



# Selective serotonin reuptake inhibitors in the treatment of generalized anxiety disorder

David Baldwin<sup>†</sup>, Christel Buis and Andrew Mayers

Selective serotonin reuptake inhibitors have proven efficacy in the treatment of panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder and social anxiety disorder. Accumulating data shows that selective serotonin reuptake inhibitor treatment can also be efficacious in patients with generalized anxiety disorder. This review summarizes the findings of randomized controlled trials of selective serotonin reuptake inhibitor treatment for generalized anxiety disorder, examines the strengths and weaknesses of other therapeutic approaches and considers potential new treatments for patients with this chronic and disabling anxiety disorder.

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## Introductory overview

### *Clinical features & epidemiology of generalized anxiety disorder*

Generalized anxiety disorder (GAD) is characterized by inappropriate or excessive anxiety and worrying that is persistent and not restricted to particular circumstances. Common symptoms include:

- Apprehension, with worries about future misfortune
- Inner tension and difficulty in concentrating; motor tension, with restlessness
- Tremor and headache
- Autonomic anxiety, with excessive perspiration, dry mouth and epigastric discomfort

The lifetime prevalence in the general population is around 5–6%, the 12-month prevalence varying according to diagnostic criteria – from 1.5% with *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) to 3.1% with DSM-III-R criteria [1]. The age of onset of GAD differs from that with other anxiety disorders, the majority of cases presenting aged around 35–45 years [2–4]. GAD is probably the most common anxiety disorder among the elderly population (55–85 years) [5]. Symptoms fluctuate in intensity over time, but GAD is usually a chronic condition [6]. The functional impairment is similar in magnitude to that with major depression [3,7].

GAD is amongst the most common psychiatric disorders seen in general practice. The point prevalence of ICD-10 defined GAD in European primary care settings was 4.8% for GAD without other comorbid depressive or anxiety disorders and 3.7% for GAD with depression: a further 4.1% had 'subthreshold' GAD [6]. Comorbid GAD is associated with more severe symptoms, greater functional impairment, a more prolonged course, decreased productivity and higher use of health services [6–9]. Comorbid depressive symptoms improve the chances of a patient being recognized as having a psychological problem, though not necessarily GAD [6].

### *Pathophysiology of generalized anxiety disorder*

Serotonin (5-hydroxytryptamine, 5-HT) 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 are low in patients with GAD – symptoms may be worsened by administration of the 5-HT<sub>1</sub>/5-HT<sub>2</sub> receptor agonist, m-chlorophenylpiperazine; and patients with GAD show a reduction in binding of the selective serotonin reuptake inhibitor (SSRI) paroxetine to platelets [10]. Disturbances of the noradrenergic system are

<sup>†</sup>Author for correspondence  
University Department of Mental  
Health, Royal South Hants  
Hospital, Southampton  
SO14 0YG, UK  
Tel.: +44 2380 825533  
Fax: +44 2380 234243  
dsb1@soton.ac.uk

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paroxetine, sertraline, SSRI

also likely to be important: in GAD patients, challenge with the  $\alpha_2$  receptor antagonist yohimbine produces little increase in plasma 3-methoxy-4-hydroxyphenylglycol, compared with that seen in healthy controls [11]. Further evidence for a role of noradrenergic disturbance comes from the observation that  $^3\text{H}$ -yohimbine binding to platelets is reduced, compared with that in controls or patients with major depression [12]. Finally, the GABA/benzodiazepine system is also implicated in the pathophysiology of GAD: untreated patients have a reduced number of platelet membrane benzodiazepine binding sites, the number increasing after diazepam treatment – an investigation of lymphocyte membrane benzodiazepine binding sites produced similar findings [13,14]. Further evidence of a role for disturbances of these systems in the pathophysiology of GAD comes from treatment studies involving certain SSRIs, the serotonin–norepinephrine reuptake inhibitor venlafaxine, certain benzodiazepine anxiolytics and the novel anxiolytic pregabalin.

#### Treatment with selective serotonin reuptake inhibitors

##### *Citalopram*

No controlled trials with citalopram have yet been presented or published. An early randomized controlled trial comparing two dose ranges of citalopram and imipramine in 472 primary care depressed patients found that both treatments produced reduced mean scores on the Hamilton Rating Scale for Depression (HAM-D) anxiety factor [15]. A more recent study comparing citalopram and paroxetine in 104 patients with DSM-IV major depression or mixed anxiety–depressive disorder found that both treatments were associated with significant reductions in the HAM-A total score [16]. By contrast, the results of a 24-week, double-blind, placebo-controlled treatment study comparing citalopram and sertraline in 323 patients with DSM-IV major depressive disorder indicate that citalopram was more efficacious than placebo in reducing mean scores on the HAM-D anxiety cluster ( $p < 0.01$ ), there being no significant difference on this measure between sertraline treatment and placebo [17].

