Generalized anxiety disorder: comorbidity, comparative biology and treatment

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Abstract

Generalized anxiety disorder (GAD) is a severe and chronic anxiety disorder characterized by uncontrollable worrying and somatic anxiety (tension, insomnia and hypervigilance). It is a common condition, with lifetime prevalence rates for DSM-IV GAD in the general population of approx. 5–6% being reported. In addition, like other anxiety disorders, GAD also shows comorbidity with depression and most of the other anxiety disorders. This article reviews data on the prevalence of GAD, its comorbidity with depression, and its social and economic impact. Proposed neurobiological mechanisms for GAD are discussed, since an understanding of these may help in the development of future therapies. Finally, current pharmacological and non-pharmacological treatment options for GAD are reviewed, with particular attention being paid to published clinical-trial data.

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Introduction

Generalized anxiety disorder (GAD) is a severe and chronic anxiety disorder. In primary care, GAD patients rarely present with anxiety or specific worry as their main problem, but frequently complain of somatic or sleeping problems. Although anxiety is a symptom of many of the anxiety disorders (panic disorder, social anxiety disorder, obsessive–compulsive disorder, simple phobia), there are core features that distinguish the primary anxiety disorders (DSM-IV; APA, 1994). These features, including those for GAD, are shown in Figure 1. The core features of GAD identified in DSM-IV that make it a recognized and distinct disorder are persistent (6 months) uncontrollable worrying and somatic anxiety (tension, insomnia and hypervigilance).

The lifetime prevalence of DSM-IV GAD in the general population is approx. 5–6% (Wittchen et al., 2000). The figures for 12-month prevalence differ slightly according to which diagnostic criteria are used, ranging from 3.1% in the National Comorbidity Study (NCS), where DSM-III-R was used (Wittchen et al., 1994), to 1.5% in the German National Health Interview and Examination Survey (GHS), which used stricter (12 months) DSM-IV criteria (Wittchen et al., 2000). The pattern of onset of GAD is slightly different to those of the other anxiety disorders in that, although some cases occur before the age of 25 yr, the incidence of GAD greatly increases later in life (35–45 yr). GAD is also the most frequent anxiety disorder among the elderly population (55–85 yr) (Beekman et al., 1998).

As with other anxiety disorders, GAD shows comorbidity with depression and anxiety disorders. In the NCS, current psychiatric comorbidity in GAD occurred in more than half the patients (Wittchen et al., 1994). Among the most prevalent comorbid diagnoses were major depression, social and specific phobia, and panic disorder. Similarly, in patients with a lifetime diagnosis of GAD, there was often a history of major depression or dysthymia. Since only 20–25% of patients with GAD experience spontaneous remission, GAD alone is likely to cause a significant amount of disability to sufferers, and the development of GAD with secondary depression compounds the disability both for the patient and society.

This article looks at the prevalence of GAD, its comorbidity with depression, its burden and its neurobiological basis. In addition, treatment options for GAD...
are reviewed with particular attention being given to published clinical-trial data.

**Generalized anxiety disorder and depression**

**Prevalence**

In general, anxiety and depression are highly comorbid. In primary care, comorbidity rates of current anxiety cases with depression as high as 19.2% have been reported (Stein et al., 1995). In the community, the NCS found that 14% of the population had three or more comorbid psychiatric disorders (Kessler et al., 1994). The NCS estimated 12-month and lifetime prevalence rates for GAD (using DSM-III-R criteria) to be 3.1 and 5.1%, respectively (Kessler et al., 1994; Wittchen et al., 1994). The lowest lifetime prevalence rate was found in the 15–24 yr age group (2.0%), while the highest was reported for the 45–55 yr age group (6.9%). Current psychiatric comorbidity in GAD occurred in 66.3% of patients in the NCS, with major depression being one of the most prevalent co-existing conditions (Wittchen et al., 1994). Secondary analyses of the NCS data have demonstrated that 80% of people with lifetime GAD had a comorbid mood disorder at some time during their life (Judd et al., 1998). In addition, unipolar disorders were found to occur in 67% of subjects with GAD. More recently, these findings were confirmed in a study which found that 12-month comorbidity of GAD includes other anxiety disorders in 56% of cases, and depression in 59% of cases (Wittchen et al., unpublished observations).

