Remission of Generalized Anxiety Disorder: A Review of the Paroxetine Clinical Trials Database

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Objective: Paroxetine is a potent selective serotonin reuptake inhibitor with antidepressant and anxiolytic activity that is effective in the treatment of generalized anxiety disorder (GAD), improving the core symptoms of anxiety, worry, and tension. The majority of patients with GAD have chronic symptomatology and significant comorbid mood and anxiety disorders that often require ongoing pharmacotherapy. This article reviews the efficacy and tolerability of paroxetine in the short- and long-term treatment of GAD including remission data.

Data sources: Data from more than 1800 outpatients with DSM-IV–defined GAD were analyzed from 3 short-term (8-week) studies and a longer (6-month) relapse prevention study. These studies were all randomized, double-blind, placebo-controlled trials of paroxetine.

Data synthesis: The results emphasize the benefit of paroxetine treatment in GAD, enabling a substantial proportion of patients to achieve clinical remission and preventing relapse. Long-term treatment with paroxetine also shows good tolerability with no evidence of weight gain.

Conclusion: Given the high comorbidity of psychiatric depression and anxiety, the long-term efficacy and tolerability of paroxetine are important considerations when selecting a first-line therapy for patients with GAD.

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Despite recognition of the existence of persistent generalized anxiety, the diagnostic term *generalized anxiety disorder* (GAD) was not included in classification systems until the publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III).[1] Originally, GAD was a residual diagnosis when no other diagnosis was possible; however, it has now been accepted as a distinct disorder. Revisions to the diagnostic criteria of GAD in subsequent DSM-III-R and DSM-IV[2] classifications have increased the minimum duration of the symptoms of the disorder to 6 months, focused on the worry and psychic symptoms, and introduced the requirement of significant distress or impairment in social and occupational functioning.[3] In addition to chronic anxiety and worry, patients with GAD suffer from somatic anxiety symptoms such as tension, restlessness, fatigue, difficulty in concentrating, irritability, and sleep disturbance.[4]

The lifetime prevalence rate for GAD in the general population has been estimated at 5% using DSM-III/DSM-III-R criteria.[5,6] One-year prevalence in the general population using DSM-IV criteria has recently been determined at 1.5%.[7] Moreover, there is a substantial prevalence of comorbid psychiatric conditions associated with GAD, major depression being one of the most common.[6,7] In the study by Carter et al.,[7] which presented data from a large national representative sample in Germany, 59.1% of all 12-month GAD cases fulfilled criteria for current major depression and 55.9% fulfilled criteria for other current anxiety disorders.

The burden of GAD is increased with comorbidity. As a result, GAD is associated with a significant economic burden owing to decreased work productivity and increased use of health care services. Indeed, GAD ranks third among the anxiety disorders (after posttraumatic stress disorder [PTSD] and panic disorder) in the rate of primary care service usage (physicians', social workers', counselors', and nurse practitioners' time).[8] Up to one third of patients with GAD seek help for their symptoms, most commonly from their primary care physicians.[9] In a World Health Organization study on the prevalence and recognition of anxiety syndromes in 5 European primary care settings,[10] 22.2% of anxiety-related problems reported to the primary care physician were in pa-

tients who had GAD, 6.7% in patients who had subthreshold GAD, 8.8% in patients who had agoraphobia with or without panic disorder, 3.3% in patients who had panic disorder, and 36.8% in patients who had other conditions, mainly depression. The remaining patients did not have any specific condition.

