

# Current Considerations in the Treatment of Generalized Anxiety Disorder

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## Contents

Abstract	103
1. Co-Morbidity	105
2. Impact of Generalized Anxiety Disorder (GAD) on Patients	105
3. Symptoms of GAD	106
4. Diagnosis and Assessment of GAD	107
5. Pharmacological and Genetic Basis of GAD	107
6. Treatment of GAD	108
6.1 Treatment Guidelines	108
6.2 Selective Serotonin Reuptake Inhibitors	109
6.3 Serotonin Noradrenaline Reuptake Inhibitors	110
6.4 Pregabalin	111
6.5 Buspirone	111
6.6 Imipramine	111
6.7 Benzodiazepines	111
6.8 Limitations of First-Line Treatment Options	112
7. Treatment Response and Remission	112
8. Use of Nonpharmacological Approaches for Patients with GAD	112
9. Atypical Antipsychotics in GAD	113
10. Discussion	115
11. Conclusions	116

## Abstract

Generalized anxiety disorder (GAD) is a chronic disorder that frequently co-occurs with a variety of co-morbidities in patients with somatic conditions and other mental disorders. GAD is highly prevalent and is one of the most common anxiety disorders seen by primary care physicians. The individual and societal cost associated with GAD is high and the marked level of impairment experienced by patients with this disorder is equivalent in magnitude to that reported in patients with major depressive disorder. Furthermore, patients with GAD are at risk of suicide or suicide attempts, and are frequent users of healthcare services. Thus, GAD is a serious and chronic condition that requires appropriate long-term treatment.

The focus of acute treatment for patients with GAD is the improvement of symptoms, while the primary goal of long-term clinical management is remission, i.e. the complete resolution of both symptoms and functional impairment.

The consensus across current treatment guidelines is that first-line treatment for patients with GAD should consist of an antidepressant, either a selective serotonin reuptake inhibitor (SSRI) such as sertraline, paroxetine or escitalopram, or a selective serotonin noradrenaline (norepinephrine) reuptake inhibitor (SNRI) such as venlafaxine or duloxetine. However, the SSRIs and SNRIs have efficacy limitations, such as lack of response in many patients, a 2- to 4-week delay before the onset of symptom relief, lack of full remission, and risk of relapse. In addition, there are troublesome adverse effects associated with both the SSRIs and SNRIs.

Evidence from early clinical studies of the atypical antipsychotics in the treatment of anxiety and GAD indicate that they may have a potential role in the treatment of GAD, either as monotherapy or as augmentation to standard treatment.

Generalized anxiety disorder (GAD) is a chronic disorder that is highly prevalent; in the US the 12-month and lifetime prevalence rates of GAD were estimated to be 3.1% and 5.7%, respectively.<sup>[1-3]</sup> In primary care, the prevalence of GAD is typically higher than that observed in the community, making it one of the most common anxiety disorders seen by primary care physicians. For example, in a large European primary care study (n=13 677), 8.3% of patients who presented to their general practitioner were diagnosed as having GAD.<sup>[4]</sup>

Patients with GAD are frequent users of healthcare services. In a US study of high utilizers of healthcare services, DSM-III-R<sup>[5]</sup> diagnoses were made on a sample of 119 distressed high utilizers, 22% of whom had a diagnosis of GAD.<sup>[6]</sup> More recently, the Mental Health Supplement to the Ontario Health Survey (a survey of 8116 Canadian respondents aged 15–64 years) showed that four or more visits made to a primary care physician over a 12-month period indicated a 35% chance of the patient having GAD.<sup>[7]</sup> This survey also showed that patients who sought help from mental health services in the past year had a 50% chance of having GAD.

GAD follows a chronic course during the first 5 years that may last up to 20 years, and is associated with low rates of remission and moderate rates of relapse/recurrence following remission.<sup>[8]</sup> In the US National Comorbidity Survey (NCS) conducted in 8098 subjects aged 15–54 years,

GAD was twice as common among women as it was among men and, as age increased, so did the lifetime prevalence.<sup>[9]</sup> Multivariate logistic regression analysis showed that being older than 24 years of age, separated, widowed, divorced, unemployed or a homemaker were significant correlates of GAD.<sup>[9]</sup>

Epidemiology studies consistently indicate that GAD may occur at any point in a person's lifetime,<sup>[10]</sup> but is relatively uncommon before the age of 20 years, with a mean age at onset of 21 years.<sup>[10,11]</sup> However, the age of onset has a bimodal distribution – onset occurs earlier when GAD is the primary presentation and later when GAD is secondary.<sup>[11]</sup>

While GAD represents an illness that may have presented with significant GAD symptoms when patients are aged in their 20s, childhood risk factors have been identified, such as internalizing problems, conduct problems and a somewhat more inhibited temperament.<sup>[12]</sup> Children with family members who have an anxiety disorder have a higher risk of developing over-anxious disorder of childhood and GAD. For example, adults with anxiety disorders have children with greater than expected rates of behavioural inhibition (60–76%).<sup>[13-15]</sup> Furthermore, in a study of a clinically derived sample of 31 children (60 parents) and an epidemiologically derived (longitudinal) sample of 40 children (75 parents), it was found that inhibited children had parents with greater than expected rates of anxiety disorders (75% if the child was inhibited

and anxious; 29% if the child was inhibited only).<sup>[16]</sup>

Schwartz et al.<sup>[17]</sup> reported that the parents of children with stable behavioural inhibition had higher rates of multiple childhood anxiety disorders (25% vs 3.6%) and that the higher rates of anxiety disorder continued into their adulthood (35% vs 7.3%). Similarly, Biederman et al.<sup>[13]</sup> reported that compared with healthy children, behaviourally inhibited children had an increased risk for at least one anxiety disorder (22% vs 0%), for over-anxious disorder or childhood GAD (27.8% vs 0%) and for phobic disorders (31.8% vs 5.3%).