**Nature and course**

Long-term follow-up studies have shown that depression often develops secondary to anxiety and this sequence occurs considerably more frequently than depression followed by anxiety (Angst and Vollrath, 1991; Breslau et al., 1995; Kendell, 1974; Wittchen et al., 1991). This is supported by a prospective study, the Early Developmental Stages of Psychopathology (EDSP) study, which looked at the proportions of patients with pure and comorbid anxiety disorders at baseline in a representative population sample (3021 subjects aged 14–24 yr) and followed the development of their comorbid major depression with time (Wittchen et al., 1998). At a 5-yr follow-up assessment, the proportion of the study population with pure anxiety at baseline had decreased by almost 50%, while the comorbid group had increased proportionately, particularly for GAD, panic disorder and agoraphobia [Figure 2(a, b)]. The odds ratios show the risk of having an anxiety disorder comorbid with depression was increased at the 5-yr follow-up. Therefore, anxiety seems to be the primary disorder, with depression developing as a secondary disorder.

**Impact**

Moderate or severe social disability has been reported in 27% of GAD sufferers in primary care, with a mean loss of 4.6 work days due to disability in the previous month (Weiller et al., 1998). This rose to 59% when GAD was accompanied by major depression, with the mean number of lost work days increasing to 8.0 d in the previous month. Social disability associated with GAD has been equated to that in chronic physical illness in terms of severity (Maier et al., 2000). In the combined analysis of the NCS and Midlife Development in the US Survey (Kessler et al., 1999), as well as data from GHS (Wittchen et al., 2000), ‘pure GAD’ was associated with marked impairment. Moreover, this
impairment was equivalent in magnitude to that caused by major depression. However, the highest levels of impairment were seen when GAD was comorbid with major depression.

In common with social anxiety disorder and panic disorder, when GAD is comorbid with depression the suicide attempt rate rises, adding further emotional and financial burden to the families of sufferers (Figure 3) (Wunderlich et al., 1998).

In the GHS study, the percentage of patients with a reduction of at least 50% in daily activity during the past month was greater for patients with comorbid GAD and major depressive disorder (MDD), when compared with those with either GAD or MDD alone (Carter et al., 2001; Wittchen et al., 2000).

There is a high prevalence of GAD and MDD in patients with unexplained somatic complaints (Brown et al., 1990; Maier and Falkai, 1999). GAD appears to be commonly associated with chest pain (Carter and Maddock, 1992; Logue et al., 1993), chronic fatigue syndrome (Fischler et al., 1997), irritable bowel syndrome (Lydiard et al., 1993), and chronic medical illnesses (hypertension, diabetes, and heart disease) (Maier and Falkai, 1999; Sherbourne et al., 1996). As most GAD patients present with somatic complaints in primary care (Hidalgo and Davidson, 2001), there is a

### Table: Percentage Reduction in Daily Activity

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percentage of Patients with Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anxiety</td>
<td>21.2</td>
</tr>
<tr>
<td>Separation anxiety</td>
<td>2.2</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>14.7</td>
</tr>
<tr>
<td>Social phobia</td>
<td>5.1</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>2.2</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>2.1</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### Figure 2

Figure 2. Early Developmental Stages of Psychopathology study: proportion of representative study population (n = 3021) with pure and comorbid anxiety disorders at (a) baseline and (b) 5-year follow-up.
substantial use or ‘misuse’ of health-care services. More than 50% of the overall economic burden of anxiety disorders is accounted for by the direct costs of non-psychiatric medical treatment (Greenberg et al., 1999). Furthermore, hospitalizations are more prevalent in GAD patients with comorbid conditions, with internal medicine and emergency admission being the most frequently used services (Souètre et al., 1994).

Differential diagnosis

The DSM-IV definition of GAD has helped to clarify its diagnosis. The diagnosis of GAD should be reserved for patients with chronic worries about many things. The DSM-IV criteria include excessive worrying most of the day, and most days for 6 months. The patients realize they are worrying, wish they could stop, but are unable to do so. The anxiety is free floating and is not confined to having a panic attack, being embarrassed in public or being the product of an obsession. In addition to this constant worrying, three physical symptoms must be present, the commonest ones being fatigue, irritability, tension, insomnia or restlessness.

For patients with somatic symptoms, such as headaches, fatigue, muscular tension and problems sleeping, and in whom no physical cause can be found, the diagnosis of anxiety, particularly GAD, should be considered. When questioned further these patients describe having difficulty in dealing with uncertainty in everyday life; often they will also admit to general worrying (nothing specific) and this tends to be uncontrollable (Andrews and Garrity, 2000).

Neurological mechanisms of GAD

Unipolar disorders have been reported to be more frequently comorbid with GAD than bipolar disorders, suggesting that GAD and major depression share the same genetic origin (Judd et al., 1998). The fact that symptoms of GAD and depression may respond to the same treatment supports the possibility of a common neurobiological dysfunction.

