Paroxetine Treatment of Generalized Anxiety Disorder

By David V. Sheehan, MD, MBA, and C. Gloria Mao, PharmD

ABSTRACT ~ Generalized anxiety disorder (GAD) is a prevalent and disabling anxiety dis-order, conservatively believed to affect at least 5% of the general population. Cardinal symptoms of GAD include chronic and uncontrollable worry, anxiety, and tension, which result in difficulty fulfilling social, professional, and family roles. Treatment options include benzodiazepines, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR. Because of the high comorbidity of GAD with other psychiatric disorders, pharmacologic therapy should possess both anxiolytic and antidepressive properties for best outcomes. The SSRIs are a good treatment option, and paroxetine is the best studied SSRI for GAD and the only SSRI to date approved by the US Food and Drug Administration for this indication. Results of randomized, controlled studies of paroxetine have demonstrated its efficacy in the short-term treatment of GAD, in achieving and sustaining full remission, and in preventing relapse. This article provides an overview of GAD and a discussion of studies of paroxetine treatment in this anxiety disorder. Psychopharmacology Bulletin. 2003;37(Suppl 1):64–75.

INTRODUCTION

Generalized anxiety disorder (GAD) is a widespread and highly disabling disorder with a lifetime prevalence of 5.1% in the general population.[1] Estimates of an 8% current prevalence of GAD in the primary care setting are higher than in the general population, suggesting that patients with GAD are high utilizers of primary care resources.[2] Generalized anxiety disorder is underdiagnosed and commonly overlooked in the presence of comorbid conditions.[3] The appropriate treatment of GAD is a prerequisite for interrupting the cycle of chronic illness, psychiatric comorbidity, physical complaints, functional disability, and unnecessary utilization of healthcare resources.[4-8]

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Optimal treatment of GAD involves education about the disorder, psychotherapy, and pharmacologic management. Patients and their families should be educated in order to better understand the etiology, symptoms, natural course, associated comorbidities, and control of GAD. However, education and psychotherapy alone are rarely adequate to achieve and sustain full remission, which should be the treatment goal for all patients. Treatment with effective agents, such as imipramine, the selective serotonin reuptake inhibitors (SSRIs), or venlafaxine XR are necessary for attaining full remission and resumption of normal social, occupational, educational, and family roles. Failure to appropriately treat GAD may result in the development of depression or panic disorder along with other adverse health behaviors (eg, alcohol/substance use). Timely diagnosis and treatment of GAD have a significant impact on outcomes.

OVERVIEW OF GENERALIZED ANXIETY DISORDER

GAD is characterized by the hallmark features of chronic, uncontrollable, and excessive worry, anxiety, and tension. Patients ruminate excessively and often describe themselves as "worry worts." The anxiety of GAD manifests as edginess, insomnia, and fatigue, as well as poor concentration and coping strategies, distorted cognitive processes, and unrealistic assessments of situations, which compound the disability associated with GAD.[9-11] Muscle tension is a predominant somatic symptom of GAD in addition to palpitations and gastrointestinal distress.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (*DSM-IV*) requires that a diagnosis of GAD includes significantly impaired functioning that persists for at least 6 months,[9] although many clinical observations suggest that GAD also may be a chronic disorder consisting of intermittent exacerbations precipitated by stressful life events.[12,13] The onset of GAD symptoms is gradual, and patients eventually experience difficulty achieving their full potential at work, in school, at home, and in social situations. The age of onset of GAD generally occurs between the years of 13 and 30.[14] Women are more likely to have GAD than men.[1]

GAD typically occurs in association with a range of comorbid psychiatric disorders in the vast majority (90%) of patients. Most commonly, patients have comorbid major depressive disorder, which occurs in 62% of patients diagnosed with GAD. Of these, 38% report that they experienced an episode of depression within the past 30 days.[15] Other comorbid conditions frequently occurring in patients with GAD are alcohol abuse, social anxiety disorder, and panic disorder (Figure 1). Some researchers believe the high rates of comorbidity in GAD can be attributed to common neurobiological pathways, causing an overlap in symptoms and response to treatment.