In addition, data from a prospective, longitudinal community study conducted in 3021 adolescents and young adults<sup>[18]</sup> have shown that >50% of patients with GAD have had a major depressive episode by the age of 18 years.<sup>[19]</sup>

## 1. Co-Morbidity

GAD is often co-morbid with mood and anxiety disorders (table I).<sup>[9,20]</sup> In the US community-based NCS conducted in 8098 persons (aged 15–54 years), 90.4% of respondents with lifetime GAD reported having at least one other lifetime mental health disorder.<sup>[9,21]</sup>

More recently, a German community study of 4181 adults (aged 18–65 years) estimated the 12-month prevalence of GAD according to DSM-IV<sup>[22]</sup> criteria to be 1.5%.<sup>[23]</sup> Of the 12-month GAD cases, 93% had another DSM-IV disorder, 59% fulfilled the criteria for major depressive disorder (MDD) and 56% fulfilled the criteria for any other anxiety disorder.<sup>[23]</sup> Specific phobia (29%) and social phobia (29%) were the anxiety disorders that were most frequently co-morbid with GAD.<sup>[23]</sup> The proportion of patients with 12-month GAD and any co-morbid DSM-IV eating disorder, co-morbid alcohol abuse/dependence and drug abuse/dependence were 2.5%, 6.4% and 1.4%, respectively. Furthermore, a prospective community-based study in young adults found that GAD is negatively associated with being overweight.<sup>[24]</sup>

GAD may occur as the primary disorder (i.e. pre-dating other disorders) or as a secondary

**Table I.** Lifetime prevalence of co-morbidities associated with generalized anxiety disorder<sup>[9,20]</sup>

Co-morbidity	Prevalence (%)
Major depressive disorder	60.9–82.4
Dysthymia	37.7–39.5
Specific (simple) phobia	33.6–35.1
Social phobia (social anxiety disorder)	34.0–34.4
Agoraphobia	20.7–25.7
Panic disorder	21.8–23.5
Mania	7.9–10.5
Substance abuse	33.1
Alcohol use or dependence	37.6
Drug use or dependence	27.6

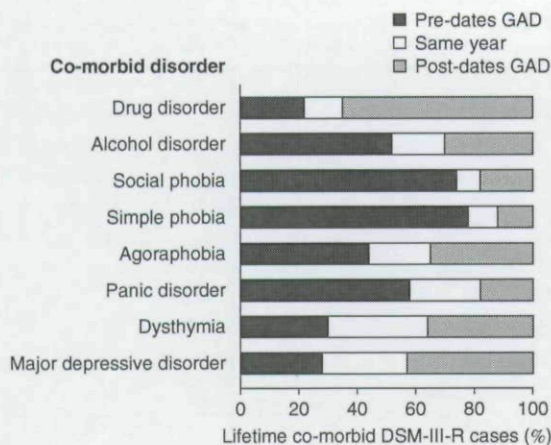
disorder (i.e. developing after other disorders).<sup>[25]</sup> For example, MDD most often develops in the same year or after the onset of GAD, whereas social phobia typically pre-dates the onset of GAD (figure 1).<sup>[25]</sup>

Bipolar disorder and GAD are also commonly co-morbid, with the proportion of patients with bipolar disorder having a lifetime GAD diagnosis reported to be 18.4%.<sup>[26]</sup>

## 2. Impact of Generalized Anxiety Disorder (GAD) on Patients

The quality of life and level of functioning in patients with GAD is, in reality, lower than that perceived by others. Henning et al.<sup>[27]</sup> found that patients with GAD reported statistically significantly less satisfaction with their quality of life than non-anxious controls (mean total Quality of Life Inventory [QOLI]<sup>[28]</sup> score 0.06 vs 2.47;  $p < 0.001$ ). In addition, the degree of lowered social functioning experienced by patients with GAD<sup>[29]</sup> is greater than that reported by patients with chronic medical conditions such as arthritis, diabetes and advanced coronary artery disease.<sup>[30]</sup>

The marked degree of impairment experienced by patients with GAD is equivalent in magnitude to that seen with MDD.<sup>[29,31,32]</sup> A German survey of 4181 respondents (aged 18–65 years) found a high level of impairment and low quality of life associated with 'pure' GAD without MDD ( $n=33$ ), 'pure' MDD ( $n=344$ ) and co-morbid



**Fig. 1.** The relative onset of mood and anxiety disorders that occur co-morbidly with generalized anxiety disorder (GAD) [reproduced from Stein,<sup>[25]</sup> with permission from Physicians Postgraduate Press. Copyright 2001].

GAD and MDD ( $n=40$ ) after controlling for age, gender and other psychopathology.<sup>[29]</sup> In fact, respondents with pure GAD had significantly lower quality of life scores on several of the Short Form-36 Health Survey scales<sup>[33]</sup> than respondents with pure MDD. The results of this survey confirm the status of GAD as an independent diagnosis.

In addition to the high level of impairment, patients with GAD are at risk of suicide or suicide attempts. In the European Study on the Epidemiology of Mental Disorders (a large community survey of 21 425 respondents), GAD was found to be strongly related to suicidality, with a rate ratio of 2.3 for lifetime attempts and 1.8 for lifetime ideation.<sup>[34]</sup> This compares with rate ratios for major depressive episodes of 4.8 and 2.9 for lifetime attempts and lifetime ideation, respectively.

The development of other psychiatric disorders is another possible consequence of GAD; even without a past history of GAD, patients experiencing a current episode of the disorder have an increased risk of developing other mental disorders.<sup>[35]</sup> Furthermore, it has been shown that a prior history of GAD increases the risk of developing MDD.<sup>[36]</sup> The impact of psychiatric co-morbidity is great; patients with GAD and a co-morbid psychiatric condition experience

increased psychological and social impairment, have an extended course and poorer outcome, and are higher utilizers of healthcare resources than patients with GAD alone.<sup>[37,38]</sup> A similar effect is seen when GAD occurs with a co-morbid somatic condition.<sup>[37,38]</sup>

The economic burden of GAD is also high. In a German study of 3021 respondents (aged 14–24 years), subjects with GAD had a greater number of days lost from work in the past month than subjects with no mental disorder (8 days vs <2 days).<sup>[39]</sup> More recently, an Australian population survey indicated that in full-time workers, GAD, MDD and personality disorders are all predictive of lost work productivity (work impairment).<sup>[40]</sup>