The exact neurological mechanisms behind GAD, however, have not yet been fully elucidated. Neuro-imaging techniques, such as positron emission tomography and single positron emission computed tomography, have enabled cerebral blood flow and metabolic activity in various regions of the brain to be assessed. At rest, patients with GAD show no differences in baseline cerebral blood flow compared with normal controls (Brawman-Mintzer and Lydiard, 1997; Drevets et al., 1997). In contrast, patients with depression at rest show reduced cerebral blood flow in the frontal, parietal and temporal areas (Austin et al., 1992; Goodwin, 1997). Regional glucose metabolism during a passive viewing task was higher in the occipital, temporal and frontal lobes, and in the cerebellum and thalamus of patients with GAD, relative to normal controls (Wu et al., 1991). Both increased and decreased activity were seen in the basal ganglia at that time (Buchsbaum et al., 1987; Wu et al., 1997). In depressed patients, cerebral metabolic activity decreased in the limbic system, temporal frontal lobes and basal ganglia (Ho et al., 1996; Hurwitz et al., 1990; Mayberg et al., 1997). When asked to perform vigilance tasks, patients with GAD showed increased activity in the basal ganglia, while depressed patients had decreased activity in basal ganglia and right parietal metabolism (Wu et al., 1991). It seems, therefore, that hyperactive brain circuits occur in GAD, whereas underactive brain circuits might be associated with depression. A hypothesis to explain the activity of brain circuits and the symptoms of GAD is shown in Figure 4.

Figure 3. Risk of suicide attempt with depression and anxiety (Wunderlich et al., 1998).
Several studies have indicated that peripheral benzodiazepine receptors have a role to play in the mechanism of GAD (Chiu et al., 2001; Rocca et al., 1991, 1998; Sacerdote et al., 1999). The numbers of peripheral benzodiazepine receptor-binding sites in lymphocyte membranes taken from patients with GAD are significantly reduced (by 45%) compared with controls and return to normal following the patient’s recovery after long-term therapy (Rocca et al., 1991). Chiu et al. (2001) found a statistically significant increase in peripheral benzodiazepine receptor density in platelets in patients with GAD compared with normal controls, suggesting that dysregulation of peripheral benzodiazepine receptors may be a possible mechanism in GAD.

A considerable amount of attention has been focused on the serotonin (5-HT) system and, therefore, it is perhaps currently the best understood underlying mechanism. 5-HT is widely distributed throughout the brain and, in particular, in regions associated with anxiety. In patients with GAD, 5-HT levels in the cerebrospinal fluid (CSF) are reduced compared with control patients (Brewerton et al., 1995). In comparison, patients with depression have normal concentrations of 5-HT in the CSF, although levels may be reduced in suicidal patients (Asberg, 1997).

The serotonergic function in patients with depression and GAD has been investigated by examining the neuroendocrine and mood responses to the non-specific 5-HT₁ and 5-HT₂ agonist m-chlorophenylpiperazine (m-CPP). In depressed patients, no behavioural changes were noticed in response to the m-CPP challenge, although patients had a blunted growth hormone response in comparison with controls, suggesting an altered endocrine sensitivity (Anand et al., 1994). In the case of GAD patients, challenge with m-CPP resulted in anger and anxiety, similar to the typical symptoms of GAD (Germine et al., 1992).

To explain the role of 5-HT in a stress-sensitive disorder such as GAD, it is proposed that there are two distinct serotonergic pathways originating from the dorsal raphe nucleus (Deakin and Graeff, 1991). Serotonergic neurons arising from the median raphe nucleus, which innervate the 5-HT₁A receptors in the temporal lobe and hippocampus, are thought to be implicated in coping with chronic adversity and depression, whereas serotonergic connections between the dorsal raphe and amygdala may play an important role in regulating anxiety.

Further support for the role of 5-HT in anxiety and depression can be found in 5-HT depletion studies with tryptophan (Goddard et al., 1994; Salomon et al., 1993). By reducing the dietary availability of the 5-HT precursor tryptophan, a decrease in 5-HT synthesis occurs. Depletion of 5-HT in the brain may cause a relapse in depressed patients receiving selective serotonin re-uptake inhibitors (SSRIs), but as yet there have been no studies of this procedure in patients with GAD.

Another method of studying the role of 5-HT in GAD is to look at the activation of the hypothalamic–pituitary–adrenal (HPA) axis, which is an important component of the normal stress response. In depression, plasma cortisol levels and corticotrophin-releasing factor levels have been found to be significantly increased (Catalan et al., 1998). However, in GAD patients, plasma cortisol levels have been shown to be normal, as have plasma levels of corticotrophin-releasing factor (Kelly and Cooper, 1998).

