Taking the apathy out of depression — is it time to revisit your formulary?

Paul Jerram, head of medicines management at Isle of Wight NHS primary care trust, gives a personal view on antidepressant prescribing

The art of prescribing has long since given way to science as evidenced-based medicine has become the norm. Prescribing has lost much of its mystery and, in many cases, clinician choice has become subservient to formularies. However, guidelines have to be as simple as possible or risk being ignored. With health care organisations required to operate within finite budgets, both formularies and guidelines are used to control costs. Switching patients’ medicines simply to reduce cost — once taboo — has become commonplace and there are now many comparators against which prescribing performance can be measured.

Although most clinicians appear content to work with a limited choice of drugs within a particular class, mental health is an area of medicine that appears to require a huge range of medicines on any local formulary. In this area, it could be argued that clinician choice reigns supreme and senior clinicians often seem to support different drugs from their colleagues. The rationale for any particular choice often appears missing to a generalist working across many areas and often clinicians are unable to explain why one drug is more appropriate than another.

Although minor differences in efficacy between drugs within some drug classes are ignored for the sake of simplicity or cost control, this appears not to apply to mental health. Is this appropriate? Why do we have different standards? Clinicians may switch statins and proton pump inhibitors with impunity, seemingly supported by the National Institute for Health and Clinical Excellence and chasing cost savings, but often appear reluctant to switch antipsychotics or antidepressants.

Rationale

Can we assume all antidepressants are the same? Depression is the most common mental disorder in the community and a major cause of disability. It is one of the most common reasons for people to consult a GP. Although 5 to 10 per cent of people seen in primary care have major depression, it is only one of the most common causes of disability. It is one of the most common reasons for people to consult a GP. Although 5 to 10 per cent of people seen in primary care have major depression, it is only one of the most common causes of disability. It is one of the most common causes of disability. It is one of the most common causes of disability.

Around half of those affected by depression have no further episodes but the remainder go on to have at least one more episode of major depression and those who have early onset depression (before 20 years of age) are particularly vulnerable to relapse.

Antidepressants are not recommended for the initial treatment of mild depression because the risk-benefit ratio is poor and because there is a high placebo response rate. However, they are appropriate for treating moderate to severe depression.

A number of studies and reviews have recently examined the comparative efficacy and acceptability of antidepressants. Study results have, however, been variable and opinion is still divided into two opposing views.

Little difference

One view is that there is little to differentiate between second generation antidepressants in terms of efficacy. Recent British Association of Psychopharmacology guidelines recommend that practitioners match the choice of an antidepressant drug to individual patient requirements as far as possible: choosing, wherever possible, drugs that are better tolerated and safer in overdose. BAP guidance suggests that practitioners consider a number of factors, in consultation with patients, to select an antidepressant (see Panel 1).

Panel 1: Factors to consider in choosing an antidepressant

- Patient preference
- Associated psychiatric disorder
- Previous treatment response to a particular drug
- Tolerability and adverse effects of a previously given drug
- Side effect profile
- Low lethality in overdose if the patient has a history of or is likely to overdose
- Concurrent medical illness or condition that may make antidepressant less well tolerated
- Family history of differential antidepressant response

Panel 2: Drugs included in the Cipriani analysis

- Bupropion (not marketed in the UK)
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Milnacipran (not marketed in the UK)
- Mirtazapine
- Paroxetine
- Reboxetine
- Sertraline
- Venlafaxine

NICE guidelines for depression issued in 2004 recommended selective serotonin reuptake inhibitors (SSRIs) in preference to tricyclic antidepressants (TCAs) because they are as effective but are less likely to be discontinued because of side effects. NICE also suggested that prescribers consider using generic SSRIs. There is evidence that formulary committees interpreted this to mean that SSRIs should be prescribed on the basis of cost and this has meant that fluoxetine and citalopram have become first-line treatments. In fact, NICE does advise...
that when a generic SSRI is prescribed, fluoxetine and citalopram would be reasonable choices because they are generally associated with fewer discontinuation or withdrawal symptoms.1

NICE guidelines also suggest that patient preference, past experience of treatment and particular patient characteristics should influence the choice of drug. Consequently, the Isle of Wight joint formulary lists fluoxetine and citalopram as first-line pharmacological treatments for depressive disorders. This strategy is supported by evidence that suggests there is little to differentiate between second-generation antidepressants in terms of efficacy and that other differences, such as onset of action or adverse events, may be relevant to drug choice.2

Important differences The second view is that there are important differences in terms of efficacy and acceptability between commonly prescribed antidepressants. A recent independent study published in The Lancet concluded that SSRIs do have different efficacy and acceptability profiles. The multiple treatments meta-analyses by Cipriani et al. estimated the relative efficacy of antidepressant drugs (see Panel 2 for drugs analysed) that had only been compared indirectly.5

This study analysed data from 11 randomised clinical trials from 1991 to 2007, assessing the acute treatment phase in adults with unipolar major depressive disorder. Almost 26,000 cases were used to compare efficacy and acceptability. Of the 12 newer antidepressants assessed, four emerged as superior in efficacy: escitalopram, mirtazapine, sertraline and venlafaxine. Reboxetine was significantly less effective than the 11 other agents.

In terms of acceptability, four agents were better tolerated: bupropion, citalopram, escitalopram and sertraline. So, from this work it appears that escitalopram and sertraline have advantages over other antidepressants in terms of both efficacy and acceptability. In addition a Cochrane review and a separate analysis by Bandolier support the concept of important differences in efficacy between antidepressants.

This stance is not without criticism, however, and the clinical significance of the differences in efficacy among antidepressants demonstrated by the Cipriani study has been called into question by the National Prescribing Centre.6

Application in practice Although the debate is likely to continue for the foreseeable future, this topic does cause me to reflect on a local strategy to address safety concerns relating to the prescribing of venlafaxine for patients with resistant depression that was in place on the Isle of Wight some years ago. Because of safety warnings relating to cardiovascular toxicity, at the time there was a desire to reduce the use of venlafaxine. Escitalopram was a fairly new antidepressant and, although within our strategic health authority the drug was being benchmarked (less was best) and its use was not supported by neighbouring primary care trusts, it did have strong support from one of our leading mental health clinicians as a potential substitute for venlafaxine. Escitalopram was prescribed for new patients and where it was deemed clinically appropriate it was substituting in existing patients for venlafaxine at patient review. This had the desired effect of reducing the use of venlafaxine, and clinicians remarked as to escitalopram’s effectiveness in treating this patient group. The lower side effect profile was also popular with patients. As the drug was, at that time, cheaper than venlafaxine it also had the advantage of producing a cost saving.

The success of this strategy was significant because it was in total contrast to strategies in neighbouring PCTs that opposed escitalopram use. Of course, this is all purely anecdotal but the Cipriani conclusion regarding efficacy and acceptability does appear to be favoured.

Cipriani et al concluded that “clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline” and that these agents “might be the best choice when starting treatment for moderate to severe major depression because they have the best possible balance between efficacy and acceptability”. Prudent engagement of a patient in treatment selection involves discussion of risk-benefit ratio of each treatment options. For people with depression and anxiety, choice can have an enormous impact on their recovery because it is fundamental in ensuring access to a personalised health service that is aligned with the complexity of their lives.

The Cipriani paper is not without critics and further evidence is necessary before the matter is concluded but perhaps it is time to re-examine our antidepressant formularies. Certainly I can now understand why our mental health clinicians value formulary expansion and resist formulary restriction.

References