In the US, the total medical costs (inpatient, outpatient and prescription drug charges) of treating patients with any anxiety disorder were estimated to be \$US6475 per patient per year (based on 1999 costs), with the estimate increased by \$US2138 for patients with GAD.<sup>[41]</sup> In Europe, the annual excess cost of GAD in 2003 was estimated to be €917 per person.<sup>[42]</sup> In an earlier study, the 3-month total costs of GAD (adjusted for 2003 costs) were estimated to be €954 per patient for patients with pure GAD and €1633 for patients with GAD plus co-morbidity.<sup>[43,44]</sup> Outpatient services, absenteeism from work and hospitalization were the greatest components of the total costs.<sup>[43]</sup>

### 3. Symptoms of GAD

GAD is characterized by excessive generalized worrying and marked symptoms of hypervigilance, hyperarousal and nonspecific anxiety. Patients also frequently experience somatic complaints, such as tension, fatigue, sleep disturbance, chest pain, irritable bowel syndrome and co-morbid physical conditions, such as diabetes and heart disease.<sup>[10]</sup>

Recent work assessing psychological features related to GAD has focused on features of worry as the likely driving force behind this disorder. Intolerance of uncertainty has been identified as an important construct of worry<sup>[45]</sup> and there is a strong link between intolerance of

uncertainty and GAD.<sup>[46]</sup> Intolerance of uncertainty may also be considered to be a key feature of GAD.<sup>[47]</sup>

#### 4. Diagnosis and Assessment of GAD

Different diagnostic criteria for GAD are used in different countries; in Europe the International Statistical Classification of Diseases, 10th revision (ICD-10)<sup>[48]</sup> and, more recently, the second edition of the ICD-10<sup>[49]</sup> tend to be employed. ICD-10 has a broader spectrum of associated symptoms than the DSM-IV criteria used in the US (table II).<sup>[22,50]</sup> DSM-IV criteria are the most frequently used in clinical trials. These criteria stipulate that patients must have excessive anxiety and worry for 6 months, plus three or more of six specific symptoms (table II). DSM-V guidelines are currently being developed, with publication expected in 2011. GAD is one disorder whose diagnostic criteria may be revised; it is thought that the DSM-IV requirements of 6-month duration, excessive worry and three associated symptoms may exclude a substantial number of people with clinically significant anxiety from being diagnosed as having GAD.<sup>[51]</sup>

To aid accurate diagnosis (and to rule out other possible diagnoses), the patient's medical and family histories should be assessed, taking note of recent life events and other health problems such as depression and substance or alcohol abuse/dependence. It is also important to consider that patients with GAD have probably made multiple visits to their primary care physician or may have consulted different types of physicians, such as gastrointestinal specialists, and have a history of assessments and consultations where no definitive diagnosis was made.

The main tool used in the clinical setting to assess the severity of symptoms of GAD is the Hamilton Anxiety Scale (HAM-A).<sup>[50]</sup> However, the HAM-A is a 14-item, clinician-rated scale and is quite time consuming to perform. Recently, scales specific for GAD have been developed, such as the Generalized Anxiety Disorder Inventory (GADI)<sup>[52]</sup> and the GAD-7.<sup>[53]</sup> Worry may be the most important factor in predicting

the severity of GAD, specifically in the induction of symptoms of GAD, and the Penn State Worry Questionnaire (PSWQ), a 16-item, self-rated questionnaire that assesses pathological worry and captures the excessiveness and uncontrollability characteristic of pathological worry, is an important tool for assessing this.<sup>[54]</sup> It has a strong sensitivity and specificity in distinguishing patients with GAD from those without GAD. Table III summarizes the major advantages and disadvantages of these scales.

#### 5. Pharmacological and Genetic Basis of GAD

There is a variety of evidence implicating the dysfunction of GABA, noradrenergic and serotonergic systems in the expression of GAD.<sup>[55,56]</sup> This includes evidence that, in patients with GAD, the number of platelet  $\alpha_2$ -adrenergic receptors is reduced, and there are reduced platelet serotonin sites and reduced serotonin levels in CSF. Also, the benzodiazepine receptors in peripheral tissues are reduced.<sup>[57,58]</sup> Patients with GAD respond to treatment with benzodiazepines, further supporting the fact that these

**Table II.** International Statistical Classification of Diseases, 10th revision (ICD-10) and DSM-IV diagnostic criteria for generalized anxiety disorder (GAD)

##### ICD-10 criteria<sup>[48,49]</sup>

For a diagnosis of GAD, patients must have anxiety that is generalized and persistent but not restricted to, or even strongly predominating in, any particular environmental circumstances, i.e. it is 'free-floating'. Dominant symptoms are variable but include persistent nervousness, trembling, muscular tensions and epigastric discomfort. Fears that the patient or a relative will shortly become ill or have an accident are often expressed

##### DSM-IV criteria<sup>[22]</sup>

For a diagnosis of GAD, patients must have excessive anxiety and worry for 6 months, plus have three or more of the following symptoms:

- restlessness
- fatigue
- difficulty concentrating
- irritability
- muscle tension
- sleep disturbance

**Table III.** Summary of the main disease severity scales that may be used to assess generalized anxiety disorder (GAD)

Scale and type	Advantages	Disadvantages
<b>Clinician rated</b>		
Hamilton Anxiety Scale (HAM-A) <sup>[50]</sup>	Current 'gold standard' scale and reference scale in clinical trials Assesses severity of anxiety symptoms	Time consuming; takes 10–15 minutes to complete (14-item scale) Needs a trained rater
<b>Self rated</b>		
GAD Inventory (GADI) <sup>[52]</sup>	Specific for GAD Assesses symptom profile and severity	Time consuming (18-item scale) Not yet well established
GAD-7 <sup>[53]</sup>	Brief, 7-item scale Specific for GAD Good screening tool	Not yet well established
Penn State Worry Questionnaire (PSWQ) <sup>[54]</sup>	Good measure of pathological worry	Time consuming (16-item scale) Specific for general worry
Intolerance of Uncertainty Scale (IUS) <sup>[45]</sup>	Good measure of a potentially important aetiological factor in GAD	Does not specifically measure severity Has not been assessed as an outcome measure

patients may have a deficiency in the GABA/benzodiazepine system. These three neurotransmitter systems are involved in the body's response to stress (processing fear and anxiety responses).

The involvement of the serotonin 5-HT<sub>1A</sub> receptor subtype has been demonstrated in patients with GAD in clinical trials of buspirone, and may be the result of a neurochemical imbalance involving serotonin. Serotonin is widely distributed throughout the brain, particularly in regions associated with anxiety.<sup>[59]</sup> The selective serotonin reuptake inhibitors (SSRIs) bind to the serotonin transporter to prevent the reuptake of serotonin from the synaptic cleft.