##### *Escitalopram*

Citalopram is a racemic mixture of two enantiomers, of which only the S-isomer (escitalopram) has significant serotonin reuptake inhibitory properties [18]. Escitalopram is more selective and more potent than citalopram and has been found to be more efficacious than the parent compound in a pooled analysis of randomized controlled trials in patients with major depressive disorder [19]. Preliminary data in patients with GAD indicate that escitalopram is significantly more efficacious than placebo and an extensive clinical trial program is underway in this area [20].

##### *Fluoxetine*

There are no published treatment studies in adults with DSM-IV GAD. An open pilot treatment study in 16 children and adolescents (9–18 years) with mixed anxiety disorders showed that fluoxetine might be of only limited benefit [21]. Double-blind treatment studies in depressed patients indicate that

fluoxetine is as efficacious as imipramine, clomipramine or amitriptyline in relieving anxiety symptoms in depression, but the efficacy of fluoxetine in comorbid depression and GAD is not proven [22].

##### *Fluvoxamine*

The efficacy of fluvoxamine as a treatment for GAD has not been established. However, in a small ( $n = 30$ ) open study of patients with comorbid major depression and GAD, fluvoxamine showed significant improvement in both anxiety and depressive symptoms [23]. This finding requires replication in patients with GAD before the efficacy of fluvoxamine can be assumed.

##### *Paroxetine*

The efficacy of paroxetine in short-term treatment of GAD has been evaluated in four randomized double-blind controlled studies [24]. The first evaluation of paroxetine was in a comparator-controlled trial involving 81 patients with a DSM-IV diagnosis of GAD, paroxetine being compared with imipramine and 2'-chlorodesmethyl-diazepam in an 8-week treatment study [25]. Paroxetine showed superior efficacy to 2'-chlorodesmethyl-diazepam and similar efficacy to imipramine. Paroxetine treatment differed significantly ( $p < 0.05$ ) from 2'-chlorodesmethyl-diazepam from week 4 onwards, while imipramine only did so at study end-point. The second investigation was an 8-week, dose-finding study involving 566 patients, performed in the USA. In this study, paroxetine treatment (20 or 40 mg/day) was significantly superior to placebo ( $p < 0.001$ ) in reducing both the mean HAM-A total score and the mean scores on HAM-A items 1 (anxious mood) and 2 (tension). Response rates were 68 and 81% with paroxetine 20 and 40 mg/day, respectively, compared with 52% of patients in the placebo group (observed case data) (FIGURE 1). By the end of the study, the mean change from baseline on a health-related quality of life questionnaire (Euro-QoL-5D) and visual analog scale was significantly greater for both paroxetine-treatment groups indicating a significant improvement in quality of life.

The third treatment study was an 8-week, flexible-dose study conducted in 326 US patients with GAD. Paroxetine (20–50 mg/day) was significantly superior to placebo ( $p < 0.05$ ) in reducing mean HAM-A total score and mean scores on HAM-A items 1 and 2 and was generally well-tolerated [26] (FIGURE 2). A fourth study of similar design conducted in 372 patients in Europe has revealed similar reductions in HAM-A total score and HAM-A items 1 and 2. Paroxetine has recently been found efficacious in long-term treatment, there being significantly ( $p < 0.001$ ) fewer relapses with paroxetine (10.9%) than with placebo (33.9%) in a 6-month, relapse-prevention study [27].

The effects of treatment may extend beyond symptom reduction and improved quality of life. A small ( $n = 29$ ) uncontrolled pilot study showed 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 ( $p = 0.0004$ ) [28]. The placebo-controlled paroxetine treatment studies

also showed that as symptoms of GAD resolve there is an associated improvement in symptom-related disability, assessed using the patient-rated Sheehan Disability Scale (SDS) which covers impairment in social, work and family life. At endpoint in all three studies, a statistically significant difference between paroxetine and placebo was seen in the SDS total score (flexible-dose study 1 difference = -1.8,  $p = 0.037$ ; study 2 difference = -2.4,  $p = 0.001$ ; fixed-dose study for 20 mg/day regimen, difference = -3.1,  $p < 0.001$ ; for 40 mg/day regimen, difference = -3.6,  $p < 0.001$ ) [29].

#### Sertraline

No clinical trials of sertraline in the treatment of GAD have been reported. Double-blind treatment studies indicate that sertraline is efficacious in relieving anxiety symptoms within depression and the symptoms and impairment associated with panic disorder, social phobia, post-traumatic disorder and obsessive-compulsive disorder, but its efficacy in GAD cannot be assumed.