The dexamethasone suppression test is a commonly used marker for HPA axis function. In normal patients, a single dose of 1 mg of dexamethasone at night,
dependent on weight, is sufficient to inhibit cortisol secretion (100%) for 24 h. In a study of GAD patients by Brawman-Mintzer and Lydiard (1997), a non-suppression rate of around 30% was reported. By comparison, in a study of depressed patients, a higher non-suppression rate of almost 50% was seen (Staner et al., 1994). These results point towards possible abnormalities in HPA regulation in GAD patients.

It is also likely that the noradrenergic neurotransmitter systems are involved in GAD; Sevy et al. (1989) found levels of plasma noradrenaline to be greater in patients with GAD than in either patients with MDD or normal controls. A later study also found plasma noradrenaline levels to be elevated in patients with GAD compared to normal subjects (Kelly and Cooper, 1998). However, in this study the difference was not as great as that seen between depressed patients and controls. In addition, the study by Sevy et al. (1989) indicated that the number of α2-adrenoceptors were reduced in patients with GAD compared with patients with MDD or normal controls. A study of platelet α2-adrenoceptor binding confirms this finding (Cameron et al., 1990).

It is hoped that further study into the neurobiological mechanisms of GAD may lead to a better understanding of this condition. In turn, this may result in the development of new drug therapies or in the more effective use of existing treatments.

Treatment of GAD

Early treatment of anxiety disorders is important as it may prevent the development of treatment resistance and secondary depression. The additional burden of undetected anxiety in the further course of depression must be considered. In fact, a life-cycle assessment of mental disorders is always a prudent start to any treatment plan. Effective treatment of GAD can be achieved with both pharmacological and non-pharmacological approaches.

Psychotherapy

There have not been many randomized, controlled clinical trials of psychotherapy in patients with DSM-III-R or DSM-IV GAD. Techniques that have been studied include cognitive behavioural therapy (CBT), behavioural therapy, analytical psychotherapy, anxiety management and applied relaxation (Butler et al., 1991; Durham et al., 1994; Fisher and Durham, 1999; Ladouceur et al., 2000; Ost and Breitholtz, 2000). In general, these studies were conducted in small groups of patients, were not blinded, and were controlled by another psychotherapy treatment or a waiting-list control. However, they consistently demonstrate that psychotherapies may be effective in the treatment of GAD.

In one of the largest studies involving 80 patients (with DSM-III-R GAD), who had completed treatment with either CBT, analytical psychotherapy or anxiety management, CBT was found to be the most effective treatment although improvements were seen in all three groups (Durham et al., 1994). Approximately 50% of the patients in the CBT group had considerably improved at the 6-months follow-up.

Fisher and Durham (1999) have combined the data from six randomized clinical trials of psychotherapy in GAD (diagnosed using DSM-III-R or DSM-IV criteria). The overall recovery rate was 40% and the techniques with the best recovery rates at 6 months follow-up were CBT and applied relaxation (50–60%).

More recently, in a study of 36 patients with DSM-III-R GAD, CBT and applied relaxation were both found to produce significant improvements, with no difference between the two therapies being observed (Ost and Breitholtz, 2000). At 12 months follow-up, 56% patients treated with CBT and 67% treated with applied relaxation had clinically significantly improved.

A CBT that targets intolerance of uncertainty, erroneous beliefs about worry, poor problem orientation and cognitive avoidance has been assessed in 26 patients with GAD (diagnosed using DSM-IV criteria) and a waiting-list control group (Ladouceur et al., 2000). Statistically and clinically significant changes were seen post-test and at 6 and 12 months follow-up, and 77% of patients no longer met diagnostic criteria for GAD at these time-points.

Pharmacotherapy

The types of medication chosen by clinicians for the treatment of GAD have changed during the past 10 yr. A survey of international experts’ opinions showed that in 1992 benzodiazepines were most likely to be selected as first-line therapy for GAD, however in 1997, SSRIs were more frequently recommended for this condition (Uhlenhuth et al., 1999). A naturalistic study in the USA reported a similar finding: there was a decrease in treatment of non-comorbid GAD with benzodiazepines and an increase in the use of antidepressants in 1996 compared with 1989–1991 (Salzman et al., 2001). The benzodiazepines have been found to be efficacious in the treatment of GAD, with a rapid and good effect on somatic symptoms (Rickels et al., 1983; Shader and Greenblatt, 1993). However, the most likely reason for the move away from their use is
The risk of dependence associated with these agents (Murphy et al., 1989).

