Evidence-based pharmacotherapy of generalized anxiety disorder

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Abstract

Generalized anxiety disorder (GAD) is a common and often disabling disorder. This paper reviews the pharmacological treatment of GAD, based on the findings of published meta-analyses and randomized placebo-controlled studies. In doing so, it aims to address three fundamental questions: What is the first-line treatment for GAD? How long should treatment continue? What is the best intervention in patients who do not respond to first-line and second-line treatments? Due to their efficacy in GAD and comorbid anxiety and depressive disorders, their tolerability and safety, certain selective serotonin re-uptake inhibitors (escitalopram, paroxetine, sertraline) should be considered the first-line treatment for most patients, although the serotonin-noradrenaline re-uptake inhibitor venlafaxine is a reasonable alternative. Little is known about the optimal length of therapy after response to acute treatment but relapse-prevention studies with paroxetine suggest that continuation treatment should last for at least 6 months. The management of patients who do not respond to first-line treatment is uncertain, but some patients may benefit from certain tricyclic antidepressants, buspirone, or pregabalin.

Received 24 February 2004; Reviewed 13 July 2004; Accepted 13 July 2004

Key words: Drug treatment, Generalized Anxiety Disorder.

Introduction

Generalized anxiety disorder (GAD) is a common, typically chronic and disabling mental disorder associated with substantial medical and psychiatric comorbidity and occupational impairment. It is characterized by inappropriate or excessive anxiety and worrying that persists over time and is not restricted to a particular set of circumstances. Common features include apprehension, with worries about future misfortune; inner tension and difficulty in concentrating; motor tension, with restlessness, tremor and headache; and autonomic anxiety symptoms, with excessive perspiration, dry mouth and epigastric discomfort. The last decade has seen major increases in understanding of the epidemiology and neurobiology of the condition, together with development and widespread availability of a range of treatment approaches.

The lifetime prevalence of GAD in the general population is around 5–6%, the 12-month prevalence varying according to diagnostic criteria – from 1.5% with DSM-IV to 3.1% with DSM-III-R criteria (Wittchen, 2002). The age of onset of GAD differs from that with other anxiety disorders, the majority of cases presenting aged between 35–45 yr (Carter et al., 2001; Wittchen et al., 2000; Yonkers et al., 2000). It is probably the most common anxiety disorder among the older population (55–85 years) (Beekman et al., 1998). Typically, symptoms fluctuate in intensity over time, but GAD is usually a chronic condition (Weiller et al., 1998). The functional impairment associated with GAD is similar in severity to that seen with major depression (Kessler et al., 1999; Wittchen et al., 2000).

GAD is amongst the most common mental disorders seen in primary care. The point prevalence (defined according to ICD-10 criteria) in European primary-care settings was 4.8% for GAD without comorbid depressive or anxiety disorders, and 3.7% for GAD with depression: a further 4.1% had ‘sub-threshold’ GAD (Weiller et al., 1998). Comorbid GAD is associated with more severe symptoms, greater
functional impairment, a more prolonged course and decreased productivity (Kessler et al., 1999; Weiller et al., 1998) and higher use of health services (Greenberg et al., 1999; Maier and Falkai, 1999). Co-morbid depressive symptoms are associated with an improved chance of a patient being recognized as having a psychological problem, though not necessarily as having GAD (Weiller et al., 1998).

The pathophysiology of GAD is uncertain, but disturbances in neurotransmission of serotonin (5-hydroxytryptamine, 5-HT), noradrenaline, gamma-aminobutyric acid (GABA), cholecystokinin, and corticotropin-releasing factor may all be important. Serotonin is integrally involved in the mediation of anxiety, through serotonergic innervation of the limbic system, hypothalamus and thalamus. Levels of the serotonin metabolite 5-hydroxyindoleacetic acid in cerebrospinal fluid in patients with GAD are low; and anxiety symptoms may be worsened by administration of the 5-HT1/5-HT2 receptor agonist, m-chlorophenylpiperazine. In addition, patients with GAD show a reduction in binding of the selective serotonin re-uptake inhibitor (SSRI) paroxetine to platelets (Connor and Davidson, 1998).