The findings of the randomized controlled trials with paroxetine indicate that SSRI treatment can be efficacious in GAD. There are many further research needs, such as:

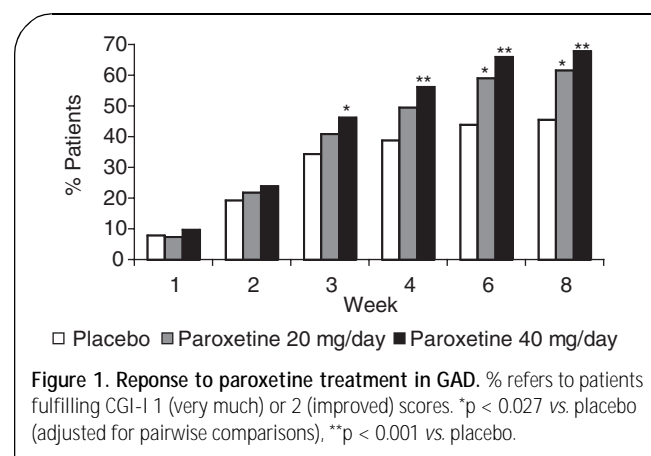
- Establishing the comparative efficacy and acceptability of differing treatments, in both short- and long-term treatment
- Examining the effects of combining SSRI treatment with psychological approaches, such as cognitive-behavioral therapy
- Evaluating the effectiveness of treatment in wider clinical practice

#### Other treatment approaches

##### Other antidepressant drugs

##### Nefazodone

Nefazodone inhibits the reuptake of both serotonin and norepinephrine, although its strongest action is antagonism of the 5-HT<sub>2a</sub> receptor. Studies in patients with major depression and associated anxiety indicate that nefazodone can significantly reduce anxiety symptoms and a small open-label evaluation suggests that it can improve the symptoms of GAD [30,31].



##### Venlafaxine

This serotonin-norepinephrine reuptake inhibitor has proven efficacy in the treatment of depression and GAD. A preliminary study in depressed outpatients indicated that once-daily venlafaxine was efficacious in relieving anxiety symptoms and suggested it might therefore have a role in the management of patients with GAD [32]. This supposition was confirmed by the findings of two studies of short-term treatment of GAD with venlafaxine [33,34]. In one study, venlafaxine was significantly superior to the active comparator buspirone in reducing anxiety symptoms and there was some evidence that venlafaxine had an earlier onset of action [33]. Three other placebo-controlled studies of venlafaxine in the short-term treatment of GAD have been presented [35,36]. Efficacy is reported in two of the three studies of venlafaxine compared with placebo, but until these studies are published fully it is difficult to make a detailed assessment.

The long-term efficacy of venlafaxine extended-release capsules has been shown through the results of a 6-month, randomized, double-blind, placebo-controlled, parallel-group study [37]. These 6-month results were replicated in a second placebo-controlled study [38]. The single relapse prevention study, over a period of 4 months, did not show efficacy for venlafaxine, compared with placebo. Evidence supporting a dose-response relationship for venlafaxine is reported in the 6-month studies, with higher doses associated with a better response.

##### Mirtazapine

The primary mechanism of action of mirtazapine is through antagonism of presynaptic  $\alpha_2$  receptors and heteroreceptors. No studies of mirtazapine in GAD have been reported, although a small placebo-controlled study of outpatients with primary anxiety disorders indicated that it could reduce anxiety symptoms and improve overall functioning [39]. A meta-analysis of eight double-blind controlled treatment studies in patients with major depression suggests that mirtazapine is efficacious in reducing anxiety-related items of the HAMD [40].