The azapirone, buspirone, was approved for the treatment of anxiety in 1986; it has been shown to reduce the symptoms of anxiety in patients with GAD, without the risk of dependence (Murphy et al., 1989). Other controlled clinical trials in patients with GAD have confirmed that its efficacy is similar to that of the benzodiazepines (Delle Chiaie et al., 1995; Laakmann et al., 1998; Strand et al., 1990). A large ($n = 230$), double-blind study of buspirone in comparison with oxazepam demonstrated that the two treatments were similar with regard to efficacy and adverse events reported (Strand et al., 1990).

In the early 1990s, the tricyclic antidepressant, imipramine, was shown to be effective in the treatment of patients with GAD who did not have depression or panic disorder (Rickels et al., 1993). Subsequently, other antidepressant agents have been investigated in the treatment of GAD, including the SSRIs and the 5-HT and noradrenaline reuptake inhibitor, venlafaxine.

The efficacy and safety of once-daily venlafaxine (extended release formulation) in GAD has been studied in both short- and long-term, placebo-controlled trials (Allgulander et al., 2001; Davidson et al., 1999; Gelenberg et al., 2000; Rickels et al., 2000). In two 8-wk studies in outpatients with GAD, but without MDD, venlafaxine (75, 150, or 225 mg/d) was shown to be more effective than placebo (Davidson et al., 1999; Rickels et al., 2000). Over a longer period, a 24-wk dose-finding study in 541 outpatients with GAD showed that venlafaxine was more effective than placebo (Allgulander et al., 2001). The difference was apparent from week 2, however, only the two higher doses (75 and 150 mg/d) maintained efficacy throughout the duration of the study. Another long-term (28 wk) study demonstrated the efficacy of venlafaxine (75, 150, or 225 mg/d) compared with placebo in 251 outpatients with GAD (Gelenberg et al., 2000). Treatment emergent adverse events reported in this study included nausea, somnolence and dry mouth.

Of the SSRIs, paroxetine, has been the most extensively studied in the treatment of GAD. It has been investigated in a large clinical trial programme involving 1264 patients with GAD (without major depression) in three 8-wk, double-blind, randomized studies of either a fixed or flexible dose (Bellew et al., 2000a,b; Hewett et al., 2001; Pollack et al., 2001). The first of these studies, a dose-finding study in 566 patients with GAD showed paroxetine (20 or 40 mg/d) to be significantly superior to placebo in reducing HAMA total score (Bellew et al., 2000a) (Figure 5). In addition, reductions in HAMA items 1 and 2 with paroxetine were significantly superior to those with placebo. A total of 68% of patients treated with 20 mg/d paroxetine and 80% of those on the 40 mg/d dose were considered responders compared with 52% of placebo-treated patients. Paroxetine also improved work, family and social life disability associated with GAD. The impaired quality of life in patients with GAD (compared with the general population) showed a significant improvement by the end of the study; mean change from baseline in the EuroQol-5D visual analogue scale was significantly greater for both paroxetine groups compared with placebo (Bellew et al., 2000b).

Similarly, in the second study, a flexible dose study in 326 patients with GAD, paroxetine (20–50 mg/d) was found to be significantly superior to placebo with regard to change from baseline in HAMA total score (Figure 6) and HAMA items 1 and 2 (Pollack et al., 2001).

The third study in 372 patients with GAD also employed a flexible dosing regimen of paroxetine
At week 8, a numerical (but not statistical) difference in HAMA total score in favour of paroxetine over placebo was observed. This was also true for HAMA item 2, whereas for HAMA item 1 the improvement seen with paroxetine was statistically significantly greater than that of the placebo group. In addition, all three of these studies found paroxetine to be well tolerated in patients with GAD.

The SSRI, sertraline, has been investigated in one small ($n=22$) placebo-controlled, double-blind study of children and adolescents (aged 5–17 yr) with DSM-IV GAD (Rynn et al., 2001). Sertraline significantly improved the HAMA total score compared with placebo and was well tolerated. However, larger studies are warranted to further investigate the safety and efficacy of sertraline in patients with GAD.

Whether other members of the SSRI class will demonstrate efficacy in GAD needs to be determined in randomized, double-blind, placebo-controlled studies.

**Conclusion**

GAD is a prevalent and chronic anxiety disorder with a fluctuating course. It is also frequently comorbid with depression and other anxiety disorders. Due to the disability and socio-economic burden associated with GAD, it needs to be effectively treated. In the past, benzodiazepines were commonly prescribed, however, the problem of addiction means that these agents are less useful. Clinicians now appear to favour antidepressants for the treatment of GAD. Data from recent controlled clinical trials in patients with GAD support the use of antidepressants, such as venlafaxine and the SSRI, paroxetine, for this indication.

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