Disturbances of the noradrenergic system may also be important. The α₂-adrenoceptor antagonist yohimbine increases noradrenergic cell firing and induces anxiety, whereas the α₂-adrenoceptor agonist clonidine reduces firing rates and inhibits anxiety. In GAD patients, challenge with yohimbine is associated with a blunting of the increase in plasma 3-methoxy-4-hydroxyphenylglycol, compared to that seen in healthy controls (Charney et al., 1989). In addition, [³H]yohimbine binding to platelets is reduced, compared to controls or patients with major depression (Sevy et al., 1989).

The GABA/benzodiazepine receptor system also appears implicated in the pathophysiology of GAD. Untreated patients have a reduced number of benzodiazepine-binding sites on platelet membranes, the number increasing after diazepam treatment (Weizman et al., 1987); an investigation of lymphocyte membrane benzodiazepine-binding sites has produced similar findings (Rocca et al., 1991). The reduction in binding sites may explain the reduction in saccadic eye movement velocity seen in GAD, as this velocity has been used as a marker of functional integrity of the GABA/benzodiazepine system (Connor and Davidson, 1998).

The best evidence for a role of disturbances in these neurotransmitter systems in the pathophysiology of GAD comes from randomized placebo-controlled treatment studies involving certain SSRIs, the serotonin-noradrenaline re-uptake inhibitor (SNRI) venlafaxine, certain benzodiazepine anxiolytics, and the novel anxiolytic pregabalin. The results of these studies are reviewed below, the focus being on addressing three fundamental questions:

- What is the first-line treatment for GAD?
- How long should treatment continue?
- What is the best intervention after non-response to first-line and second-line treatments?

Search strategy

We conducted a computerized literature search of electronic databases (MEDLINE, Embase and PsychInfo) for the years 1980–2003 using a strategy which combined the terms (generalised/generalized anxiety disorder) with (randomised/randomized controlled trial). In addition, we consulted with colleagues about other potential treatment studies, not identified by the search; examined published systematic reviews in the Cochrane Collaboration database; and attempted to identify recently completed treatment studies, currently only available as scientific conference abstracts.

Which is the first-line treatment for GAD?

Summary of published clinical trials of SSRIs and venlafaxine

Citalopram

No randomized controlled trials with citalopram in GAD have been published. A randomized controlled trial comparing two dose ranges of citalopram and imipramine in 472 primary-care depressed patients found that the treatments were associated with a similar reduction in mean score on the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967) anxiety factor (Rosenberg et al., 1994). Another study comparing citalopram and paroxetine in 104 patients with either DSM-IV major depression or mixed anxiety-depressive disorder (Jefferson and Greist, 1994) found that both treatments were associated with significant reductions in total score on the Hamilton Rating Scale for Anxiety (HAMA; Hamilton, 1959). By contrast, the results of a 24-wk double-blind, placebo-controlled treatment study comparing citalopram and sertraline in 323 patients with DSM-IV major depressive disorder indicate that citalopram, but not sertraline, was significantly more efficacious than placebo in reducing the mean score on the HAMD anxiety cluster (p < 0.01) (Stahl, 2000).
Escitalopram

Citalopram is a racemic mixture of two enantiomers, of which only the S-isomer (escitalopram) has significant serotonin reuptake inhibitory properties (Hyttel et al., 1992). Escitalopram is more selective and more potent than citalopram, and has been found to be significantly more efficacious than citalopram on some measures in a pooled analysis of randomized controlled trials in patients with major depressive disorder (Gorman et al., 2002). The results of three 8-wk randomized, double-blind placebo-controlled, parallel-group trials in patients with DSM-IV GAD all indicate that escitalopram is significantly more efficacious than placebo, in reducing anxiety symptoms as measured by the HAMA (Davidson et al., 2002). Further investigations of the efficacy of fixed doses of escitalopram and paroxetine, and of escitalopram in the prevention of relapse are currently underway.

Fluoxetine

There are no published controlled treatment studies in adults with DSM-IV GAD. An open pilot treatment study in 16 children and adolescents (aged between 9–18 yr) with mixed anxiety disorders showed that fluoxetine was of only limited benefit (Fairbanks et al., 1997). Double-blind treatment studies in depressed patients have indicated that fluoxetine is as efficacious as imipramine, clomipramine or amitriptyline in relieving anxiety symptoms in depression, but the efficacy of fluoxetine in patients with comorbid depression and GAD is not proven (Hurst and Lamb, 2000).

Fluvoxamine

The efficacy of fluvoxamine as a treatment for GAD is not established. A small (n = 30) open study in patients with comorbid major depression and GAD showed that fluvoxamine treatment was associated with significant improvement in both anxiety and depressive symptoms (Sonawalla et al., 1999), but this result needs to be replicated in patients with GAD before the efficacy of fluvoxamine in that disorder can be assumed.