Benzodiazepines have been used for the treatment of GAD and have demonstrated good efficacy when used as short-term therapy. However, long-term therapy has been associated with physical dependence.[11,12] Current pharmacotherapy for the treatment of GAD is centered on tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Tricyclic antidepressants are at least as effective as benzodiazepines and may be superior in long-term therapy.[11,13,14] In one study of patients with DSM-III–defined GAD, the greatest improvement in anxiety ratings during the first 2 weeks of treatment was for patients taking diazepam compared with imipramine and trazodone; however, by the end of the 8-week study, moderate-to-marked improvement was reported in a similar proportion of patients in each treatment group.[11] Selective serotonin reuptake inhibitors have been shown to be effective in the treatment of GAD and other anxiety disorders that may be comorbid with GAD, including panic disorder, social anxiety disorder/phobia, PTSD, and obsessive-compulsive disorder (OCD).[15–19] Controlled clinical trials have demonstrated that the SSRI paroxetine has similar efficacy to TCAs in the treatment of GAD.[20] In addition, both paroxetine and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have proven efficacy in the treatment of patients with DSM-IV–defined GAD.[21–25]

This article reviews the efficacy and tolerability of paroxetine in the short- and long-term treatment of GAD using data from the GAD clinical trials database (Paroxetine Clinical Trials Database, GlaxoSmithKline, Philadelphia, Pa.) and includes new analyses of patients meeting criteria for clinical remission.

PATIENTS AND METHOD

The studies considered in this review include all placebo-controlled short- and long-term studies of immediate-release paroxetine conducted by the manufacturer (GlaxoSmithKline) in adult patients with DSM-IV–defined GAD, including 3 previously published[24–26] and 1 previously presented but unpublished study.[27] Patients with other concurrent Axis I disorders were excluded from all the studies.

Data from a total of 1264 adult patients who participated in 3 short-term (8-week), randomized, double-blind, placebo-controlled studies[24,26,27] were included in the database, as were data from 561 adult patients from a randomized, multicenter, double-blind, placebo-controlled, long-term relapse prevention study.[25] In the short-term studies, patients received fixed or flexible doses of paroxetine (20–50 mg) for 8 weeks. In the 32-week relapse prevention study, patients with a Clinical Global Impressions-Severity of Illness scale (CGI-S) score of ≥ 4 (moderately ill to extremely ill) received single-blind paroxetine (20–50 mg) for 8 weeks. Patients whose CGI-S score had decreased by at least 2 points to a score of ≤ 3 at week 8 were then randomly assigned to double-blind treatment with either paroxetine or placebo for a further 24 weeks. The study was designed to show the benefit of maintenance treatment with paroxetine, hence the selection of responders for the double-blind phase of the trial. Relapse was defined as an increase of at least 2 points on the CGI-S (relative to the patient's score at the end of the single-blind treatment phase) to a score of ≥ 4 or withdrawal resulting from lack of efficacy.

As an initial assessment, the efficacy of paroxetine on the core symptoms of anxiety in each of the studies was reviewed. Mean change from baseline on the Hamilton Rating Scale for Anxiety (HAM-A) total score was the primary efficacy measure in the short-term studies and a secondary efficacy measure in the long-term study. The primary efficacy measure in the long-term study was the proportion of patients relapsing. The HAM-A is an internationally accepted and validated measurement tool for the assessment of efficacy in anxiety disorders. It is a clinician-administered scale and consists of 14 questions, each rated on a 5-point scale from 0 (not present) to 4 (very severe). Other secondary efficacy variables common to all studies were the mean change from baseline for HAM-A items 1 and 2 and the psychic and somatic anxiety subscales. The efficacy of paroxetine was also determined by examining the CGI-S score and the Sheehan Disability Scale (SDS) total score as an indication of improvement in functional status achieved with paroxetine in the treatment of GAD.

Although the efficacy of treatment for GAD has previously been measured by the achievement of a clinical response defined as a 50% symptomatic improvement relative to baseline,[28] there is a growing consensus that the treatment goal should be the ability to achieve remission. The following criteria for remission of GAD have been proposed: HAM-A total score of ≤ 7 and/or SDS score < 5.[28–30] Using each of the above remission criteria, retrospective analyses of each study and pooled data from the clinical trials database were conducted to assess the remission rates achieved in the short- and long-term clinical trials of paroxetine for the treatment of GAD.