The mode of action of SSRIs in GAD, although not fully elucidated, is thought to be similar to that occurring in panic disorder, in which two opposing theories are currently suggested to explain the role of serotonin dysfunction: (i) serotonin excess, where the action of serotonin is anxiogenic; and (ii) serotonin deficit, where the action of serotonin is anxiolytic.<sup>[60]</sup> In the former, patients have an increased level of serotonin release or have supersensitive post-synaptic receptors. This theory suggests an explanation for the time course of early adverse events associated with the later beneficial action of SSRIs; i.e. the initial exacerbation of symptoms following SSRI administration may well be related to an increased level of serotonin in the synapse acting on

the supersensitive post-synaptic receptors. This is then followed by a gradual downregulation of these receptors.

For the second theory, following treatment with an SSRI, the initial exacerbation of symptoms occurs because of a decrease in serotonin release by an action on the pre-synaptic inhibitory 5-HT<sub>1A</sub> autoreceptor. Antidepressant response occurs following the gradual desensitization of these autoreceptors and the resultant increase in serotonin levels.

The role of the serotonin and noradrenaline systems in both GAD and MDD suggests that there may be a neurobiological link between these two disorders. This may explain the high level of co-morbidity between GAD and MDD, although the two are distinct and separate conditions. Twin and family-based studies have shown a clear genetic influence in GAD, with a heritability of approximately 15–40%.<sup>[61,62]</sup> Recent evidence from a Swedish twin study of 23 280 members of same-sex twin pairs indicates that GAD and MDD are closely related genetically.<sup>[63]</sup>

## 6. Treatment of GAD

### 6.1 Treatment Guidelines

While the focus of acute treatment for GAD must include the improvement of symptoms, the primary goal of long-term clinical management

of patients with GAD is remission, i.e. the complete resolution of both symptoms and functional impairment. Recurrence prevention is another long-term consideration. It is also important to consider patient-specific goals, e.g. the improvement of troubling symptoms, including problems with sleep or concentration, chronic agitation, irritability, recurrent headaches or muscle pain. Factors such as anticipated adverse effects, a history of prior response in the patient or a family member, patient preference and cost should be considered when deciding which treatment to initiate.

Globally, there are several guideline committees that have reported their recommendations and treatment algorithms for patients with GAD, including the World Federation of Societies of Biological Psychiatry,<sup>[64]</sup> the British Association for Psychopharmacology,<sup>[65]</sup> the National Institute for Health and Clinical Excellence,<sup>[66]</sup> and the Canadian Psychiatric Association (CPA) (table IV).<sup>[47]</sup>

In general, the consensus across treatment guidelines is that first-line pharmacotherapy for patients with GAD should consist of an antidepressant, either an SSRI, such as paroxetine and escitalopram, or a selective serotonin norepinephrine inhibitor (SNRI), such as venlafaxine

or duloxetine (in the US). The CPA guidelines are the most recent and these attribute the highest level (level 1: meta-analysis or replicated randomized clinical trial including a placebo arm) to the evidence supporting the use of paroxetine, escitalopram and venlafaxine as first-line treatment options for GAD.<sup>[47]</sup> The CPA consider that clinical trial data are sufficient to suggest that the SSRI sertraline may be an effective first-line treatment option; however, this agent is not currently licensed for GAD.<sup>[47]</sup> The CPA recommends imipramine, buspirone, benzodiazepines and pregabalin as second-line treatment options. Clinical trial evidence for these agents is strong (level 1); however, the CPA considers that the clinical experience with these agents does not support their use as first-line options because of adverse effects (imipramine, benzodiazepines), lack of efficacy (buspirone) or paucity of data (pregabalin).

The available evidence for agents that show efficacy in the treatment of GAD is considered in more detail in sections 6.2–6.7.

## 6.2 Selective Serotonin Reuptake Inhibitors

Paroxetine was the first SSRI to be licensed for the treatment of GAD and is consequently the

**Table IV.** Major organizations that have published guidelines/recommendations for the treatment of generalized anxiety disorder (GAD)

Organization (year of guidelines)	Guideline	First-line pharmacotherapy options for GAD
World Federation of Societies of Biological Psychiatry (2002)	Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders <sup>[64]</sup>	SSRI: paroxetine SNRI: venlafaxine
British Association for Psychopharmacology (2005)	Evidence-based guidelines for the pharmacological treatment of anxiety disorders <sup>[65]</sup>	<i>Acute treatment:</i> SSRIs: paroxetine, escitalopram, sertraline SNRI: venlafaxine Benzodiazepines: alprazolam, diazepam TCA: imipramine Buspirone Antihistamines: hydroxyzine <i>Longer-term treatment:</i> SSRIs: paroxetine, escitalopram
National Institute for Health and Clinical Excellence (2004)	Management of anxiety (panic disorder, with or without agoraphobia, and generalized anxiety disorder) in adults in primary, secondary and community care <sup>[66]</sup>	SSRI: paroxetine SNRI: venlafaxine Benzodiazepines (not to be used beyond 2–4 wk) Antihistamines: hydroxyzine
Canadian Psychiatric Association (2006)	Management of anxiety disorders <sup>[47]</sup>	SSRIs: paroxetine, escitalopram, sertraline SNRI: venlafaxine

SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

most studied in this indication. The efficacy of paroxetine in the treatment of DSM-IV GAD has been established in four randomized, double-blind, placebo-controlled studies (three short-term studies and a study of 6 months' duration) in more than 1800 patients.<sup>[67]</sup> Of the three short-term studies, two found a statistically significant difference between paroxetine and placebo in the primary outcome variable of change in HAM-A total score. In the largest of the short-term studies (566 outpatients with GAD and no other axis I disorder), response ('very much improved' or 'much improved' on the Clinical Global Impression-Improvement [CGI-I]<sup>[68]</sup> score) at 8 weeks was achieved by 62% and 68% of patients in the 20 and 40 mg/day paroxetine groups, respectively, and by 46% in the placebo group.<sup>[69]</sup> Remission rates (defined as a HAM-A score of  $\leq 7$ ) were similar in the three short-term studies for paroxetine (36.0%, 33.0% and 39.2% vs 22.7% [ $p=0.0071$ ], 20.0% [ $p=0.0025$ ] and 32.2% [ $p=0.1646$ ] for placebo, respectively).<sup>[69-71]</sup> Paroxetine was also demonstrated to be effective in the long-term treatment of GAD, with significantly fewer paroxetine-treated patients than placebo-treated patients relapsing during the 6 months of assessment (relapse rates of 10.9% and 39.9%, respectively;  $p<0.001$ ).<sup>[72]</sup> In addition, after 6 months, 73% of paroxetine-treated patients achieved remission (HAM-A  $\leq 7$ ) compared with 34% of placebo-treated patients.