Paroxetine

The efficacy of paroxetine in the short-term treatment of patients with GAD has been evaluated in four randomized, double-blind, placebo-controlled studies (Baldwin, 2001). The first evaluation was an 8-wk comparator-controlled trial involving 81 patients with a DSM-IV diagnosis of GAD, paroxetine being compared to imipramine and the benzodiazepine 2-chlorodesmethyl-diazepam. Paroxetine was superior to 2-chlorodesmethyl-diazepam and had similar efficacy to imipramine: in addition, paroxetine treatment differed significantly (p < 0.05) from 2-chlorodesmethyl-diazepam from week 4 onwards, while imipramine only did so at the end of the study (Rocca et al., 1997).

The second investigation was an 8-wk, fixed-dose study involving 566 patients, performed in the USA (Rickels et al., 2003). Paroxetine treatment (20 or 40 mg/d) was significantly superior to placebo (p < 0.001) in reducing both the mean HAMA total score, and the mean scores on HAMA items 1 (anxious mood) and 2 (tension), considered by some to reflect the most important symptoms of GAD. There was no dose–response relationship in the mean change in HAMA scores, but overall response rates were 68% and 81% with paroxetine 20 and 40 mg/d respectively, compared with 52% of patients in the placebo group (p < 0.001). By the end of the study, the mean change from baseline on a health-related quality-of-life questionnaire (EuroQol-5D) and visual analogue scale was significantly greater for both paroxetine-treatment groups, indicating a significant improvement in quality of life.

The third randomized controlled trial was an 8-wk, flexible-dose study conducted in 326 US patients with GAD. Paroxetine (20–50 mg/d) was significantly superior to placebo (p < 0.05) in reducing both the mean HAMA total score, and the mean scores on HAMA items 1 and 2, and was generally well tolerated (Pollack et al., 2001). A fourth study of similar design conducted in 372 patients in Europe has revealed similar reductions in HAMA total score and HAMA items 1 and 2.

The effects of paroxetine treatment appear to extend beyond simple symptom reduction or improved quality of life. A small (n = 29) uncontrolled study showed that paroxetine treatment was associated with a reduction in maladaptive personality traits, with significant decreases in harm avoidance (p = 0.0001) and novelty seeking (p = 0.006), and a significant increase in self-directedness (p = 0.0004) (Allgulander et al., 1998). The placebo-controlled paroxetine-treatment studies also show that as symptoms of GAD resolve there is an associated improvement in symptom-related disability, assessed using the patient-rated Sheehan Disability Scale (SDS; Sheehan et al., 1996) which covers symptom-related impairment in social, work and family life. At end-point in all three studies, there was a statistically significant difference between paroxetine and placebo in the SDS total score.
Venlafaxine

A preliminary study (Feighner et al., 1998) in depressed outpatients indicated that once-daily treatment with the SNRI venlafaxine was efficacious in relieving anxiety symptoms, and suggested it might, therefore, have a role in the management of patients with GAD. The evidence for the efficacy of venlafaxine in the short-term and long-term treatment of GAD is now based upon the results of five randomized placebo-controlled trials, two of which involved an active comparator (diazepam or buspirone).

Pooled analysis of these five placebo-controlled trials, which includes 1839 patients with a DSM-IV diagnosis of GAD, provides good evidence for venlafaxine in short-term treatment. In these studies, the effect size for venlafaxine (i.e. difference from placebo in mean HAMA score at study end-point) ranges between 1.6 and 4.2, with a mean effect size from the pooled data of 2.78 (Gorman, 2002). In a further analysis, which examined the effects of age on treat-

ment response, venlafaxine was superior to placebo in both younger (p < 0.001) and older (p < 0.01) sub-groups of patients (Katz et al., 2002).

In the first comparator-controlled study, which included 564 patients, there was no significant advantage for either active treatment (75 mg/d venlafaxine XL, or 15 mg/d diazepam) over placebo in the intention-to-treat last observation carried forward analysis. However, in a second analysis, which omitted those study centres that had been unable to distinguish diazepam from placebo (designated the ‘verum-sensitive population’), there were significant advantages for both venlafaxine and diazepam over placebo, in the reduction of HAMA total score and other efficacy measures (Hackett et al., 2000).