Safety was primarily assessed by adverse event monitoring, clinical laboratory evaluations, vital signs, and body weight measurements. The adverse events presented in this review are treatment-emergent adverse events defined as those that had onset dates on the day or after the first dose of double-blind medication through to the end of the double-blind treatment phase. Safety data are presented for the intent-to-treat population, defined as all

Table 1. Demographic Data for the Short- and Long-Term Studies of Paroxetine in the Treatment of Generalized Anxiety Disorder (GAD)

	Short-Term Studies			Long-Term Study Stocchi et al,[25] 2003	
Variable	Rickels et al,[24] 2003	Pollack et al,[26] 2001	Hewett et al,[27] 2001	Single-Blind Phase	Double-Blind Phase
Study duration, wk	8	8	8	8	24
Patients, N[a]	565	324	364	652	561
Paroxetine					
20 mg	188	…	…	…	…
40 mg	197	…	…	…	…
Flexible dose	…	161	181	652	274
Placebo	180	163	183	…	287
Female, %					
Paroxetine					
20 mg	54.5	…	…	…	…
40 mg	56.3	…	…	…	…
Flexible dose	…	61.1	74.3	63.8	62.8
Placebo	56.1	65.9	66.5	…	64.8
Age, mean (SD), y					
Paroxetine					
20 mg	40.2 (12.3)	…	…	…	…
40 mg	40.5 (13.1)	…	…	…	…
Flexible dose	…	39.7 (12.0)	46.5 (14.9)	43.2 (13.1)	43.0 (12.7)
Placebo	40.8 (12.6)	41.2 (12.2)	45.4 (15.0)	…	43.7 (13.1)
Duration of GAD, mean (SD), y					
Paroxetine					
20 mg	8.7 (10.3)	…	…	…	…
40 mg	9.9 (11.9)	…	…	…	…
Flexible dose	…	11.1 (12.3)	7.8 (8.5)	6.5 (9.2)	5.7 (8.6)
Placebo	11.0 (13.4)	10.2 (11.7)	6.8 (7.7)	…	6.0 (8.3)
Baseline HAM-A total score, mean (SE)					
Paroxetine					
20 mg	23.8 (0.3)	…	…	…	…
40 mg	23.3 (0.3)	…	…	…	…
Flexible dose	…	23.9 (0.3)	26.0 (0.4)	26.5 (4.8)	8.2 (0.3)
Placebo	23.9 (0.3)	23.6 (0.3)	25.9 (0.4)	…	7.9 (0.3)

[a]Intent-to-treat safety population.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

patients who were randomized and received study medication and had at least one therapy safety evaluation. A comparison of the safety profile of paroxetine in GAD with its established indications of major depression, OCD, panic disorder, and social anxiety disorder is also presented.

Statistical Analyses

For continuous variables (i.e., HAM-A, CGI-S, SDS), the mean change from baseline was analyzed via analysis of variance. The statistical model utilized endpoint scores and included effects for treatment and investigational site for the acute studies. For the long-term relapse study, the model contained treatment and region (eastern, northern, and southern Europe) effects. There were no significant treatment-by–investigational site or treatment-by-region interactions in the respective models.

Remission rates were calculated using the last-observation-carried-forward (LOCF) method, which allowed inclusion of patients who were withdrawn early. The data from the acute studies were analyzed via logistic regression models with treatment, baseline, and study effects. As before, there were no significant treatment-by-study interactions. For the long-term study, the logistic regression model contained treatment, baseline, and region effects. When the remission data from individual studies were analyzed, study effect was not included in the model. All hypothesis tests were 2-sided. When comparing individual dose groups against placebo, Dunnett's multiple comparison procedure was used to maintain an overall α level of 5%. This procedure led to an adjusted significance level of 2.7% for the individual comparisons between paroxetine dose groups and placebo. Main effects were tested using 2-tailed significance levels of 5%; interactions were tested at the 10% level. The odds ratios of remission rates for paroxetine versus placebo were calculated along with their associated 95% confidence intervals (CIs).

RESULTS

Efficacy

Demographic data for the short- and long-term studies are shown in Table 1. The treatment groups were well matched with respect to age, sex, and duration of GAD.

