# Remission Rates in Patients With Anxiety Disorders Treated With Paroxetine

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***Background:*** Approximately 50% to 60% of patients with depression and/or anxiety respond to treatment, but only a minority achieve remission. The continued presence of subsyndromal symptoms in treated depressed (and probably anxious) patients leads to higher relapse rates and increased utilization of health care resources. It is proposed that remission is the appropriate target in the treatment of both depression and the anxiety disorders.

***Aims:*** Rigorous criteria for remission have been proposed for the anxiety disorders and are currently being applied in clinical studies. Using these criteria, data from the paroxetine clinical study database were retrospectively analyzed to determine remission rates following paroxetine treatment across a range of anxiety disorders in the largest analysis of remission data in the anxiety disorders to date.

***Method:*** These analyses included data from 16 short-term and 6 long-term, randomized, placebo-controlled studies in panic disorder, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder (short term only), and generalized anxiety disorder (DSM-III-R or DSM-IV). Separate analyses were performed for each disorder, with short- and long-term data analyzed separately.

***Results:*** In general, across the range of anxiety disorders studied, in both short- and long-term studies, remission rates were higher for paroxetine compared with placebo, using disorder-specific, global, and functional remission criteria both individually and combined. Remission occurred in a moderate proportion of paroxetine-treated patients after only 8 to 12 weeks of treatment, and longer-term therapy led to even higher remission rates.

***Conclusion:*** Paroxetine has demonstrated efficacy in treating patients to remission across the range of anxiety disorders studied. Our findings strongly suggest that continuing treatment with paroxetine (and probably other SSRI antidepressants) for 2 to 12 months increases the proportion of patients achieving clinical remission.

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The 5 principal anxiety disorders—panic disorder, social anxiety disorder, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD)—are common psychiatric conditions, and taken together they have an estimated yearly prevalence in the United States of 15%.[1] Both the economic cost to society and the personal burden of the anxiety disorders are high. A recent analysis estimated the annual cost of anxiety disorders in the United States in 1990 to be $42.3 billion, or $1542 per sufferer,[2] and comparable to depression.

The anxiety disorders rarely remit spontaneously, and usually develop into chronic, often lifelong, conditions requiring long-term pharmacologic treatment. Until recently, treatment efficacy was generally measured only by attainment of a response—usually defined as a ≥ 50% improvement from baseline in the Hamilton Rating Scale for Anxiety (HAM-A) total score for most anxiety disorders. However, of the 50% to 60% of patients who respond to treatment, only a minority achieves remission or full recovery.[3] The continued presence of subsyndromal symptoms in treated patients with depression, even in the responder population, results in higher relapse rates,[4,5] impaired functioning, and increased utilization of healthcare resources,[6] and the same is thought to be true in the anxiety disorders. These factors have led clinicians increasingly to recognize the need to treat anxiety disorders until remission of anxiety symptoms and functional recovery are achieved. Furthermore, the National Mental Health Association (NMHA) convened an expert panel of U.S. mental health clinicians, researchers, consumers, and advocates to participate in a roundtable discussion, "The Science of Remission, The Art of Recovery," held in New York, N.Y. on November 30, 2001. The panel

agreed that the aim of depression and anxiety treatment should be remission (defined as the virtual elimination of symptoms), functional recovery, and complete recovery of quality of life, rather than partial improvement of the illness.

Selective serotonin reuptake inhibitors (SSRIs) are now considered the first-line therapy for patients with anxiety disorders.[7–12] SSRIs have replaced anxiolytics such as benzodiazepines as the treatment of choice, especially since most anxiety disorders follow a chronic course. Management of anxiety disorders is complicated by high rates of comorbidity, especially with depression, and individual anxiety disorders occur as "pure" conditions in only a small minority of patients.[13–16] The presence of coexisting psychiatric disorders increases the risk of high illness severity and chronicity, and patients with comorbid psychiatric conditions take longer to achieve remission.[17] Large, well-controlled, multicenter studies have demonstrated the effectiveness of paroxetine in all 5 anxiety disorders and of the other SSRIs in some of the disorders. This wide-ranging efficacy enables paroxetine monotherapy (and probably other SSRIs) to be used for the effective treatment of comorbid anxiety and depressive conditions.