The efficacy of escitalopram (10 mg/day for the first 4 weeks and then flexible doses from 10–20 mg/day;  $n=158$ ) for the treatment of DSM-IV GAD was assessed versus placebo ( $n=157$ ) in an 8-week, double-blind study.<sup>[73]</sup> At week 8, response rates were 68% for escitalopram and 41% for placebo ( $p<0.01$  vs placebo) and remission rates (HAM-A score  $\leq 7$ ) were 36% for escitalopram and 16% for placebo ( $p<0.01$  vs placebo). In a relapse prevention study conducted in 491 patients with GAD, following 6–18 months of treatment, a statistically significantly greater proportion of patients relapsed in the placebo group than in the escitalopram group (56% vs 19%;  $p<0.001$ ).<sup>[74]</sup>

Sertraline (50–200 mg/day) [not currently licensed for GAD] was recently evaluated in a

10-week, double-blind study in 326 outpatients with DSM-IV GAD.<sup>[75]</sup> The reduction in HAM-A total score at endpoint was statistically significant ( $p=0.032$ ). Response rates (defined as a 50% decrease in HAM-A total score at endpoint) were significantly higher ( $p=0.05$ ) for sertraline (59.2%) than placebo (48.2%), and CGI response rates were 64.6% and 54.3%, respectively. Remission rates were not reported in this study. These results support those of a previous 12-week, double-blind, placebo-controlled study of sertraline in 370 patients with DSM-IV GAD.<sup>[76]</sup> In this study, HAM-A response rates were 59% and 29% for sertraline and placebo, respectively, and response rates based on CGI improvement were significantly greater with sertraline than placebo (63% vs 37%;  $p<0.001$ ). Remission (defined as a HAM-A score of  $<7$ ) was also significantly greater with sertraline (31%) than placebo (18%;  $p=0.002$ ). In a small, double-blind, head-to-head study in 55 patients with DSM-IV GAD, sertraline and paroxetine were found to be similarly effective in the short-term (8 weeks) treatment of GAD, with both agents significantly reducing mean HAM-A scores from baseline to endpoint ( $p<0.001$ ).<sup>[77]</sup> There were no differences between the two treatments in terms of response (HAM-A response rates were 68% for paroxetine and 61% for sertraline) or remission (remission rates based on a HAM-A score of  $<7$  were 40% vs 50%, respectively).

### 6.3 Serotonin Noradrenaline Reuptake Inhibitors

In a double-blind study conducted in 251 outpatients with DSM-IV GAD (without MDD), response rates during weeks 6–8 were  $\geq 69\%$  for venlafaxine (75, 150 or 225 mg/day as required;  $n=124$ ) compared with 42–46% for placebo ( $n=127$ ) [ $p<0.001$ ].<sup>[78]</sup> This study did not report remission rates. A small, 8-week, double-blind study in outpatients with DSM-IV GAD reported remission rates (HAM-A total score of  $\leq 7$ ) of 62.5% for venlafaxine ( $n=24$ ) and 9.1% for placebo ( $n=11$ ) [ $p<0.001$ ].<sup>[79]</sup> However, an earlier double-blind study in primary care patients with GAD (with or without MDD) found



remission rates at week 24 for venlafaxine-treated patients to be lower (27.9%) and similar to placebo (18.9%) [ $p=0.11$ ].<sup>[80]</sup>

Duloxetine has recently been approved in the US for the treatment of GAD.<sup>[81]</sup> Its efficacy has been demonstrated in three randomized, placebo-controlled studies (two 10-week flexible-dose studies and one 9-week fixed-dose study) conducted in over 1100 patients with GAD.<sup>[82]</sup> The pooled results from these studies showed that duloxetine significantly improved the HAM-A total score from baseline to endpoint compared with placebo (mean improvement 11.1 vs 8.0;  $p \leq 0.001$ ). Furthermore, in a 10-week active-comparator study in nearly 500 patients with GAD, duloxetine and venlafaxine both produced significantly greater improvements from baseline in HAM-A total score compared with placebo. Compared to placebo, the efficacy of duloxetine and venlafaxine was similar. Discontinuation-emergent adverse events were significantly greater in the venlafaxine group (26.9%;  $p=0.04$ ), but not the duloxetine group (19.4%;  $p=0.448$ ), compared with placebo.<sup>[83]</sup>

#### 6.4 Pregabalin

The antiepileptic pregabalin is approved in Europe for the treatment of GAD. It is not considered a first-line option for GAD and is currently only recommended for patients who do not achieve full remission or who are intolerant to SSRIs or SNRIs.<sup>[84,85]</sup> The efficacy of pregabalin (400 or 600 mg/day) was demonstrated in a 6-week, randomized, double-blind, active-comparator study in outpatients with moderate to severe DSM-IV GAD ( $n=421$ ).<sup>[86]</sup> There were significantly greater improvements in HAM-A total score at endpoint with both pregabalin and venlafaxine (75 mg/day) than with placebo. The proportion of patients with a  $\geq 50\%$  reduction in HAM-A score at endpoint was comparable for treatment with pregabalin 400 mg/day and venlafaxine 75 mg/day. Only pregabalin produced significant improvement, compared with placebo, in all *a priori* and secondary measures. Discontinuation rates were greater for venlafaxine than for pregabalin. These results confirm the findings of four

previous placebo-controlled studies of pregabalin in GAD.<sup>[86]</sup>

#### 6.5 Buspirone

Buspirone is the only azapirone licensed for the treatment of anxiety. Its efficacy in GAD has been studied in several trials: 6 studies versus placebo, 12 studies versus benzodiazepines, and 1 study versus venlafaxine (reviewed by Chessick et al.<sup>[87]</sup>). A Cochrane systematic review of the results from these studies found that the efficacy of buspirone in the treatment of GAD was superior to placebo, but similar to that of the benzodiazepines.<sup>[87]</sup> In addition, in 365 outpatients with GAD without co-morbid MDD, venlafaxine and buspirone were more effective than placebo, and venlafaxine was significantly superior to buspirone on the Hospital Anxiety and Depression (HAD) anxiety subscale.<sup>[88,89]</sup> Limitations of buspirone include its slow onset of action of at least 2 weeks.<sup>[90]</sup> In addition, it has been suggested that the efficacy of azapirones in patients previously treated with benzodiazepines may be limited;<sup>[87]</sup> their efficacy in these patients requires further investigation. Common adverse effects reported with buspirone include headache, nausea, dizziness and gastrointestinal problems.<sup>[91]</sup>