Table 2. Mean Change From Baseline at Study Endpoint for Efficacy Parameters in Short-Term Studies of Paroxetine in Generalized Anxiety Disorder

	Placebo		Paroxetine		Difference in Mean Change From Baseline	Placebo Versus Paroxetine	
Efficacy Assessment	N	Mean (SE) Change From Baseline	N	Mean (SE) Change From Baseline		CI	p
Rickels et al,[24] 2003							
Total HAM-A score							
20 mg	180	–9.6 (0.7)	188	–12.5 (0.6)	–2.9	–4.6 to –1.2	< .001[a]
40 mg		…	197	–12.2 (0.6)	–2.6	–4.2 to –0.9	< .001[a]
CGI-S scale score							
20 mg	180	–1.1 (0.1)	188	–1.6 (0.1)	–0.5	–0.8 to –0.3	< .001[a]
40 mg		…	197	–1.6 (0.1)	–0.5	–0.8 to –0.2	< .001[a]
SDS total score							
20 mg	155	–3.0 (0.7)	164	–6.1 (0.6)	–3.1	–4.8 to –1.3	< .001[a]
40 mg		…	175	–6.6 (0.6)	–3.6	–5.3 to –1.9	< .001[a]
Pollack et al,[26] 2001							
Total HAM-A score	163	–9.5 (0.7)	161	–11.8 (0.7)	–2.3	–4.0 to –0.6	.008[b]
CGI-S scale score	…	–1.0 (0.1)	…	–1.2 (0.1)	–0.3	–0.5 to 0.0	.042[b]
SDS total score	…	–2.8 (0.6)	…	–5.2 (0.6)	–2.4	–3.9 to –1.0	.001[b]
Hewett et al,[27] 2001							
Total HAM-A score	183	–11.3 (0.8)	181	–12.4 (0.8)	–1.1	–2.8 to –0.5	.171
CGI-S scale score	183	–1.2 (0.1)	181	–1.5 (0.1)	–0.3	–0.5 to 0.0	.027[b]
SDS total score	183	–3.2 (0.8)	181	–5.0 (0.8)	–1.8	–3.5 to –0.1	.037

[a]Significance for $\alpha = .027$ to maintain overall .05 level of significance.
[b]Significance for $\alpha = .05$.
Abbreviations: CI = confidence interval, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, SDS = Sheehan Disability Scale.

Table 3. Remission Rates in Short-Term Studies of Paroxetine in Generalized Anxiety Disorder

	Percent Remitted		Paroxetine Versus Placebo		
Study	Placebo	Paroxetine	Odds Ratio	CI	p
Rickels et al,[24] 2003					
Total HAM-A score ≤ 7	20.0	33.0[a]	1.93	1.26 to 2.94	.0025
SDS score < 5	28.4	38.6[a]	1.76	1.13 to 2.74	.0128
Pollack et al,[26] 2001					
Total HAM-A score ≤ 7	22.7	36.0	1.97	1.20 to 3.23	.0071
SDS score < 5	24.5	34.2	1.92	1.13 to 3.26	.0154
Hewett et al,[27] 2001					
Total HAM-A score ≤ 7	32.2	39.2	1.36	0.88 to 2.09	.1646
SDS score < 5	24.5	44.6	2.70	1.57 to 4.63	.0030

[a]20- and 40-mg groups combined.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, SDS = Sheehan Disability Scale.

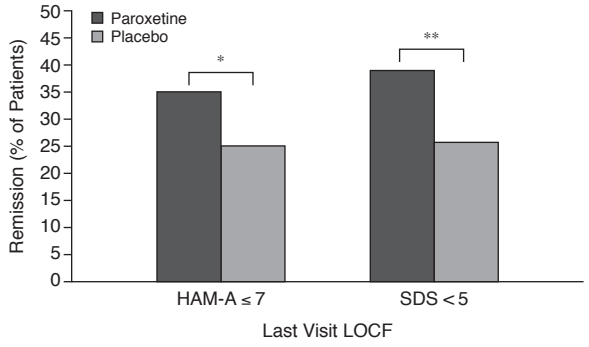
Short-term studies. The results from the 3 short-term studies indicate that paroxetine (20–50 mg/day) is effective in the treatment of GAD (Table 2).[24,26,27] Two of the 3 studies[24,26] demonstrated statistically significant differences from placebo on the primary outcome variable (change in HAM-A total score), while all 3 studies demonstrated significant differences on the CGI-S and the functional disability associated with GAD as measured using the SDS (Table 2).