Stringent criteria for remission have been proposed for each of the anxiety disorders by international opinion leaders.[18–20] These criteria support the use of an objective score to define remission in terms of a return to a symptom-free status/wellness. Ideally, the criteria should be absolute scores comparable to that of a "normal, not ill at all" population. The design of the multiple, worldwide paroxetine studies of the 5 anxiety disorders preceded this debate, and therefore prospective studies of these remission criteria are not yet available. However, in the reanalysis of these trials, the best criteria that could be applied retrospectively were used, i.e., utilizing the data that were collected to fit retrospective remission criteria. Therefore, a retrospective analysis of remission rates achieved in 22 short- and long-term clinical studies of paroxetine, across a range of anxiety disorders, was undertaken and is reported in this article. This analysis is the largest analysis of remission rates in the anxiety disorders to date.

## METHOD

The studies reviewed in this retrospective analysis included all available placebo-controlled studies in the paroxetine database (references 21–39 and data on file [studies 223, 118, 127], GlaxoSmithKline, Research Triangle Park, N.C.) and included data from patients with DSM-III-R– or DSM-IV–defined panic disorder (with or without agoraphobia), social anxiety disorder, OCD, PTSD (short-term studies only), and GAD participating in short- and long-term clinical studies. Patients with other concurrent Axis I disorders were excluded in all except the PTSD studies. In these, concurrent affective and anxiety disorders were allowed, provided that PTSD was considered the principal diagnosis (i.e., the main focus of attention or need for treatment) and the onset of PTSD preceded that of the concurrent disorders. Furthermore, in all other studies, patients could not have had another Axis I disorder as a principal diagnosis within 6 months of screening.

Data were pooled for paroxetine and placebo treatment groups in each anxiety disorder except where any statistically significant interactions between study and treatment were identified. Data from any active comparator arms are not included in this review. A total of 16 short-term and 6 long-term studies were included in the remission analyses. Short- and long-term studies were analyzed separately (Tables 1 and 2). All but 1 of the long-term studies were relapse prevention studies (references 35, 37–39, and data on file [study 127], GlaxoSmithKline, Research Triangle Park, N.C.), and all patients had received paroxetine for between 2 and 6 months during the initial single-blind or open-label phase. Responders to paroxetine were then randomly assigned to receive paroxetine or placebo during the double-blind phase of the study. In these relapse prevention studies, the long-term baseline was defined as the point of randomization following the single-blind or open-label phase. The remaining study[36] was an extension of a short-term panic disorder study (12 weeks).[23] Here, the long-term baseline was defined as the last measurement taken before the beginning of the extension phase. In all of the long-term studies, patients were followed up for a period of between 3 and 12 months.

### Criteria for Remission

Remission was defined using accepted remission criteria and included clinically relevant endpoints (Table 3).[3,18,20,40] For panic disorder, the following remission criteria were used: no panic attacks for the short-term studies, and no panic attacks, a HAM-A[41] score of ≤ 7, a Marks-Sheehan Phobia Scale (MSPS)[42] fear score of ≤ 1, and an MSPS avoidance score of 0 for the long-term studies,[42] as many experts agree that patients need to be free of anticipatory anxiety and avoidance and return to previously avoided situations to be considered in remission.[11,18,40] For social anxiety disorder, the recommended and rigorous criterion for remission, a Liebowitz Social Anxiety Scale (LSAS)[20] score of ≤ 30, was utilized. For GAD, the criterion utilized was a HAM-A score of ≤ 7. There are no widely accepted remission criteria for OCD and PTSD. Therefore, in the OCD analyses, a Yale-Brown Obsessive Compulsive Scale (YBOCS)[43] score of ≤ 8 (W. K. Goodman, M.D., oral communication, February 2002) was utilized.[42] The Clinician-Administered PTSD Scale (CAPS-2)[44] is the standard assessment tool for PTSD. Recently, a CAPS-2 score of less than 20 has been