#### 6.6 Imipramine

Imipramine, a TCA, has been shown to be effective in treating the symptoms of anxiety in patients with GAD from the third week of therapy.<sup>[92]</sup> However, the incidence of adverse events was higher in imipramine-treated patients than in patients treated with the benzodiazepine diazepam.

#### 6.7 Benzodiazepines

There is evidence that benzodiazepines are effective in the treatment of GAD, particularly as they offer rapid relief of anxiety symptoms.<sup>[93]</sup> Adverse effects are usually mild and can include sedation and psychomotor impairment.<sup>[93]</sup> However, the long-term use of benzodiazepines in GAD is not recommended because of concerns over dependence;<sup>[65,66]</sup> withdrawal symptoms

have been reported in up to 44% of patients who have received benzodiazepines for as few as 4–6 weeks.<sup>[93]</sup> Furthermore, benzodiazepines are not effective for the symptoms of MDD, which is often co-morbid in patients with GAD, and may also cause MDD in the long term.

### 6.8 Limitations of First-Line Treatment Options

Despite being considered first-line treatment options in GAD, SSRIs and SNRIs have efficacy limitations, including lack of response in many patients (response rates in GAD clinical trials are approximately 60–70%<sup>[69,73,78]</sup>), a 2- to 4-week delay before the onset of symptom relief,<sup>[94]</sup> slow response (it may be 6–12 weeks before significant improvements are achieved),<sup>[47]</sup> lack of full remission, i.e. residual symptoms remain in a high proportion of patients (30–60% of patients do not achieve remission<sup>[69-73,79]</sup>) and risk of relapse (relapse rates in GAD clinical trials are 10–20%<sup>[72,74]</sup>).

In addition, the adverse effects associated with both SSRIs and SNRIs include sexual dysfunction, nausea, gastrointestinal problems, headache and sweating.<sup>[91,95,96]</sup> In addition, for the SSRIs, adverse effects (occurring at varying frequencies) include increased nervousness, vomiting and weight gain (with paroxetine). With SNRIs, additional adverse effects include potential blood pressure changes (with duloxetine and venlafaxine) and insomnia.<sup>[96,97]</sup>

A further issue with SSRIs and SNRIs is that abrupt discontinuation of therapy with these agents may lead to discontinuation or withdrawal symptoms.<sup>[98,99]</sup> Therefore, when stopping treatment, it is important that SSRIs or venlafaxine are gradually tapered over a period of a few weeks in order to diminish the occurrence of discontinuation symptoms.<sup>[100]</sup> Unfortunately, this is not always possible as patients may independently decide to discontinue their treatment.

In October 2004, the US FDA instructed manufacturers of antidepressants (including SSRIs and SNRIs) to amend product labelling to include a black-box warning and expanded warning statements regarding an increased risk of suicidality (suicidal thinking and behaviour) in

paediatric and adolescent patients receiving these agents.<sup>[101]</sup> In May 2007, the FDA proposed updates to the existing black-box warnings for all antidepressants to include information about the increased risks of suicidal thinking and behaviour during initial treatment in patients aged 18–24 years.<sup>[102]</sup> In a recent study of patients without psychosis who were hospitalized because of a suicide attempt, the authors found that fluoxetine was associated with the lowest risk of suicide (relative risk [RR] 0.52; 95% CI 0.30, 0.93), whereas venlafaxine was associated with the highest risk (RR 1.61; 95% CI 1.01, 2.57).<sup>[103]</sup>

## 7. Treatment Response and Remission

For many patients with GAD, initial pharmacotherapy will not lead to remission (defined as a HAM-A total score of  $\leq 7$ ); clinical trial data indicate that following initial therapy with an SSRI, approximately two-thirds (61–67%) of patients will not achieve remission.<sup>[67,69-71]</sup> For venlafaxine, data suggest that approximately 37% of patients with GAD will not achieve remission following 8 weeks of treatment.<sup>[79]</sup>

The definition of refractory or treatment-resistant GAD varies in the literature; however, treatment resistance is typically defined as a poor, partial or lack of response after adequate treatment with at least two antidepressants (from different classes). The following strategies may be considered for patients who do not achieve an appropriate response following first-line treatment: (i) increasing the dose of the SSRI/SNRI; (ii) changing to a different agent of the same class; (iii) switching therapy to an agent of a different class; or (iv) augmentation therapy. Currently, there are limited comparative clinical trial data on augmentation therapy.

## 8. Use of Nonpharmacological Approaches for Patients with GAD

The key symptom of GAD is excessive generalized worrying; thus, it is a condition underpinned by cognitive processes. Therefore, psychotherapeutic approaches to the clinical management of GAD should not be ignored. A complete review of all

available literature on this topic is beyond the scope of this paper; however, a brief overview is given below.

There are a limited number of studies investigating the nonpharmacological treatment of GAD. Most of these focus on cognitive-behavioural therapy (CBT). CBT is a psychotherapeutic approach designed to alter behaviour and cognition that produces and maintains emotional distress.<sup>[104]</sup> CBT for GAD may include psychoeducation, symptom management techniques, cognitive restructuring, worry exposure and self-monitoring. Recently, a Cochrane systematic review of studies assessing psychological therapies in patients with GAD identified 22 studies (1060 subjects) that were eligible for inclusion in meta-analyses.<sup>[105]</sup> The results showed that CBT-based psychological therapies were effective in reducing anxiety over the short term in patients with GAD. The authors concluded that available evidence comparing other psychological therapies with CBT was limited; therefore, conclusions about which psychological therapy is more effective could not be drawn.