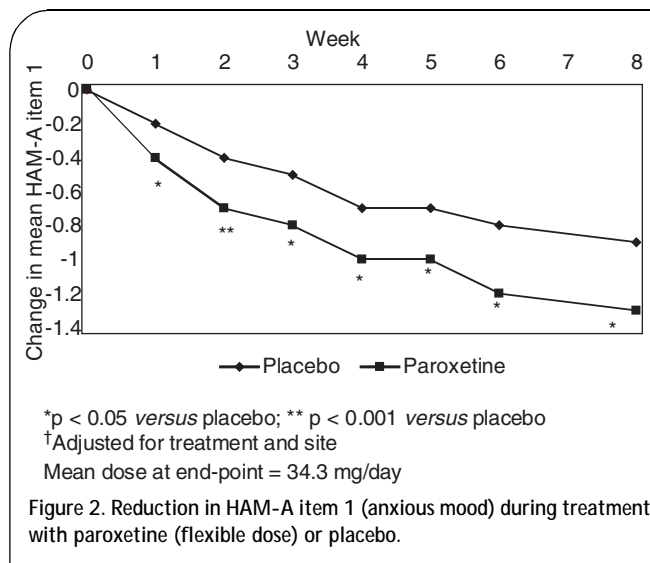
##### Other serotonergic drugs

##### Buspirone

Buspirone is an azapirone anxiolytic drug, with partial agonist properties at 5-HT<sub>1a</sub> receptors, which has proven efficacy in the treatment of patients with GAD [41]. An early study established that buspirone had comparable efficacy with diazepam in patients with generalized anxiety and a meta-analysis of eight controlled treatment studies indicates that buspirone has comparable efficacy with benzodiazepines in the management of GAD [42,43]. It also appears efficacious in reducing associated depressive symptoms in patients with GAD, but is not an accepted treatment for patients with major depression [44]. However, not all studies with buspirone have been positive [45,46].

##### Flesinoxan

Flesinoxan is a related drug, which acts as a full agonist at somatodendritic 5-HT<sub>1a</sub> receptors: it too has been found efficacious



in the treatment of GAD. A five-arm study comparing three doses of fleoxetine, alprazolam and placebo found that both the highest dose of fleoxetine and alprazolam were significantly more efficacious than placebo in reducing anxiety symptoms, rated by the HAM-A, but there is little further information on the efficacy of the drug [47].

#### Benzodiazepines

A systematic review of randomized controlled trials has established that benzodiazepines are an effective and rapid treatment for many patients with GAD [48]. However, the benzodiazepines are far from ideal anxiolytic drugs. The untoward 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 and dependence and withdrawal symptoms on stopping the drug. As such, many authorities counsel that benzodiazepines should be reserved for short-term use (up to 4 weeks) and prescribed at low dosage [49]. Others have argued that benzodiazepines are clearly efficacious and withholding treatment on the basis of potential risk of dependence is unjustified and detrimental to overall well-being [50].

Other potential future approaches to the management of patients with GAD include treatment with subtype selective benzodiazepines, cholecystokinin (CCK) antagonists and the novel drug, pregabalin. There is good evidence for the efficacy of the  $\beta$ -carboline abercarnil, which acts as an agonist (full or partial, depending on site) at the benzodiazepine-GABA complex [51]. Four placebo-controlled studies have provided evidence for the efficacy of abercarnil in the management of patients with GAD [52-55]. Treatment studies with CCK antagonists have produced disappointing results: a 4-week, multi-center, double-blind, placebo-controlled, parallel-group study with the CCK-B antagonist CI-988 failed to reveal efficacy, but interpretation of the findings is difficult because of a significant treatment-by-center interaction [56].

#### Pregabalin

Pregabalin is a novel psychotropic drug with anticonvulsant, anxiolytic and analgesic properties. The mechanism of action is unknown, although it binds to an auxiliary subunit ( $\alpha_2\delta$ ) of voltage-gated calcium channels, thereby increasing whole brain GABA [57]. 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 or venlafaxine [58,59]. Further studies with pregabalin are nearing completion.

#### Psychological treatments

A systematic review of 35 randomized controlled trials has found that cognitive therapy, using a combination of interventions, such as anxiety management training, relaxation, cognitive restructuring and exposure, is more effective than remaining on a waiting list, anxiety management alone, or nondirective therapy [60]. Furthermore, a 1-year follow-up found that cognitive therapy was associated with better outcomes than either analytic psychotherapy or anxiety management training [61].

It is uncertain whether there is an advantage for combining pharmacological and psychological treatment approaches in the management of patients with GAD, over using single approaches alone [62]. In a comparative study of behavior and cognitive therapy in 40 patients with GAD, concomitant treatment with benzodiazepines significantly reduced the proportion of patients with a good outcome (8% with benzodiazepines, 86% without) [63,64]. By contrast, a 10-week treatment study in general practice patients with GAD found that the combination of diazepam and cognitive-behavioral therapy was more effective than either treatment given alone, in terms of the onset of improvement and clinical response at the end of the study [65].

Larger studies in patients with major depression show that combining antidepressant drugs with cognitive therapy may be significantly more effective than either treatment given alone, but this cannot necessarily be assumed to be the case in patients with anxiety disorders [66]. A recent study found that combination treatment with imipramine and cognitive-behavior therapy was not more effective than either treatment as a monotherapy in the acute treatment of patients with panic disorder, although the addition of cognitive-behavior therapy to imipramine conferred some advantages in subsequent maintenance treatment [67].