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GAD is associated with substantial rates of impairment and healthcare consumption. Findings of the National Comorbidity Survey demonstrate that 11% of the survey participants with GAD reported 6 or more days of impaired functioning at work during the past month, and 24% endorsed high levels of impaired social role functioning.[15,16] The extent of work and social impairment attributed to pure GAD in this survey is comparable to rates seen with major depressive disorder, and the highest rates of impairment occur in persons with both GAD and major depressive disorder.[16] Aside from lost productivity, individuals with GAD also are extensive utilizers of healthcare resources. As many as 66% seek professional help from either a general medical practitioner or mental health specialist, and 44% receive maintenance medications to control their symptoms. Taken in the aggregate, the lost productivity and healthcare-seeking behavior of persons with GAD place an enormous economic burden on society.[15]

The annual cost of anxiety disorders in the United States was estimated to be $42.3 billion in 1990.[17] Present-day estimates would surely be much higher. The majority of the cost associated with anxiety disorders is attributed to nonpsychiatric medical care, which involves expenses incurred with misdiagnosis or mistreatment of anxiety disorders, totalling nearly $23 billion.[17] Only by properly diagnosing and treating GAD and educating patients and their families will these excess costs be brought under control.

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FIGURE 1

**PSYCHIATRIC COMORBIDITY ASSOCIATED WITH
GENERALIZED ANXIETY DISORDER**
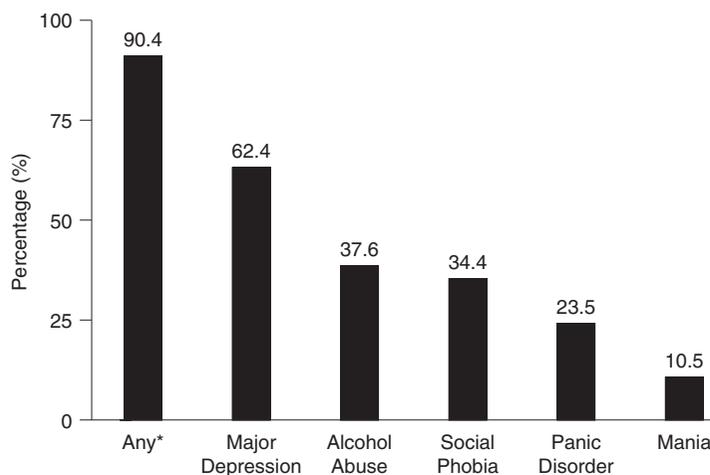
*Any is defined as mania, major depression, dysthymia, panic disorder, agoraphobia, simple phobia, social phobia, alcohol abuse, and drug abuse.[1]

TREATMENT OF GENERALIZED ANXIETY DISORDER

Traditionally, patients with GAD were treated with benzodiazepines, which are useful in the short term for rapid relief of tension and anxiety symptoms.[18,19] However, rebound anxiety and withdrawal symptoms may arise while tapering patients off of benzodiazepines. In addition, benzodiazepines are not effective treatments for depression, which is the most common comorbidity in GAD, limiting their therapeutic value in GAD. The tricyclic antidepressants (TCAs) also are treatment options for GAD. Randomized, controlled trials have shown that although the TCAs are effective treatment of GAD, they are associated with a heavy burden of side effects that hinders medication adherence in the short and long term for many patients.[20] The SSRIs paroxetine,[21-23] sertraline,[24] and citalopram,[25] and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR,[26-28] have been studied in the treatment of GAD. However, the publications from the paroxetine and venlafaxine XR databases are much more extensive in scope, depth, and quality of analysis than reports of citalopram (a retrospective case series) or sertraline (small sample size; N=22 patients).

Psychotherapeutic interventions also are useful, often as an adjunctive treatment to psychopharmacologic therapy. Cognitive behavior therapy has demonstrated some value in promoting recovery,[29-31] along with the development of better coping skills and lifestyle modifications. Relaxation techniques and management of insomnia may benefit some individuals. Activities and therapies such as these often enable patients to participate in normal daily activities and roles. Currently, psychotherapy is rarely used, which represents a gap in therapy.[12]

PAROXETINE TREATMENT OF GENERALIZED ANXIETY DISORDER

Paroxetine, which is the best studied SSRI for use in the treatment of GAD, received Food and Drug Administration approval for this indication in the spring of 2001. The clinical trials database for paroxetine is large, and published studies for GAD consist of a head-to-head comparison with imipramine and a benzodiazepine,[32] a fixed-dose, placebo-controlled trial,[21] a flexible-dose, placebo-controlled trial,[22] and a long-term, placebo-controlled, relapse-prevention trial.[23] These studies helped contribute to progress in the field of anxiety disorders by demonstrating treatment efficacy using rigorous criteria for response and remission of GAD.

