Treating generalised anxiety disorder: room to improve

In a Pfizer-sponsored satellite meeting at the Latest Advances in Psychiatry Symposium in London in March, Dr David Baldwin, Reader in Psychiatry and Honorary Consultant Psychiatrist at University of Southampton, reviewed the drug treatment of generalised anxiety disorder. Medical writer, Mark Greener, reports.

Generalised anxiety disorder (GAD) is relatively common – one in every 20 people suffers from the condition during their lifetime. GAD potentially causes significant morbidity, increases the risk of concurrent disorders, and is associated with considerable economic costs. Indeed, the distress associated with GAD can be so marked as to induce suicide ideation and attempts.

Drugs are a mainstay of GAD management. Unfortunately, current pharmacological interventions leave considerable room for improvement. For example, many patients fail to show an adequate response. Eight to 12 weeks’ treatment with SSRI's in adults with GAD produces response rates of 52-68 per cent, compared with 37-63 per cent with placebo. SNRIs produce response rates of between 49 per cent and 81 per cent during treatment that lasts 8 to 28 weeks. This compares with response rates of 33 per cent to 48 per cent with placebo. During treatment with pregabalin lasting between four and eight weeks, the response rates were 44 per cent to 61 per cent, compared with 28 per cent to 48 per cent with placebo. A recent systematic review and meta-analysis indicated less risk of discontinuation due to inefficacy with benzodiazepines, compared with placebo (relative risk [RR] 0.29), in patients with GAD. On the other hand, benzodiazepines’ impact on all-cause patient discontinuation was inconclusive (RR 0.78).

However, there is no consensus about the definition of symptomatic remission, which complicates evaluation of the evidence base. When changes in Clinical Global Impressions scale (CGI) and disorder-specific symptom scores in studies assessing escitalopram’s effect ranged from 0.32 to 0.59 on the CGI-S and CGI-I and from 0.32 to 0.50 on disease-specific rating scales. A comparison of the two scoring systems suggests that a 50 per cent reduction in scores on the former (a typical measure of remission) might be too conservative.

### Predicting prognosis in GAD

Several factors influence prognosis in GAD, which further complicates the evidence base. A shorter duration of symptoms, co-morbid dysthymia, psychiatric co-morbidity (such as a history of depression or panic disorder), and severity of psychosocial impairment predict a better prognosis. Lower symptom severity, a history of benzodiazepine use and a longer duration of untreated illness seem to predict a worse outcome.

Furthermore, certain side-effects can compromise outcomes. For example, GPs and psychiatrists do not routinely address sexual dysfunction in anxiety disorders, which can adversely affect self-esteem, mood and relationships. Sexual dysfunction in anxiety disorders can arise from several possible causes, including antidepressants. The prevalence and severity of sexual dysfunction varies between and within psychopharmacological classes. Pregabalin seems to be associated with a relatively low risk of sexual dysfunction. For example, in clinical studies, the rates of abnormal ejaculation and impotence in GAD were 4 per cent and 3 per cent respectively. This compared with none and 1 per cent respectively in the placebo arms. Sexual dysfunction associated with GAD tends to persist and is hard to treat. Therefore, prescribers should consider a treatment’s propensity to cause sexual dysfunction when selecting the most appropriate intervention for each patient.

Sleep disturbances both add to the burden imposed by GAD and complicate management. Between 7 per cent and 14 per cent of cases of chronic insomnia are associated with GAD and the presence of sleep disturbances supports the diagnosis. Moreover, insomnia is often a prodromal symptom that heralds a full relapse and is a common persistent residual symptom. However, SSRIs can be associated with sleep disturbances. In a study assessing escitalopram and paroxetine in GAD, the rates of fatigue and insomnia were 2.9 per cent and 2.2 per cent respectively with placebo. The rates for escitalopram 20mg were 16.5 per cent and 10.5 per cent respectively, and 8.6 per cent and 10.8 per cent for paroxetine 20mg.

In contrast, the PEACE study suggests that pregabalin reduces sleep problems and disturbances compared with placebo.

### Rethinking the time course

Psychiatrists generally regard GAD as a chronic disease waxing and waning in intensity. However, a...
recent 22-year follow-up study that enrolled 105 patients, found that 52 per cent were symptom free, while 29 per cent experienced sub-threshold symptoms. Sixteen per cent endured symptoms daily over the previous 12 months. Therefore, rather than following a chronic course, GAD symptoms tend to resolve and reappear. Against this background, many patients will cease pharmacological treatment during the course of the disease and, therefore, potentially experience discontinuation symptoms.

Discontinuation symptoms are typically mild and transitory, but are occasionally severe and distressing. As predicting which patients are most likely to endure discontinuation symptoms is problematic, many GPs and psychiatrists taper the dose. However, studies have not established unequivocally the value of tapering. On the other hand, it is clear that antidepressants differ in their propensity to cause discontinuation symptoms. The risk with pre-gabalin is dose-related. However, doses of 150-400mg seem to be associated with rates that are not statistically significantly different from placebo.

The longitudinal course of many cases of GAD suggests that relapse prevention is rational. Paroxetine, escitalopram, duloxetine, quetiapine and pregabalin reduce the risk of relapse. For example, one study enrolled GAD patients who previously responded to pregabalin. Patients received pregabalin (450mg daily) or placebo for 24 weeks. By the end of the study, 65 per cent taking placebo had relapsed compared with 42 per cent of pregabalin users. No safety concerns emerged during long-term treatment.

There are several possible options if patients do not show an adequate response, including: increasing the dose; switching to an alternative, eg cognitive behavioural therapy (CBT), buspirone, agomelatine or quetiapine; augmentation with olanzapine or risperidone; combinations of drug and psychological treatment; and complementary approaches. For example, azapirones are effective in the acute treatment of GAD, especially if patients are benzodiazepine-naive. However, azapirones are less well tolerated than benzodiazepines. The role of CBT in GAD is currently unclear. There is a need for a large randomised controlled trial of CBT versus SSRIs alone and the two treatments in combination.

Finally, several possible targets could yield new treatments for GAD, which could increase the options available for patients who do not respond adequately to first-line therapies. These include: melatonin receptor agonists; nicotinic receptor antagonists and partial agonists; metabotropic glutamate receptor and cholecystokinin antagonists; neuropeptide Y and adenosine A1 and A2A receptor agonists.

Nevertheless, there is a need to expand the evidence base in GAD to help optimise the use of new and existing treatments. For example, studies need to characterise neuropsychological or genetic factors that predict response and to ascertain the impact of co-morbid depressive disorders on outcomes. There is also a need for dose escalation studies after initial non-response and larger placebo-controlled augmentation trials of, for example, pregabalin, buspirone, agomelatine and antipsychotics. Nevertheless, the growing pharmacological armamentarium for GAD offers GPs and psychiatrists the prospect of better managing this common and often debilitating disease.

References


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