Remission rates for the short-term studies are presented in Table 3. Utilizing the criterion of a HAM-A total score of ≤ 7 at last study visit yielded significant differences in favor of paroxetine versus placebo in 2 of 3 studies,[24,26] with remission rates on active treatment ranging from 33% to 39% and odds ratios relative to placebo of 1.36 to 1.97. Utilizing the criterion of SDS score < 5 yielded significant differences in favor of paroxetine in all 3 studies, with remission rates of 34% to 45% and odds ratios of 1.76 to 2.70. Combined results for the short-term studies are depicted in Figure 1. Utilizing both criteria yielded significant differences in favor of paroxetine over placebo, with odds ratios ranging from 1.7 to 2.0.

Long-term study. Significantly fewer patients randomly assigned to continue on paroxetine relapsed during the 24-week double-blind phase compared with those switched to placebo (10.9% vs. 39.9%, treatment difference = –28.9%, 95% CI = –35.7 to –22.1, p < .001). Patients receiving placebo were almost 5 times more likely to relapse than those receiving paroxetine (estimated hazard ratio = 0.213, 95% CI = 0.1 to 0.3, p < .001).[25]

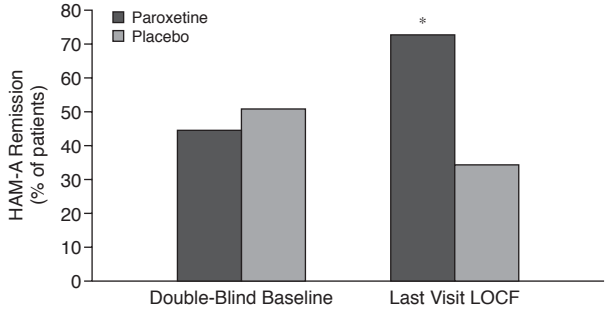
At the beginning of the double-blind maintenance phase, following 8 weeks of single-blind paroxetine treatment, 48% of patients had achieved the HAM-A remission criterion (45% of those patients randomly assigned

Figure 1. Generalized Anxiety Disorder Short-Term Studies: Remission Rates Achieved Using HAM-A and SDS Criteria (LOCF)[a,b]



[a]Data from Rickels et al.,[24] Hewett et al.,[26] and Pollack et al.[27]
[b]Not all patients eligible for analysis had data. Total Ns for last visit LOCF were paroxetine, 735 and placebo, 529; Ns for HAM-A analysis were paroxetine, 727 and placebo, 526; and Ns for SDS analysis were paroxetine, 630 and placebo, 449.
*Odds ratio = 1.7, 95% CI = 1.3 to 2.2, p < .001.
**Odds ratio = 2.0, 95% CI = 1.5 to 2.7, p < .001.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, SDS = Sheehan Disability Scale.

Figure 2. Generalized Anxiety Disorder Long-Term Study: Remission Rates According to HAM-A Score ≤ 7 Criterion at Double-Blind Baseline and Last Visit (LOCF)[a,b]



[a]Data from Stocchi et al.[25]
[b]At double-blind baseline, all study patients were taking paroxetine for 8 weeks. Not all patients eligible for analysis had data. Total Ns for double-blind baseline and last visit LOCF were paroxetine, 274 and placebo, 287; Ns for HAM-A analysis were paroxetine, 274 and placebo, 285.
*Odds ratio = 6.4, 95% CI = 4.3 to 9.4, p < .001 vs. placebo.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward.

to receive subsequent paroxetine continuation and 51% of those randomly assigned to receive placebo substitution). At the double-blind maintenance phase LOCF endpoint, the HAM-A remission rate in those patients maintained on paroxetine treatment for up to 6 months had increased to 73%, whereas it had decreased to 34% in those switched to placebo (odds ratio = 6.4, 95% CI = 4.3 to 9.4, p < .001, Figure 2).