Comparative Tricyclic Antidepressant and Benzodiazepine Trial

An early comparative trial of paroxetine, imipramine, and 2'-chlordesmethyldiazepam (a benzodiazepine not available in the United States)[32] demonstrated both efficacy and tolerability of paroxetine

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and prompted further investigation of paroxetine treatment of GAD. Eligible patients fulfilled *DSM-IV* criteria for GAD with scores of 18 or higher on the Hamilton Anxiety Rating Scale (HAM-A), 38 or higher on the State Trait Anxiety Inventory (STAIX-2), and scores of 14 or less on the Hamilton Rating Scale for Depression (HAM-D). Patients with significant comorbid Axis 1 disorders were excluded. Eighty-one patients were randomized to receive an 8-week course of paroxetine 20 mg daily, imipramine 50 to 100 mg daily, or 2'-chlordesmethyldiazepam 3 to 6 mg daily. Use of concomitant psychoactive drugs was not permitted, and efficacy was measured by HAM-A, HAM-D, Clinical Global Impression of improvement (CGI-I) and severity (CGI-S), and the COVI Anxiety Rating Scale (CARS).

Not unexpectedly, the greatest improvement in HAM-A at 2 weeks was in patients receiving 2'-chlordesmethyldiazepam. However, by week 4 and onward, both the paroxetine and imipramine groups demonstrated greater improvement than benzodiazepine-treated patients. At week 4, this difference was statistically significant between paroxetine and benzodiazepine patients, whereas only at study termination was imipramine statistically superior to the benzodiazepine. By week 4, paroxetine and imipramine were more effective than 2'-chlordesmethyldiazepam in treating psychic symptoms of GAD (Figure 2) and had

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FIGURE 2

**CLINICAL IMPROVEMENT AFTER 2, 4, AND 8 WEEKS
OF TREATMENT FOR GAD**
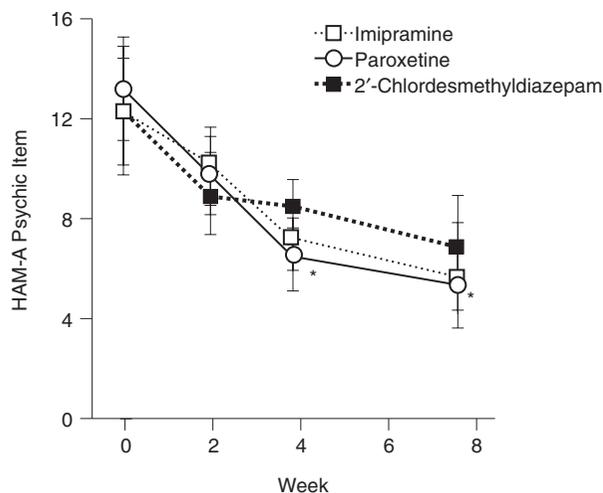
*P<.05
HAM-A=Hamilton Rating Scale for Anxiety
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similar efficacy for somatic symptoms. Moderate to marked improvement was seen in 67% of imipramine patients, 68% of paroxetine patients, and 60% of benzodiazepine patients for CGI-S scale scores. The CARS and CGI-I scores demonstrated similar results, and all 3 groups had comparable effects on the HAM-D score. With these promising results, further trials were conducted to determine the role of paroxetine in GAD management.

