence base for its management are both better understood.

Choice of drugs for depression

Treatment guidelines since 1992 have stressed the wide choice of available antidepressive agents.⁴ Prescribers have been encouraged to become familiar with at least one or two agents from each class as patients may not tolerate the first drug that they receive. Patients failing on a

full therapeutic trial of one agent may still do well on a different drug.¹⁷

Different drug classes have been recommended for different patient presentations; for example, SSRIs for moderately depressed patients and those with premorbid anxiety or panic disorders; TCAs for more severe mood disorders and those with chronic pain;¹⁰ and monoamine oxidase inhibitors (MAOIs) for atypical depression, though MAOIs' side-effect potential tends to limit their overall use.³

Benefits and adverse reactions

In terms of clinical efficacy, there appears to be no difference between TCAs and SSRIs,⁴ so prescribing choices have depended on the perceived balance of benefits to side-effects.

So much experience has accumulated with the use of TCAs that some still regard them as the 'gold standard' for antidepressive efficacy.³ The rate of response (50% or greater decrease in depression severity) has been put as high as 60–70% and the rate of true response (with no residual symptomatology) at 40%.³

Anticholinergic side-effects are the most common and involve dry mouth, urinary retention, constipation, tachycardia and blurred vision.³ Other effects include orthostatic hypotension (with the possibility

of falls and fractures) and cardiac conduction delays. Partly as a result of the latter, TCAs are reported to be the principal class of drugs responsible for death by poisoning, at least in the USA.³ This makes some GPs cautious about prescribing them, particularly in any patients judged to be at increased risk of suicide.

SSRIs have a greater safety margin than TCAs. Their most common side-effects are due to increased serotonin activity and include nausea, headache, insomnia, nervousness and agitation and sexual dysfunction. Table 3 shows the most common adverse reactions seen with these two classes of compound in 150 clinical trials involving more than 16,000 individuals in total.¹⁸ The difference in the distribution of side-effects is striking, and in all but two cases is statistically significant.¹⁸ Familiarity with these side-effects may help to guide the prescribing choice for patients with particular clinical presentations.

Newer therapies

Several newer classes of antidepressive agent have recently become available. They provide a differing pattern of receptor inhibition (Table 4, overleaf).¹⁹ For example, venlafaxine inhibits both serotonin and noradrenaline receptors. Nefazodone shows potent antagonism for the 5-HT₂ receptor and

Table 3. The most common adverse effects of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)¹⁸

Adverse effect	SSRI	TCA
	%	
Anxiety	11.00	9.00
Blurred vision	6.00	10.00*
Constipation	8.00	21.00*
Diarrhoea	12.00	3.00*
Dizziness	8.00	19.00*
Dry mouth	18.00	48.00*
Headache	15.00	11.00*
Insomnia	13.00	6.00*
Nausea	19.00	9.00*
Tremors	7.00	11.00*
Urinary disturbance	3.00	8.00

(* $p \leq 0.05$)

reboxetine is a selective inhibitor of noradrenaline receptors.^{3,19}

There is still debate about the relative efficacy of such drugs. Some rather spectacular claims have been made. For example, when combined with cognitive therapy, nefazodone was reported to produce a response rate of 73% and a remission rate of 48% in a study of some 600 patients suffering from major depression.⁸ Nonetheless, the broad conclusion so far is that these new agents all have rather similar efficacy to currently available SSRIs, but they may have a different side-effect profile.¹⁹

Thus, nefazodone and mirtazapine have a much reduced potential for disturbing sexual function, which is a major problem resulting from the use of SSRIs. Weight gain also commonly results from the use of SSRIs but is not found with nefazodone, venlafaxine or reboxetine. Nefazodone is of particular value for the treatment of depression-related sleep disturbances and reboxetine is said to target symptoms of fatigue. Nefazodone and mirtazapine combat symptoms of anxiety and agitation but possibly at the risk of daytime sedation. Venlafaxine, mirtazapine and reboxetine also have a very low potential for interaction with other drugs.¹⁹

The introduction of such compounds may therefore increase the opportunity for selective treatment of patients with particular clinical presentations beyond, for example, the current avoidance of SSRIs in patients for whom reduced sexual function might be problematic. However, optimism about new drugs has to be considered against the clinical reality of the use of existing ones. In a recent study of 250 patients starting TCAs, only 40–50% were found to be continuing

treatment at 12 weeks.¹⁹ The only patients showing clinical benefit were those with an initial diagnosis of major depression in the last three months (53% of the sample) who were receiving doses above 75 mg.

An analysis of over one million general practice records from 151 practices in the UK showed that nearly 10% of patients received prescriptions for antidepressants.²⁰ However, more than 50% of them had ceased taking their medication within six weeks and 80% within three months.²⁰ Such findings partly explain why results in general practice are frequently less favourable than those published in clinical trials. But how far the newer agents will change this situation remains to be shown.

What do the latest findings show?

The widespread belief that ‘the vast majority of antidepressant compounds ... [are] ... superior to placebo but no difference in efficacy amongst drugs has been shown’,⁴ goes back to the joint consensus statement of the Royal Colleges, which was based on evidence that had accumulated up to 1992. More sophisticated analyses have appeared in the interim but it seems that little has actually changed over the intervening decade when clinical trials have been collated into systematic reviews and meta-analyses.

