Sertraline is recommended as the first-line pharmacological option for the management of generalised anxiety disorder, based on cost-effectiveness data. Should we blindly follow this advice from NICE?

Generalised anxiety disorder: is NICE guidance the best advice?

By Asta R Prajapati, PGDip Public Health, MRPharmS.

Generalised anxiety disorder (GAD) is a common chronic condition. In Britain it affects about one in 20 adults and these patients often suffer from other mental health conditions, such as depression. According to the most recent adult psychiatric morbidity survey (2009), GAD affects 4.4% of people in England. Generally, prevalence is between 1.5 and 2.5 times higher among women than among men.

The medicines used most commonly to manage GAD are selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and, more recently, pregabalin. Other medicines licensed for the management of GAD include hydroxyzine, buspirone and propranolol, but all these lack sufficient evidence of clinical effectiveness.

In January 2011 the National Institute for Health and Clinical Excellence published guidance for the management of GAD. This article looks at the evidence underpinning this guidance as well as considerations for clinicians managing patients with the condition.

NICE recommendations

For patients with GAD who choose to take medicines, NICE recommends sertraline first line. This advice is based on an analysis of cost-effectiveness, in which data for duloxetine, escitalopram, paroxetine, pregabalin, sertraline and venlafaxine were examined. According to NICE, these medicines were included in the analysis because they have sufficient clinical evidence for use in GAD, have acceptable risk-to-benefit ratios and are deemed appropriate first-line pharmacological treatments for the condition.

The analysis determined that sertraline to be the most cost-effective pharmacological treatment option for GAD. NICE states that the cost-effectiveness of sertraline can be attributed to several factors — that it had the lowest average probability of discontinuation due to intolerable side effects, the second best probability of conditional response (response in people who have not discontinued the drug due to side effects) and the lowest cost.

Is this the right advice?

Product licence Sertraline does not have a licence for treatment of GAD. Therefore, prescribing it for this indication goes against guidance issued by the General Medical Council, the Royal College of Psychiatrists and the Medicines and Healthcare products Regulatory Agency — these organisations advise that medicines should not be prescribed for indications outside their licence if there is an available licensed alternative.

Because sertraline use for GAD is off label, NICE recommends that informed consent should be obtained and documented before the drug is prescribed.
It should be noted that the GMC is currently consulting on an update to its good practice guidance for prescribing medicines and devices, in which it has proposed that it may not be necessary to draw a patient’s attention to the licensing status of a medicine when there is authoritative clinical guidance to support a prescribing decision (this advice is under consultation and has not been issued formally).\(^8\)

It has been suggested that obtaining consent to prescribe a medicine off label may increase the anxiety of a patient who is already suffering from an anxiety disorder.\(^7\) In addition, many prescribers are uncomfortable prescribing medicines off label, especially in primary care.\(^7\)

**Data limitations** Data are lacking to support the long-term use of sertraline for the treatment of GAD.

A potential limitation of the NICE analysis is that it did not take into account less common side effects, such as hypertension (associated with SNRIs) or gastrointestinal bleeding (associated with SSRIs). Such adverse effects could result in higher treatment costs for certain patients. However, NICE argued that, due to the low frequency of these adverse effects, they were unlikely to affect the results of its economic analysis.

The robustness of the NICE analysis might also be questioned on the basis of the number of randomised controlled trials, and the total number of patients taking sertraline, that were included — half or less than that for other drugs.\(^7\) Nonetheless, NICE believes that the design of the economic modelling used in the analysis invalidates such an argument.

More data about the pharmacological treatment of GAD have come to light since NICE published its guidance. Baldwin and colleagues conducted a systematic review of the comparative efficacy and tolerability of nine medicines for GAD management (duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine and venlafaxine).\(^7\)

Of these medicines, fluoxetine, which is also not licensed for treating GAD in the UK, was ranked first for response and remission but third for tolerability. However, the strength of this finding is questionable because only one of the 27 studies included in the review examined fluoxetine. In the same study, sertraline was ranked first in terms of tolerability, but fourth and fifth for response and remission, respectively.

These findings indicate that there is scope for a cost-effectiveness analysis that includes fluoxetine, particularly since fluoxetine is slightly cheaper than sertraline.\(^7\) NICE acknowledges that the most cost-effective pharmacological option for the management of GAD can be expected to change when other medicines become available in generic form.\(^7\) It should also be noted that no other guidance currently includes fluoxetine as a first-line treatment for GAD (see Box).

**Formulation** Sertraline is only formulated as a tablet, whereas some other SSRIs are available as oral solutions; this is a practical consideration for patients with swallowing difficulties or compliance issues.

**On balance**

Despite these concerns, current evidence for the management of GAD seems to be in line with the NICE recommendations.

According to NICE, sertraline has the lowest probability of discontinuation due to adverse effects, second only to placebo, despite being associated with higher incidence of diarrhoea than other

**Guidance for the treatment of generalised anxiety disorder**

<table>
<thead>
<tr>
<th>GUIDELINE OR AUTHOR</th>
<th>RECOMMENDED MEDICINE FOR GENERALISED ANXIETY DISORDER</th>
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<tbody>
<tr>
<td>National Institute for Health and Clinical Excellence (2011)(^3)</td>
<td>Sertraline is recommended first line. If sertraline is ineffective, offer alternative selective serotonin reuptake inhibitor (SSRI) or serotonin and noradrenaline reuptake inhibitor (SNRI). If these options are not tolerated, offer pregabalin</td>
</tr>
<tr>
<td>International Psychopharmacology Algorithm Project (2010)(^9)</td>
<td>Escitalopram, duloxetine, paroxetine, sertraline or venlafaxine</td>
</tr>
<tr>
<td>Western Australian Psychotropic Drugs Committee (2008)(^10)</td>
<td>Escitalopram, paroxetine, sertraline or venlafaxine are recommended first line. Second-line options are alprazolam, bromazepam, buspirone, diazepam, duloxetine, imipramine, lorazepam, mirtazapine or pregabalin</td>
</tr>
<tr>
<td>World Federation of Societies of Biological Psychiatry (2008)(^11)</td>
<td>Duloxetine, escitalopram, paroxetine, pregabalin, sertraline or venlafaxine</td>
</tr>
<tr>
<td>British Association of Psychopharmacology (2005)(^12)</td>
<td>For acute treatment, alprazolam, buspirone, diazepam, escitalopram, imipramine, paroxetine, sertraline or venlafaxine are recommended. For long-term management, therapy with escitalopram or paroxetine is advised</td>
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SSRIs. All other medicines included in the NICE analysis were more likely to be discontinued than placebo.

In a large, robust and independent meta-analysis (including 117 randomised controlled trials and 25,928 patients) sertraline was shown to be the best choice for treating adults with moderate-to-severe depression — the authors deemed it to have the most favourable balance between benefits, acceptability and cost. The common co-existence of GAD and depression makes this study relevant.

Another consideration is drug interactions because many patients with GAD will have comorbid conditions. Of the medicines included in the NICE analysis, sertraline and escitalopram are those that are less likely to have clinically significant interactions.

On balance, the NICE recommendation of sertraline as first-line pharmacotherapy for GAD is rational on a population level, and based on what was the best available evidence at the time. Moreover, the widespread use of sertraline over other medicines could help save the NHS money — this can only be a good thing in the current financial climate. Nonetheless, individual patient variables must be considered when selecting treatments for GAD in clinical practice.

References