Table 4. Treatment-Emergent Adverse Events Reported by More Than 10% of Patients in Short-Term Studies and by Patients in a Long-Term Study of Paroxetine in Generalized Anxiety Disorder[a]

Adverse Event	Short-Term Studies (pooled data) (N = 735)[c]	Long-Term Study[b] (double-blind phase) (N = 274)[c]
Abnormal ejaculation[d]	24.7	3.9
Nausea	20.1	1.5
Headache	16.9	6.9
Somnolence	15.4	0.4
Asthenia	14.3	1.5
Dry mouth	10.9	1.8
Insomnia	10.7	4.0
Constipation	10.5	1.5

[a]Data from Rickels et al.,[24] Stocchi et al.,[25] Pollack et al.,[26] and Hewett et al.[27]
[b]Adverse events experienced during the relapse phase of the study.
[c]Number of patients taking paroxetine.
[d]Percentage corrected for sex.

The remission rate according to the SDS score of < 5 criterion was 26% prior to maintenance treatment (25% and 27% randomized to subsequent paroxetine or placebo, respectively), which increased to 58% of patients maintained on paroxetine treatment versus 31% of patients switched to placebo (odds ratio = 3.5, 95% CI = 2.2 to 5.4, p < .001).

Tolerability

Paroxetine was well tolerated in the short-term studies. At endpoint, the mean dose of paroxetine for the pooled short-term studies was 24.3 mg/day. The most frequent treatment-emergent adverse events for paroxetine in the pooled short-term studies were abnormal ejaculation and nausea (Table 4). These adverse events were mostly mild to moderate in intensity and led to few patients stopping treatment (discontinuation rates of 2.1% and 2.8% due to abnormal ejaculation and nausea, respectively). The treatment-emergent adverse events for paroxetine in GAD were consistent with those previously observed with paroxetine when used for other indications (Paroxetine Clinical Trials Database, GlaxoSmithKline, data on file; Table 5).

Similarly, in the long-term study, paroxetine was well tolerated with no unexpected adverse events reported (Table 4). The mean dose for paroxetine at endpoint was 28.4 mg/day for the double-blind phase. As expected, the incidence of treatment-emergent adverse events during the double-blind treatment phase was low, as patients may have become tolerant to adverse events seen earlier when receiving single-blind paroxetine, and patients with disturbing adverse events were unlikely to enter the relapse phase. The most frequent treatment-emergent adverse event during the double-blind phase for patients taking paroxetine was headache (6.9% vs. 5.2% for placebo). All other treatment-emergent adverse events occurred at a frequency of < 5%.

Table 5. Treatment-Emergent Adverse Events Reported by More Than 10% of Patients in Short-Term Studies (pooled data) of Paroxetine in GAD, Depression, OCD, Panic Disorder, and Social Anxiety Disorder[a]

Adverse Event	GAD (N = 735)[b]	Major Depression (N = 6145)[b]	OCD (N = 452)[b]	Panic Disorder (N = 469)[b]	Social Anxiety Disorder (N = 522)[b]
Abnormal ejaculation[c]	24.7	10.5	23.3	20.5	32.4
Nausea	20.1	22.0	23.2	22.8	24.5
Headache	16.9	19.5	25.3	25.4	22.2
Somnolence	15.4	15.9	24.4	18.8	23.4
Asthenia	14.3	11.9	21.8	13.6	22.2
Dry mouth	10.9	14.1	18.1	18.1	9.2
Insomnia	10.7	13.1	23.8	17.9	23.2
Constipation	10.5	9.4	15.7	7.9	6.5
Dizziness	6.1	10.2	12.4	14.1	11.7
Sweating	6.3	10.6	8.9	14.3	9.6
Diarrhea	9.1	9.2	10.3	11.7	9.4

[a]Data on file, Paroxetine Clinical Trials Database, GlaxoSmithKline.
[b]Number of patients taking paroxetine.
[c]Percentage corrected for sex.
Abbreviations: GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder.