Williams *et al*⁷ examined 315 outpatient trials and found that newer antidepressants (SSRIs and SNaRIs) were more effective than placebo for major depression (relative benefit 1.6) or dysthymia (relative benefit 1.7). However, they also emphasised the need for effectiveness studies to evaluate treatment benefits under the usual conditions of primary care.⁷

Table 4. Newer antidepressive agents¹⁹

Drug	Class	Therapeutic dose range (mg/day)
Venlafaxine IR	SNaRI	75–225 (divided dose)
Venlafaxine XR	SNaRI	75–225 (single dose)
Nefazodone	SNaRI	300–600 (divided dose)
Mirtazapine	NaSSI	15–45 (single dose)
Reboxetine	NaRI	8–20 (divided dose)

IR = immediate release XR = extended release SNaRI = serotonin noradrenergic reuptake-inhibitor NaSSI = noradrenergic and specific serotonergic inhibitor NaRI = noradrenaline reuptake-inhibitor

A series of excellent meta-analyses have also come from The Cochrane Library.²¹⁻²³

Dysthymia

Dysthymia is a common chronic depressive disorder. It is less severe than major depression but involves symptoms that persist for at least two years.⁶ If left untreated, two-thirds of patients are said to remain symptomatic for a decade, or longer, and even with treatment, recovery is often incomplete.⁶

Lima and Montcrieff²¹ reviewed data from 15 treatment trials of dysthymia and showed that results were similar for various classes of antidepressants. No response was seen in 70% of the placebo group.

SSRIs versus the rest – efficacy

Geddes *et al*²² analysed 99 clinical trials comparing SSRIs (n=5,044) with other antidepressants (n=4,510). They too confirmed that there was no evidence of statistically or clinically significant differences between them.

SSRIs versus the rest – adherence

Barbui *et al*²³ examined 136 randomised trials of SSRIs compared to both 'old' and 'new' tricyclics and heterocyclic drugs such as maprotiline and mianserin. They found that the odds ratio for dropping out of the trial was 1.21 in favour of SSRIs, but the absolute difference was small. Of every 100 patients taking SSRIs, 27 would drop out, compared to 30 of those taking other drugs.

The reasons for leaving the trial were interesting. Dropouts due to lack of efficacy were greater among the SSRIs. For side-effects, they were significantly greater among the TCAs and heterocyclics. There was no difference in dropouts when comparing SSRIs with heterocyclics, but the numbers were too small for reliable estimates.

Moore and McQuay²⁴ have also assessed this report and emphasise that there were fewer adverse event withdrawals on SSRIs than on amitriptyline, imipramine or clomipramine. However, they point out that many of the trials had patient numbers which were too small to generate reliable results. They conclude that 'while there are lower adverse event withdrawal rates with SSRIs, extrapolating from those to real-life situations or whole healthcare systems will not be easy'.²⁴ Attempts to distinguish between efficacy or adverse events produced by

different drugs in the same class are similarly hampered by a lack of reliable data.

A question of economics

In an era of increasing restraints on GP budgets, attention focuses not only on clinical effectiveness but also on cost-effectiveness. Are there any obvious economies to be made in treating depression?

The acquisition cost of SSRIs is far greater than that of TCAs. Set against this is the fact that the continuation rate for SSRIs is higher than that for older drugs. Since costs are incurred for managing initial treatment failures, a large number of analyses have appeared which try to answer the question of which treatment options for depression are not only the most effective, but also the most cost-effective.

Unfortunately, none of these studies gives conclusive results about cost savings in general practice. Many of them use simulation models rather than real data, and the data they do use are also derived from the clinical trial setting, with very few studies relating specifically to primary care.²⁵

The wide variety of existing publications leads to competing results. There is some suggestion that the higher drug costs of SSRIs 'are generally offset by significant savings in consumption of other medical resources'.²⁶ However, Barbui *et al*²³ showed that the risk of dropouts among patients treated with tricyclic or heterocyclic compounds is only 3% greater than that for SSRIs, not the 8-12% that has been used in some previous calculations. SSRIs may still prove to be more cost-effective because of improved compliance and a higher proportion of patients who achieve therapeutic doses, but the evidence to support such a conclusion is still very weak.

Surely the experience of switching prescriptions should help to answer this question? Physicians constantly exercise the option of starting a patient on one type of drug and then switching to another if lack of response or intolerable side-effects makes it necessary; but even here, the economic issues are unclear. Switching from an SSRI to a TCA or vice versa may give similar clinical and economic outcomes when measured at six and 24 months,²⁷ but again it is difficult to make treatment decisions on the basis of such small and isolated studies.

Conclusions

There is clearly a need for a major change in thinking about improving the management of depression in primary care.¹⁴ Outcomes among treated patients remain disappointing; 60% of primary care patients still satisfied the psychiatric criteria for depression at one-year follow-up in one large international study.²⁸

The 'effect sizes' for treatment in primary care are certainly less than those achieved in clinical trials.¹³ Clinical trials involve selected patient populations and are usually supervised by mental health experts. Further work is also needed to understand the natural course of depression in the context of primary care and 'the interplay between management and social context' which is so influential in development and recovery.¹³

Despite problems with the evidence base, clinical guidelines continue to accumulate in an attempt to improve the quality of patient care.¹¹ Little is to be gained from arguments about whether they are good or bad – they are simply inevitable.¹¹ Fortunately, most of them do not restrict drug regimens and so there remains 'considerable scope for individual clinicians to prescribe what they want', assuming that drugs are given at therapeutic levels for appropriate lengths of time.¹¹

Few attempts have so far been made to influence the economics of antidepressant prescribing in general practice. Real evidence-based information on any differences in cost-effectiveness between tricyclics, SSRIs, heterocyclics and the newer antidepressants in everyday clinical practice would be extremely valuable,²³ but generating it will require a high standard of clinical trials which, among other things, need to recruit adequate numbers of patients to produce robust estimates. In the meantime, GPs will continue to search the guidelines for information that can usefully supplement their own clinical experience.

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