Fixed-Dose Study

Data published by Rickels and associates[33] demonstrated efficacy of an 8-week course of paroxetine 20 mg and 40 mg in the treatment of GAD. Patients with a DSM-IV diagnosis of GAD and score of 20 or greater on the HAM-A without a comorbid Axis 1 disorder were eligible, but patients with depression [Montgomery Asberg Depression Rating Scale (MADRS) score of ≥18] were excluded. Eligible patients underwent a 1-week, single-blind, placebo run-in phase to eliminate early placebo responders and were randomized to receive placebo (N=180), paroxetine 20 mg daily (N=189), or paroxetine 40 mg daily (N=197). Dosing began at 10 mg and was titrated upward weekly by increments of 10 mg to reach target doses. Efficacy was measured by the HAM-A, CGI-I, CGI-S, and Sheehan Disability Scale (SDS). By week 6, the paroxetine group was statistically superior to the placebo group on the HAM-A total score ($P<.001$). The paroxetine-treated patients also demonstrated improvement on tension and anxiety items of the HAM-A ($P<.001$ for both versus placebo). In addition, significantly more patients receiving paroxetine achieved a CGI-I score of 1 or 2 by week 6 ($P<.01$ for 20 mg, $P<.001$ for 40 mg). Patient self-ratings of improvement in disability as measured by SDS yielded results that were similar to the clinician assessments.

Flexible-Dose Study

A similar trial examined the use of paroxetine with a flexible-dosing regimen.[22] Patients who fulfilled *DSM-IV* criteria for GAD with a score of 20 or higher on HAM-A without a comorbid Axis 1 disorder and scored lower than 17 on MADRS were enrolled. A 1-week, single-blind, placebo run-in phase was conducted followed by an 8-week randomized, double-blind study period during which the 324 eligible patients received 10 mg daily of paroxetine or placebo the first week and forced titration to 20 mg daily the second week. After week 2, doses were increased by 10 mg daily every 7 days, as necessary, up to a maximum of 50 mg daily. Efficacy was assessed through HAM-A, CGI-I, CGI-S, SDS, and anxiety subscale score of the Hospital Anxiety and Depression Scale (HAD).

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Response was defined as a score of 1 or 2 on the CGI-I, and 72.4% of the 161 patients receiving paroxetine were responders at study end point compared with 55.6% of the 163 patients receiving placebo (*P*=.005). Remission, which was defined as a HAM-A total score of 7 or less, was achieved by 42.5% of patients in the paroxetine group and 26.3% of patients in the placebo group (*P*=.006). Patients receiving paroxetine had statistically greater reductions in HAM-A total and anxious mood scores at weeks 6 (*P*<.05) and at week 1 (*P*<.05), respectively, compared with patients receiving placebo (Figure 3). Paroxetine was statistically superior to placebo on the psychic anxiety subscale score of the HAM-A (*P*=.002)
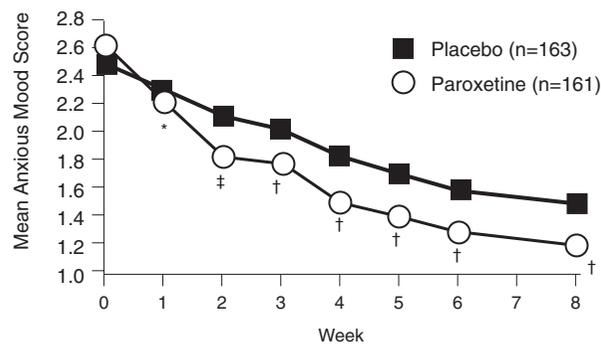

FIGURE 3

MEAN TOTAL AND ANXIOUS MOOD ITEM SCORES ON HAM-A

A. Total
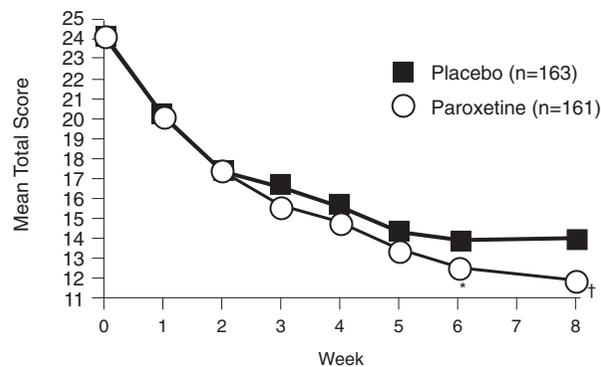
B. Anxious Mood

Presented as adjusted least square means. Asterisks represent pairwise comparisons, paroxetine versus placebo, for difference in mean change from baseline.
*P<.05, †P<.01, ‡P<.001.
HAM-A=Hamilton Rating Scale for Anxiety.