The incidence of weight gain reported as a treatment-emergent adverse event during the 24-week double-blind phase was low, occurring in 5 (1.8%) of 274 paroxetine-treated patients and 1 (0.3%) of 287 placebo patients. At study end, there was no clinically significant difference between the treatment groups in the proportion of patients experiencing a ≥ 7% increase in weight during the study (9.1% paroxetine vs. 5.9% placebo). The mean change in weight at endpoint in the patients who continued on paroxetine was 1.3 kg (SD = 4.4) compared with 0.4 kg (SD = 3.3) in those patients switched to placebo.

DISCUSSION

This is the first publication to assess the efficacy of paroxetine in patients with GAD both by examination of change in commonly employed efficacy scales as well as application of remission criteria across short- and long-term studies. Results from these studies demonstrate that paroxetine is effective in both the short- and long-term treatment of GAD. Statistically significant improvement in favor of paroxetine over placebo was seen on the HAM-A in 2 of the 3 short-term studies and in the long-term study, supporting results observed earlier by Rocca et al.[20] CGI-S and SDS total scores were statistically significantly improved with paroxetine over placebo in all studies, demonstrating substantial improvement in family, social, and work functionality, and results from the long-term study in more than 500 patients with DSM-IV–defined GAD demonstrated the efficacy of paroxetine in relapse prevention.[25]

The present retrospective analysis also demonstrated that a large proportion of patients who were treated with paroxetine achieved remission of their symptoms. Compared with placebo, a statistically significantly higher proportion of GAD patients treated with paroxetine for 8 weeks achieved remission (35% vs. 25%). Furthermore, the percent of patients experiencing remission after short-term treatment with paroxetine markedly improved with maintenance treatment from 45% to 73%. This remission rate was achieved in spite of a treatment duration that was less than the minimum 12 months recommended by at least one treatment guideline.[31]

Achieving remission of GAD is an extremely important treatment goal. Although 50% to 60% of patients with anxiety and depression are reported to respond to initial treatment, only one third go on to achieve remission or full recovery.[32] The presence of subsyndromal or residual symptoms in depression and anxiety disorders, even in patients who respond to treatment, results in higher relapse rates, impaired functioning, and increased utilization of health care resources.[33] Furthermore, management of GAD is complicated by comorbidity with other psychiatric disorders, particularly depression. Paroxetine has demonstrated efficacy in depression and in several anxiety disorders, including panic disorder, OCD, social anxiety disorder, and PTSD, making it a favorable option due not only to its ability to elicit remission of core symptoms of GAD but also to its ability to treat the disorders that are commonly comorbid with it.[18,34–37]

Paroxetine was well tolerated, with no unexpected treatment-emergent adverse events reported in any of the 4 studies. The incidence of treatment-emergent adverse events was comparable to those observed for paroxetine in its use for other psychiatric conditions. In a study comparing paroxetine to the TCA imipramine and the benzodiazepine 2'-chlordesmethyldiazepam,[20] paroxetine was better tolerated than imipramine and caused less drowsiness than 2'-chlordesmethyldiazepam. These side effects of imipramine and 2'-chlordesmethyldiazepam have been previously reported.[11] Although there has been no direct comparison of paroxetine and the SNRI venlafaxine, the

frequency of adverse events in long-term studies appears similar.[21,38] Interestingly, long-term tolerability data for paroxetine showed no evidence of significant weight gain associated with paroxetine.

Antidepressants, such as paroxetine or venlafaxine, represent a reasonable approach to attaining long-term benefit for patients with GAD.[39] The International Consensus Group on Anxiety and Depression recommends an SSRI, SNRI, or nonsedating TCA as first-line pharmacotherapy for the treatment of GAD.[40] For patients with a comorbid psychiatric disorder and a long-term condition such as GAD, an SSRI or SNRI is indicated.[40] Clearly, remission rates improve with longer treatment with paroxetine, making it an attractive option for first-line therapy for patients with GAD.

Drug names: diazepam (Valium and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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