Three earlier studies of CBT in GAD have been published.<sup>[106-108]</sup> In all the studies included in these meta-analyses, the symptoms of GAD were reduced. In addition, the effects of treatment continued or improved in the 6-12 months following treatment.<sup>[107,108]</sup>

More recently, a study in 45 patients with GAD demonstrated that at 6-month follow-up, CBT was equally effective as applied relaxation therapy.<sup>[109]</sup> In addition, recent trials in elderly patients with GAD have shown CBT to be effective. For example, in 85 patients with GAD (aged >60 years), response was higher in the CBT group (45%) than in the control group (8%).<sup>[110]</sup> Similarly, two pilot studies in older patients with GAD also demonstrated significant symptom improvements with CBT.<sup>[111]</sup>

The advantages of CBT over pharmacotherapy include patient preference and lack of troubling adverse effects. Unfortunately, CBT is not widely available, requires specialist training and entails weekly contact with the patient for 12-20 weeks, with the latter two factors having implications on both cost and availability.

## 9. Atypical Antipsychotics in GAD

Evidence is emerging that atypical antipsychotics are effective in the treatment of patients with anxiety disorders, either as monotherapy or as augmentation to standard treatment. Aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone have all been studied in patients with anxiety disorders or depression and anxiety.<sup>[112-120]</sup> Specifically in patients with GAD, olanzapine (n=24),<sup>[115]</sup> risperidone (n=40)<sup>[114]</sup> and quetiapine (n=40)<sup>[117]</sup> have been investigated in clinical trials as augmentation therapy and were shown to be effective in this role. Furthermore, quetiapine (n=38)<sup>[116]</sup> and ziprasidone (n=13)<sup>[118]</sup> have been studied as monotherapy for the treatment of patients with GAD. The design and efficacy data from these studies of the atypical antipsychotics in GAD are summarized in table V.<sup>[114-118]</sup> Although the numbers of patients included in these studies are small, the results support the potential role of atypical antipsychotics in the treatment of GAD.

In a randomized, double-blind, placebo-controlled study of olanzapine augmentation of fluoxetine, both the HAM-A and CGI-Severity of Illness response rates were statistically significantly higher than those observed in patients who received placebo, i.e. no augmentation.<sup>[115]</sup> Although no other differences in efficacy parameters were seen between the treatment groups, the authors concluded that olanzapine augmentation in patients with treatment-resistant GAD may have a beneficial anxiolytic effect. However, the increased weight observed with olanzapine in this study may be a potential problem in some patients.

Risperidone augmentation of anxiolytic therapies (including SSRIs, SNRIs, buspirone, benzodiazepines, gabapentin and combinations of these drugs) has also been shown to be statistically significantly more effective than placebo, as assessed by the HAM-A, in patients with symptomatic GAD.<sup>[114]</sup> The aim of this randomized, double-blind, placebo-controlled study was to explore the efficacy and safety of adjunctive risperidone in this patient population. From the positive results shown (effectiveness and good

**Table V.** Efficacy data from studies conducted to date of the atypical antipsychotics in generalized anxiety disorder (GAD)

Study	Drug and dosage (mg/day; mean ± SD unless stated)	Design (duration [wk])	Patient population	No. of patients	Efficacy variable(s)	Main efficacy results
<b>Augmentation therapy studies</b>						
Pollack et al. <sup>[115]</sup>	Olanzapine 8.7 ± 7.1	r, db, pc, augmentation of fluoxetine (6)	Refractory DSM-IV GAD (symptomatic after 6 wk of fluoxetine [20 mg/day])	24	Primary: HAM-A, CGI-S Secondary: HAM-D, ASI, response rates (50% reduction in HAM-A relative to baseline or CGI-S <3)	Significantly more responders in the olanzapine augmentation group than in the placebo group: HAM-A response rate 56% vs 8% (p < 0.05); CGI-S response rate 67% vs 8% (p < 0.05) No other statistically significant differences between groups
Brawman-Mintzer et al. <sup>[114]</sup>	Risperidone 1.1 ± 0.4	r, db, pc (5)	DSM-IV GAD (symptomatic despite prior anxiolytic treatment for ≥4 wk)	40	Primary: HAM-A Secondary: HAM-A subscale scores, CGI-S, HAD, MADRS, SDS, Q-LES-Q, response rates (CGI-I <3)	Risperidone augmentation was significantly more effective than placebo for the primary variable of the mean (SD) HAM-A total change scores from baseline to endpoint: -9.8 ± 5.5 vs -6.2 ± 4.9 (p < 0.05) Risperidone augmentation was significantly more effective than placebo in the change from baseline to endpoint in the mean (SD) HAM-A psychic anxiety factor scores: -6.3 ± 3.7 vs -3.8 ± 4.0 (p < 0.05) No other statistically significant differences between groups at endpoint
Katzman et al. <sup>[117]</sup>	Quetiapine 388 ± 230	op, flexible dosage [25-800 mg/day] (12)	Treatment-resistant or nonremitted DSM-IV GAD	40	Primary: HAM-A Secondary: HAM-A remission (HAM-A total score ≤10 at wk 12), CGI, PSQI, DBAS, SDI (three subscales) and PSWQ	Quetiapine significantly reduced HAM-A total scores from baseline to wk 12 by -21.7 (p < 0.001) HAM-A remission rate at endpoint: 72.5% CGI-S reduction at endpoint: -3.1 (p < 0.001) A statistically significant improvement was seen with all other efficacy variables
<b>Monotherapy studies</b>						
Brawman-Mintzer et al. <sup>[116]</sup>	Quetiapine 125 ± 81.9 Range: 25-300	db, pc (6)	Nondepressed patients with GAD; HAM-A score ≥20	38	Primary: HAM-A Secondary: HAM-A subscale scores, CGI-S, CGI-I, HAD, SDS	No significant difference between treatment groups in the reduction in HAM-A total score at endpoint Observed case analysis of HAM-A total score showed a statistically significant difference at wk 2 and 4 for quetiapine vs placebo: -11.1 vs -5.9 and -13.7 vs -8.6, respectively (p < 0.05 for both) Other measures: quetiapine numerically greater than placebo (not statistically significant)
Snyderman et al. <sup>[118]</sup>	Ziprasidone 20 mg bid	op (7)	Treatment-refractory GAD	13	HAM-A, CGI-S, CGI-I, HAM-D, HAD, SDS, HAM-A response rate (50% reduction in HAM-A relative to baseline), HAM-A remission (HAM-A score <7)	HAM-A scores were 20.31 at baseline and 9.15 at endpoint HAM-A response rate 54%; HAM-A remission rate 38%