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and in the change in the CGI severity (CGI-S) rating by study termination. Changes in CGI-S ratings were significant by study termination. At baseline, all patients were considered moderately ill and by study completion, 40% of paroxetine patients reported being "not ill" or "borderline ill" compared with 27% of placebo patients (*P*<.01). Patient assessments by the HAD and SDS scales were comparable to results seen with clinician scoring and patients reported significant improvement as early as week 3 by the HAD scale.

Relapse Prevention Study

Findings from a trial conducted by Stocchi and associates[23] established paroxetine efficacy in the short-term treatment of GAD and relapse prevention. Patients with GAD who scored 20 or higher on HAM-A with a score of 2 or higher for anxiety and tension items, but with a score less than 18 on MADRS were included in the trial. Patients with other

FIGURE 4

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PROPORTION OF PATIENTS EXPERIENCING REMISSION FROM SYMPTOMS OF GENERALIZED ANXIETY DISORDER
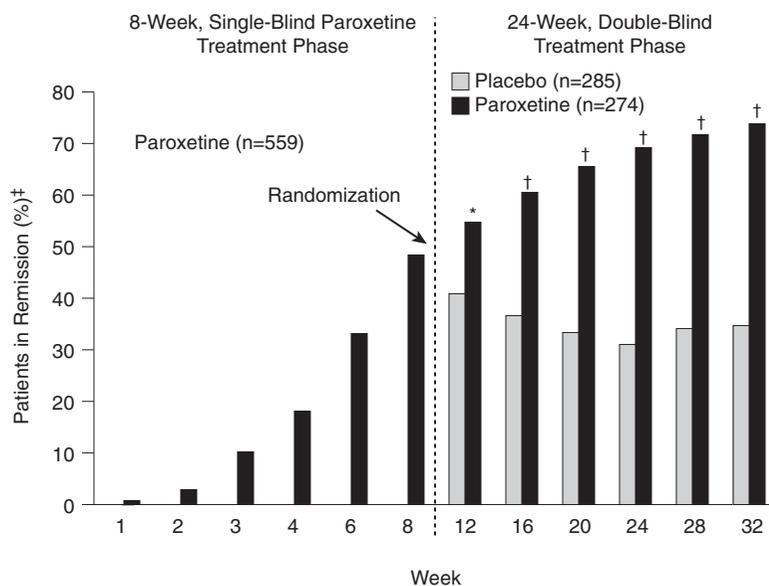
N=559 is the number of patients in the single-blind treatment phase who went through to the double-blind treatment phase. Of the ITT population of 650 patients in the single-blind treatment phase, 276 (42.5%) achieved remission by week 8.
*P=<.01, †P<.001.
HAM-A=Hamilton Rating Scale for Anxiety; ‡=not adjusted for baseline HAM-A; ITT=intent-to-treat.
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Axis 1 disorders were excluded with the same structured diagnostic interview used in all the paroxetine multi-centered, double-blind, placebo-controlled GAD trials. Qualifying patients underwent a 1-week, single-blind, placebo run-in phase to eliminate early placebo responders. Patients still considered moderately to extremely ill as measured by the CGI-S scale (score of 4 or higher) then entered an 8-week single-blind treatment phase and received paroxetine 20 mg daily for 2 weeks with titration up to 50 mg daily as necessary. Those patients whose CGI-S score decreased by 2 points or was 3 or below, after the 8-week, flexible-dose treatment period were considered responders and were then entered into the 24-week double-blind study period. During the double-blind phase, patients were randomized to either remain on same-dose paroxetine or were tapered to receive placebo. The primary end point was the relapse rate during the double-blind phase, with relapse defined as an increase of 2 or more points on the CGI-S. Secondary measures of efficacy included time to relapse and mean change from baseline for the HAM-A, SDS, and MADRS scales.
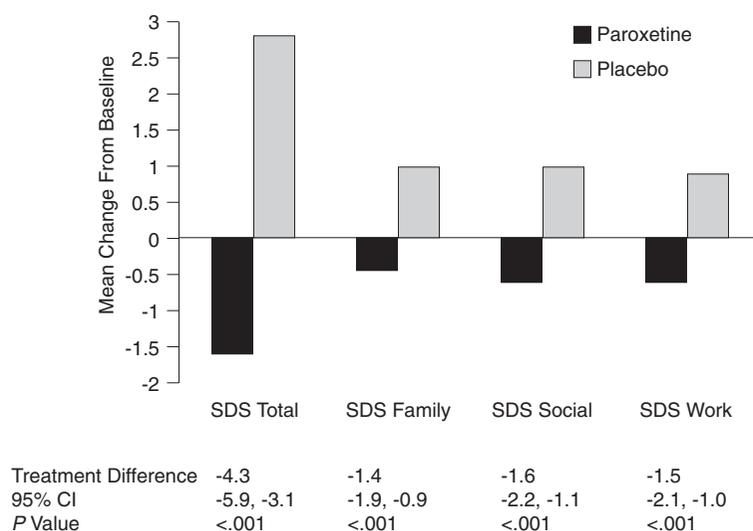
An intent-to-treat last observation carried forward (ITT/LOCF) analysis revealed relapse rates of 10.7% for the paroxetine group compared with