In the second comparator-controlled study, with 405 participating patients, there were numerical advantages for venlafaxine XL (75 or 150 mg/d) over both placebo and buspirone (30 mg/d) across a range of primary efficacy variables, but none of these reached statistical significance. There were significant advantages (p < 0.05) for venlafaxine over placebo on both the HAMA psychic anxiety item scores at study end-point, and on the HAMA anxious mood item at weeks 2, 4, 6 and 8 (p < 0.05). Venlafaxine was associated with significantly greater overall improvement, compared to buspirone, on the CGI scores at week 3 [CGI-S (Severity), week 4 (CGI-I (Improvement) and CGI-S)] and week 8 (CGI-S) (Davidson et al., 1999).

The dose–response relationship with venlafaxine was examined in two of the randomized, placebo-controlled treatment studies. In the first, lasting 8 wk, daily doses of 75, 150 and 225 mg all showed superior efficacy to placebo (p < 0.05), the most positive efficacy results being seen with the highest dosage (Rickels et al., 2000). In the second, lasting 24 wk, daily doses of 75 and 150 mg showed significantly greater improvement than patients allocated to placebo on all outcome measures (p < 0.01) whereas a daily dose of 37.5 mg was only superior on one measure at some time-points. Furthermore, there were significant advantages for the two higher doses over the lowest dose on some outcome measures (Allgulander et al., 2001).

Summary of published clinical trials of other psychotropic compounds

Benzodiazepines

A systematic review of the findings of randomized controlled trials has established that benzodiazepines are an effective and rapid treatment for many patients with GAD, having similar efficacy to cognitive therapy (Gould et al., 1997). However, the benzodiazepines...
are far from ideal in the treatment of GAD, having limited efficacy against comorbid depressive symptoms. The unwanted effects of benzodiazepines include sedation, memory disruption and psychomotor impairment, with an associated increased risk of traffic accidents. Other problems include the development of tolerance, abuse or dependence, and distressing withdrawal symptoms on stopping the drug. Many authorities counsel that benzodiazepines should be reserved for short-term use (up to 4 wk), and prescribed only at low dosage (Lader, 1999). Others have argued that benzodiazepines are clearly efficacious, and that withholding treatment from patients on the basis of a potential risk of dependence is unjustified and probably detrimental to overall well-being (Argyropoulos and Nutt, 1999).

**Pregabalin**

Pregabalin is a novel psychotropic drug with anticonvulsant, anxiolytic and analgesic properties. The mechanism of action is largely unknown, although it binds to an auxiliary subunit (\(\alpha 2\).d) of voltage-gated calcium channels, thereby increasing whole brain GABA. The results of a recently published placebo-controlled study indicate that pregabalin was superior to placebo in reducing mean HAMA score from the first week of double-blind treatment (Feltner et al., 2003). In three randomized, double-blind, placebo-controlled treatment studies (two involving an active comparator) pregabalin was significantly more efficacious in relieving symptoms than placebo and had similar overall efficacy to either alprazolam (Pande et al., 2000) or venlafaxine (Rickels et al., 2002). Further studies with pregabalin are complete, and demonstrate it has anxiolytic effects within 1 wk (Montgomery, 2003).

**Imipramine**

The tricyclic antidepressant (TCA) imipramine has proven efficacy in the treatment of patients with GAD, defined according to DSM-III criteria. In a seminal 8-wk double-blind, placebo-controlled study involving 230 patients with symptoms lasting least 4 months, a baseline HAMA score of 18 or more, and no indication of current depression or panic disorder, subjects were randomized to treatment with imipramine, diazepam, trazodone or placebo. During the first 2 wk of treatment, diazepam was associated with most improvement in anxiety symptoms, but from the third week to the study end-point imipramine had significantly greater anxiolytic efficacy, compared to diazepam (Rickels et al., 1993). However, TCAs such as imipramine have a rather poor tolerability profile due to blockade of histamine H1 receptors, \(\alpha 1\)-adrenoceptors and muscarinic receptors, which limits their long-term use in treating patients with GAD.