#### Conclusions

GAD is a common and often incapacitating medical condition, but many patients are not recognized as suffering from a potentially treatable anxiety disorder. Whilst some tricyclic antidepressants and benzodiazepines have been found efficacious in GAD, tolerability problems and other potential risks limit their long-term use in clinical practice. Buspirone is efficacious, but has limited effects in relieving comorbid major depression. The SSRI paroxetine and the selective norepinephrine reuptake inhibitor (SNRI) venlafaxine have

proven efficacy in published randomized controlled trials and both have been licensed for the treatment of GAD. There is a need for comparative treatment studies: to establish which drug has the better benefit-to-risk profile in routine clinical practice and to determine the relative efficacy of differing pharmacological and psychological treatment approaches. In view of the chronicity of GAD, studies are needed of the long-term efficacy and tolerability of differing treatments.

#### Expert opinion

Due to concerns about benzodiazepines, it seems best for clinicians to use either an SSRI or an SNRI antidepressant, when prescribing for patients with GAD. It may be that an SSRI is better tolerated, but an SNRI is more effective and it could be argued that SNRI treatment should therefore be reserved for those who do not respond to earlier treatment with an SSRI. Whichever class is used, the majority of patients will experience some reduction in symptoms within the first 2 months of treatment. There is good evidence that patients who have responded to acute treatment will continue to improve with treatment over a further 6 months and symptom diminution is often associated with a reduction in the associated social and occupational impairment. Although there is a lack of long-term studies on which to base treatment recommendations, the chronic nature of untreated GAD and the risk of developing comorbid depression suggest that treatment should continue for many years.

#### Five-year view

The next 5 years should see much further research into the pathophysiology and treatment of GAD. Clinical trial programs will be facilitated by the development of a GAD-specific rating scale and by the production of clear guidelines for establishing the efficacy of putative treatments for the disorder [68]. Neuropsychological testing may indicate who is likely to respond to drug treatment and who to psychological treatment. The efficacy of the SSRI escitalopram may well have been confirmed. New potential treatment approaches may include use of the 5-HT<sub>2a/2c</sub> antagonist deramciclane, or the anticonvulsant drug pregabalin. Drugs that act only on particular benzodiazepine receptor subtypes may well be in the late stages of development.

#### Information resources

For those with a particular interest in anxiolytic drug development, two books are likely to be especially helpful. The first is *Anxiolytic Compounds: Perspectives in Drug Development* (Wiley) by Neil Cutler, John Sramek and Neil Kurtz, the second is *Anxiolytics* (Birkhauser), edited by Mike Briley and David Nutt. There are many websites concerned with anxiety and its treatment, but the quality of these sites is highly variable.

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#### Key issues

- Generalized anxiety disorder (GAD) is a common and often incapacitating condition.
- The pathophysiology of GAD is not established, but disturbances of serotonergic and noradrenergic neurotransmission and of benzodiazepine receptor function are important.
- The selective serotonin reuptake inhibitor (SSRI) paroxetine has proven efficacy in the short-term treatment of GAD.
- The new SSRI escitalopram shows preliminary evidence for efficacy in GAD.
- The selective norepinephrine reuptake inhibitor (SNRI) venlafaxine is efficacious in both acute and continuation treatment.
- Comparative studies of paroxetine and venlafaxine are needed.
- The effect of combining drug treatment with psychological approaches needs further investigation.
- Many new potential drug treatments will be evaluated over the next 5 years.
- There will be much debate about the benefits and risks of potential long-term treatment.

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#### Affiliations

- David Baldwin, FRCPsych, Senior Lecturer in Psychiatry, Community Clinical Sciences Research Division, Faculty of Medicine, Health and Biological Sciences University Department of Mental Health, Royal South Hants Hospital, Southampton SO14 0YG, UK. Tel.: +44 2380 825533, Fax: +44 2380 234243, dsb1@soton.ac.uk

- *Christel Buis, MD, Clinical Research Fellow, Community Clinical Sciences Research Division, Faculty of Medicine, Health and Biological Sciences University Department of Mental Health, Royal South Hants Hospital, Southampton SO14 0YG, UK, Tel.: +44 23 0802 5545, Fax: +44 23 8082 4243, Christel@soton.ac.uk*
- *Andrew Mayers, BSc, Research Psychologist, Community Clinical Sciences Research Division, Faculty of Medicine, Health and Biological Sciences University Department of Mental Health, University of Southampton, Royal South Hants Hospital, Brintons Terrace, Southampton, UK, SO14 0YG, Tel.: +44 23 8082 5541, Fax: +44 23 8023 4243, a.g.mayers@soton.ac.uk*