FIGURE 5

MEAN CHANGE ON THE SDS TOTAL SCORE AND FAMILY, SOCIAL, AND WORK ITEM SCORES RELATIVE TO BASELINE DURING TREATMENT OF GAD WITH PAROXETINE VS PLACEBO

	SDS Total	SDS Family	SDS Social	SDS Work
Treatment Difference	-4.3	-1.4	-1.6	-1.5
95% CI	-5.9, -3.1	-1.9, -0.9	-2.2, -1.1	-2.1, -1.0
P Value	<.001	<.001	<.001	<.001

Double-blind treatment of generalized anxiety disorder with paroxetine vs placebo.
SDS=Sheehan Disability Scale; GAD=generalized anxiety disorder.
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41.2% for placebo-treated patients (*P*<.001). Patients who were switched from paroxetine to placebo had an odds ratio of 4.7 of relapsing compared with those who remained on paroxetine (*P*<.001). Maintaining paroxetine therapy demonstrated even higher remission rates over the 8 months of treatment. Remission, which was defined as an end point HAM-A total score of 7 or less, was achieved at the end of the 8-week single-blind treatment period by 42.5% of patients. After 6 months of double-blind treatment, remission rates increased to 73% among patients receiving paroxetine whereas patients in the placebo group deteriorated (*P*<.001) (Figure 4). Paroxetine was statistically superior to placebo in lowering the HAM-A total score by week 4 of the double-blind treatment phase (*P*<.001).

Anxiety, tension, and somatic subscale scores from HAM-A improved with paroxetine treatment by the end of the single-blind phase and were maintained through the remainder of the study in patients randomized to paroxetine. The psychic subscale score of HAM-A continued to improve during the double-blind phase and was statistically lower on paroxetine than on placebo by study completion (*P*<.001). Scores from the SDS (Figure 5) and MADRS scales also demonstrated greater improvement by study completion in patients receiving paroxetine (*P*<.001 for both). Approximately 52% of patients experienced an adverse event during the single-blind phase, most commonly including nausea, headache, and insomnia. However, during the double-blind phase, adverse event reporting was nearly the same between paroxetine and placebo groups (35.0% to 34.8%, respectively).

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CONCLUSION

During recent years, the description and treatment of GAD have undergone significant changes. Formerly believed to be a prodrome, residual, or severity marker of major depression that could be adequately treated with benzodiazepines or buspirone,[16,34] GAD is now accepted as a psychiatric disorder in its own right. Better diagnostic criteria have been developed to identify GAD in order to recognize and treat patients with this prevalent, chronic, and costly condition. However, GAD remains undertreated, possibly because of patient presentation with other comorbid disorders.

There has been a paradigm shift in the treatment of GAD. Benzodiazepines are now generally considered acceptable only for patients requiring rapid, short-term relief of anxiety symptoms. The SSRIs and venlafaxine XR are better choices for first-line treatment. Paroxetine, the most widely studied SSRI for GAD, is effective for both short-term treatment and long-term prevention of relapse. The findings of the long-term study of paroxetine in GAD[23] provide a compelling rationale for

continued psychopharmacologic treatment with full therapeutic doses. Moreover, the use of rigorous remission criteria (ie, HAM-A ≤7) in the paroxetine studies reinforces the importance of treating to full recovery, not just moderate symptom improvement. Full remission should be considered the new gold standard therapeutic goal for the treatment of GAD that will provide maximum benefit for patients and their families. ❧

DISCLOSURE

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