**5-HT1A agonists**

Buspirone is an azapirone anxiolytic drug, with partial agonist properties at 5-HT1A receptors, which has proven efficacy in the treatment of patients with GAD (Goa and Ward, 1986). An early study (Goldberg and Finnerty, 1979) established that buspirone had comparable efficacy to diazepam in patients with generalized anxiety. Not all studies with buspirone have been positive (Ansseau et al., 1990) but a meta-analysis of eight controlled treatment studies has indicated that buspirone has comparable efficacy to benzodiazepines in the management of GAD (Gammans et al., 1992). Buspirone appears efficacious in reducing associated depressive symptoms in patients with GAD, but it is not an accepted treatment for patients with major depression, and therefore, is not a suitable first-line treatment in patients with comorbid GAD and depression (Sramek et al., 1996).

Flesinoxan is a related drug, which acts as a full agonist at somatodendritic 5-HT1A receptors: it too has been found efficacious in the treatment of GAD. A five-arm study comparing three doses of flesinoxan, alprazolam and placebo found that both the highest dose of flesinoxan and alprazolam were significantly more efficacious than placebo in reducing anxiety symptoms, rated by the HAMA (Bradford and Stevens, 1994, but there is little additional information on the efficacy of the drug, and its further development has been halted.

**Hydroxyzine**

The efficacy of the antihistamine hydroxyzine in acute treatment of patients with GAD has been examined in three randomized placebo-controlled trials. A preliminary French general practice study (using observed case analysis only) found some evidence for efficacy of hydroxyzine (Darcis et al., 1995), this being supported by the findings of a UK primary-care study involving 244 patients with DSM-IV GAD, with or without comorbid depressive symptoms, which also included buspirone, although only hydroxyzine was superior to placebo (\(p < 0.02\)) on the primary outcome measure (HAMA) (Lader and Scotto, 1998). In the third study, hydroxyzine had similar efficacy to the benzodiazepine bromazepam, and superior efficacy to placebo, with numerically fewer patients experiencing
discontinuation symptoms with hydroxyzine (40.2%) than with placebo or bromazepam (each 51%) (Llorca et al., 2002).

Propranolol
A double-blind, randomized placebo- and comparator-controlled, 3-wk dose-ranging, parallel-group study has examined the efficacy of the beta-blocker propranolol (80, 160 or 320 mg/d) and the benzodiazepine chlordiazepoxide (30 or 45 mg/d) in GAD. Both propranolol and the active comparator showed significantly greater efficacy than placebo after 1 wk of double-blind treatment, but there were no advantages at study end-point (Meibach et al., 1987).

Trifluoperazine
The results of a randomized placebo-controlled, flexible-dose acute treatment study indicate that the antipsychotic drug trifluoperazine had superior efficacy from the first week of double-blind treatment, although there were markedly more treatment-emergent adverse events with trifluoperazine (62%, compared to 46% with placebo) (Mendels et al., 1986).

Taken together, the findings of the randomized placebo-controlled trials with escitalopram, paroxetine, sertraline and venlafaxine indicate that SSRI or SNRI treatment can be efficacious in the acute management of patients with GAD. There is also some evidence for the efficacy of certain benzodiazepines, buspirone, imipramine, hydroxyzine and trifluoperazine. Systematic reviews support these observations: a recent but already outdated Cochrane Collaboration review concluded that imipramine, paroxetine and venlafaxine all had superior efficacy to placebo (Kapczinski et al., 2003). Two comprehensive but similarly outdated reviews both inferred that the SSRI paroxetine offered advantages over comparator benzodiazepines, such as its efficacy in comorbid depression, and now-disputed low risk of causing discontinuation symptoms (Davidson et al., 2001; Wagstaff et al., 2002). The most recent consensus statement and guidelines on treating anxiety disorders states that SSRIs are the preferred first-line drug treatment in patients with GAD (Bandelow et al., 2002). There are of course many further research needs, such as establishing the comparative efficacy and acceptability of differing drugs in both short- and long-term treatment; examining the effects of combining drug treatment with psychological approaches such as cognitive–behavioural therapy (CBT); and evaluating the effectiveness of SSRI or SNRI treatment in patients with comorbid or resistant GAD.

How long should treatment continue?
There have been few randomized controlled trials of the treatment of patients with GAD beyond early response to acute treatment, although the findings of studies with paroxetine, venlafaxine and escitalopram all suggest that treatment should probably continue for at least a further 6 months. Two different approaches to assessing maintenance of effect have been utilized: either a relapse-prevention design, in which responders to open-label acute treatment or randomly allocated to either continue with active treatment, or to switch to placebo; or a continuation treatment design, in which responders to double-blind acute treatment continue with double-treatment for a further 6 months.