ASI = Anxiety Sensitivity Index;<sup>[121]</sup> bid = twice daily; CGI = Clinical Global Impression Scale;<sup>[68]</sup> CGI-I = CGI-Improvement Scale;<sup>[68]</sup> CGI-S = CGI-Severity Scale;<sup>[68]</sup> db = double-blind; DBAS = Dysfunctional Beliefs and Attitudes about Sleep Scale;<sup>[122]</sup> HAD = Hospital Anxiety and Depression Scale;<sup>[68]</sup> HAM-A = Hamilton Anxiety Scale;<sup>[50]</sup> HAM-D = Hamilton Depression Scale;<sup>[123]</sup> MADRS = Montgomery-Asberg Depression Rating Scale;<sup>[124]</sup> op = open-label; pc = placebo-controlled; PSQI = Pittsburgh Sleep Quality Index Scale;<sup>[125]</sup> PSWQ = Penn State Worry Questionnaire;<sup>[54]</sup> Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire;<sup>[126]</sup> r = randomized; SDI = Sheehan Disability Inventory;<sup>[127]</sup> SDS = Sheehan Disability Scale.<sup>[128]</sup>

tolerability of risperidone augmentation), the authors recommend that additional studies be conducted in a larger sample size and for a longer duration.

In an open-label study, Katzman et al.<sup>[117]</sup> demonstrated that augmentation with quetiapine in patients with treatment-resistant or non-remitted GAD (i.e. patients treated for at least 8 weeks with an adequate dose of antidepressant) resulted in statistically significant reductions in HAM-A total scores from baseline to week 12 (-21.7;  $p < 0.001$ ), with a remission rate of 72.5% at week 12.<sup>[117]</sup> Quetiapine was well tolerated in this study; the most common adverse event was sedation, with no incidence of serious adverse events and no clinically significant changes in vital signs.

A small, double-blind, placebo-controlled pilot study has indicated that quetiapine as monotherapy may be effective in the treatment of GAD (table V).<sup>[116]</sup> An open-label pilot study of ziprasidone has also provided initial evidence that this agent may be effective as monotherapy in this indication.<sup>[118]</sup> In addition, the anxiolytic effect of quetiapine monotherapy has been demonstrated in patients with bipolar depression.<sup>[129,130]</sup> It is thought that the anxiolytic effects of the atypical antipsychotics are mediated by 5-HT<sub>1A</sub> receptor agonism.<sup>[131]</sup>

Owing to the small sample sizes employed in the above pilot studies, no firm conclusions regarding tolerability of the atypical antipsychotics in patients with GAD can be made. The tolerability of these agents needs to be further investigated in larger clinical studies in patients with GAD. More extensive safety data exist for these agents in other indications; the atypical antipsychotics are generally well tolerated in patients with schizophrenia and bipolar disorder, although differences exist between agents with regard to their tolerability profiles.<sup>[132]</sup> Weight gain, extrapyramidal symptoms, prolactin elevation, lipid and glucose changes, and somnolence have been reported with atypical antipsychotics in variable degrees.<sup>[132]</sup>

Potentially, there are certain patients with GAD who may derive benefit from treatment with an atypical antipsychotic. For example,

atypical antipsychotics may prove valuable in patients with treatment-refractory GAD or in patients with psychosis or severe agitation. Further research into these patient types is clearly warranted.

## 10. Discussion

GAD was introduced as a residual category in 1980 in DSM-III.<sup>[133]</sup> In the subsequent edition, DSM-III-R,<sup>[5]</sup> the diagnostic criteria for GAD were amended, the most significant revision being that the duration of symptoms should be 6 months. There is significantly less evidence for efficacy of treatment in GAD than in MDD as a result of GAD having been formally defined later.

Current data suggest that the efficacy in GAD of antidepressants (paroxetine,<sup>[67]</sup> escitalopram<sup>[73]</sup> and venlafaxine<sup>[79]</sup>) and anxiolytics such as buspirone,<sup>[87]</sup> is less than optimal, with remission rates of <40% for SSRIs and 63% for venlafaxine. The significance of remission, both hinted at in terms of risk (potential risk of CNS damage caused by stress<sup>[134-137]</sup>) and with the subsequent risk of developing depression<sup>[36]</sup> or drug disorder,<sup>[25]</sup> all point to aiming higher and adding on to current treatment options.

Ultimately, with the goal of eradicating symptoms, the aim is to remove anything that suggests a reduction in quality of life (remission criteria should take aspects of functional impairment into account as well as symptoms<sup>[138]</sup>), as well as reducing CNS risk, and this most likely requires the addition of multiple treatments. Trials assessing augmentation of SSRIs/SNRIs with atypical antipsychotics<sup>[114,115,117]</sup> suggest that this strategy may achieve improved rates of remission.

Understanding both the psychobiology and origins of GAD, including the impact of the intolerance of uncertainty,<sup>[46]</sup> worry<sup>[45]</sup> and anxiety sensitivity,<sup>[139]</sup> as well as a suggestion of the genetics of GAD<sup>[61]</sup> and its potential origins in behavioural inhibition,<sup>[13-15]</sup> must not be overlooked. Therefore, treatment of this complicated and destructive illness needs to be looked at in view of potential phenotypic presentations and the possible variety of treatments that may be

used. Ultimately, the goal is remission and to give people with GAD a level playing field and a full chance of normal health.

## 11. Conclusions

Treatment guidelines recommend that first-line treatment for patients with GAD should consist of an antidepressant, such as an SSRI or an SNRI. The efficacy limitations of these agents, e.g. lack of response in many patients, lack of full remission and risk of relapse, means that there is a need for alternative treatment options. Early clinical studies of the atypical antipsychotics, either as monotherapy or as augmentation to standard treatment for patients with GAD, indicate that they may have a potential role in the treatment of this anxiety disorder and further randomized controlled studies are warranted.

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