In a double-blind relapse-prevention study, paroxetine was found efficacious in long-term treatment of patients with GAD, there being significantly \( p < 0.001 \) fewer relapses with paroxetine (10.9%) than with placebo (33.9%) (Stocchi et al., 2003). By contrast, the placebo-controlled relapse-prevention study with venlafaxine, over a period of 4 months, did not find greater efficacy than placebo in preventing relapse.

However, the long-term efficacy of venlafaxine XR capsules has been shown through the results of a pooled analysis of the results of two 6-month randomized, double-blind, placebo-controlled parallel-group studies. With venlafaxine, 61% of the patients who had responded but not remitted by week 8 showed remission by 6 months, whereas only 39% of non-remitting placebo-responders at 8 wk were in symptomatic remission at study end-point (Montgomery et al., 2002a). The advantage for continuing with venlafaxine was also seen in a survival analysis of patients stopping treatment due to lack of efficacy, in which patients allocated to placebo stopped double-blind treatment at a fairly constant rate from the first month of treatment, whereas few venlafaxine-treated patients discontinued after the second month. After 6 months of double-blind treatment, discontinuation rates were 10% for venlafaxine and 21% for placebo (Montgomery et al., 2002b).

A preliminary report of a relatively small \((n=123)\) randomized, 24-wk controlled flexible-dose comparison of escitalopram (10–20 mg/d) and paroxetine (20–50 mg/d) in GAD shows the two SSRIs had similar overall efficacy, at 8 and 24 wk of double-blind treatment. The proportion of patients who responded to treatment increased in both groups over time (escitalopram, from 52% to 70%; paroxetine, from 46% to 61%), as did the proportion of patients entering symptomatic remission (escitalopram, from 30% to
What is the best treatment in resistant patients?

Our literature search did not identify any placebo-controlled studies in patients who have not responded to first-line or second-line treatments. As such, the management of patients with resistant GAD is based largely on experience and anecdotal case reports. Approaches which could be employed include all those compounds described above for which there is evidence of efficacy from placebo-controlled studies, and various forms of psychological treatment, both alone and in combination with psychotropic drugs.

A systematic review of 35 randomized controlled trials has found that CBT (using a combination of approaches including exposure, cognitive restructuring, anxiety management and relaxation) is more efficacious than anxiety management alone, non-directive therapy or staying on a waiting list (Gould et al., 1997). In one long-term follow-up study, cognitive therapy appeared associated with better long-term outcomes than either placebo or drug treatment; in another, there was no difference in outcome between cognitive therapy, analytic psychotherapy and anxiety management (Durham et al., 1999).

It is unclear whether it is more helpful to combine pharmacological and psychological approaches in the management of patients with GAD, compared to using single approaches alone (Lader and Bond, 1998). Concomitant treatment with benzodiazepines was associated with markedly reduced response rates, compared to cognitive or behaviour therapy alone, in one small study (Durham and Turvey, 1987). However, in another study performed in primary care, the combination of diazepam and CBT was more efficacious than either given alone although the study was unable to detect a difference between diazepam and placebo (Power et al., 1990).

Conclusions

GAD is a common and disabling anxiety disorder: epidemiological indicates a lifetime prevalence of approx. 5%, and substantial associated social and occupational impairment, comparable to that with major depression. GAD has considerable comorbidity, with depression, other anxiety disorders and physical illness. Many patients with GAD are not recognized as suffering from a potentially treatable anxiety disorder: others are recognized as having some form of mental disorder, but are either not treated or receive treatment with drugs of unproven efficacy. Whilst some TCAs and benzodiazepines have been found efficacious in patients with GAD, tolerability problems and other risks limit their use in clinical practice. By contrast, buspirone, the SSRI escitalopram, paroxetine and sertraline, the SNRI venlafaxine, and the novel anxiolytic pregabalin all have established efficacy in placebo-controlled trials. At present, SSRIs are probably the first-line treatment, with venlafaxine being used in those patients who do not respond.

Acknowledgements

None.

Statement of Interest

The University of Southampton has received research support from a number of pharmaceutical companies that manufacture compounds that have proven or potential efficacy in the treatment of Generalized Anxiety Disorder. Dr Baldwin has acted as an advisor to some of these pharmaceutical companies and has received personal honoraria for attending advisory boards and speaking at company-sponsored satellite symposia at scientific meetings. Dr Baldwin is co-chairman of the British Association for Psychopharmacology Working Group that is charged with producing a consensus statement on the treatment of anxiety disorders.

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