**Table 1. Short-Term Studies Included in Analysis of Remission With Paroxetine Treatment for Anxiety Disorders**

| Study No. | Design | Reference | Study Duration, wk | N[a] |
|---|---|---|---|---|
| Panic disorder | | | | |
| 120 | 10, 20, 40 mg fixed dose | Ballenger et al[21] | 10 | 268 |
| 108 | 20–60 mg flexible dose | Oehrberg et al[22] | 12 | 120 |
| 187 | 10–60 mg flexible dose + clomipramine | Lecrubier et al[23] | 12 | 241[b] |
| 223 | 10–60 mg flexible dose + alprazolam | Data on file, GlaxoSmithKline, Research Triangle Park, NC | 10 | 143[b] |
| Social anxiety disorder | | | | |
| 454 | 20, 40, 60 mg fixed dose | Baldwin[24] | 12 | 364 |
| 502 | 20–50 mg flexible dose | Baldwin et al[25] | 12 | 274 |
| 382 | 20–50 mg flexible dose | Stein et al[26] | 12 | 187 |
| Obsessive-compulsive disorder | | | | |
| 116 | 20, 40, 60 mg fixed dose | Wheadon et al[27] | 12 | 339 |
| 118 | 20–60 mg flexible dose + clomipramine | Data on file, GlaxoSmithKline, Research Triangle Park, NC | 12 | 154[b] |
| 136 | 20–60 mg flexible dose + clomipramine | Zohar et al[28] | 12 | 297 |
| Posttraumatic stress disorder | | | | |
| 651 | 20, 40 mg fixed dose | Marshall et al[29] | 12 | 551 |
| 648 | 20–50 mg flexible dose | Tucker et al[30] | 12 | 307 |
| 627 | 20–50 mg flexible dose | Stein et al[31] | 12 | 322 |
| Generalized anxiety disorder | | | | |
| 641 | 20, 40 mg fixed dose | Rickels et al[32] | 8 | 566 |
| 642 | 10–50 mg flexible dose | Pollack et al[33] | 8 | 324 |
| 637 | 20–50 mg flexible dose | Hewett et al[34] | 8 | 364 |

[a]Intent-to-treat efficacy population.
[b]Includes only paroxetine- and placebo-treated patients.

**Table 2. Long-Term Studies Included in Analysis of Remission With Paroxetine Treatment for Anxiety Disorders**

| Study No. | Design | Reference | Study Duration | N[a] |
|---|---|---|---|---|
| Panic disorder | | | | |
| 222 | Extension of study 120: 3 mo double-blind maintained, 3 mo double-blind randomization | Kumar[35] | 6 mo | 95 |
| 228 | Extension of study 187: 9 mo double-blind maintained | Lecrubier and Judge[36] | 9 mo | 114 |
| Social anxiety disorder | | | | |
| 595 | 20–50 mg flexible dose; 12 wk single-blind, 24 wk double-blind | Stein et al[37] | 36 wk | 323 |
| Obsessive-compulsive disorder | | | | |
| 126 | Extension of study 116: 6 mo open-label, 6 mo double-blind randomization | Steiner et al[38] | 12 mo | 98 |
| 127 | Extension of study 118: 6 mo open-label, 6 mo double-blind randomization | Data on file, GlaxoSmithKline, Research Triangle Park, NC | 12 mo | 40 |
| Generalized anxiety disorder | | | | |
| 646 | 20–50 mg flexible dose; 8 wk single-blind, 24 wk double-blind | Stocchi et al[39] | 32 wk | 561 |

[a]Intent-to-treat safety population; includes patients from the double-blind treatment phase.

identified as representing an asymptomatic condition,[44] and this score was used to define remission in the PTSD studies.

Additional analyses were carried out for the long-term studies, using combined remission criteria to determine the proportion of patients in clinical recovery for each anxiety disorder: symptom relief was assessed by attaining an objective score on a disorder-specific scale, global recovery was assessed by a Clinical Global Impressions-Severity of Illness scale (CGI-S)[45] score of 1 ("normal, not at all ill"), and functional recovery was assessed by a total Sheehan Disability Scale (SDS)[41] score of less than 5.[19] SDS score was not used to define remission in the short-term studies.

### Statistical Analyses

The analyses were performed on the intent-to-treat (ITT) dataset, which included patients who received at least 1 dose of study medication and had at least 1 post-baseline efficacy measurement. Remission rates were calculated using the last-observation-carried-forward (LOCF) method, which allowed inclusion of patients who were withdrawn early. The analyses comprised a logistic regression on the incidence of remission. Explanatory variables included in the model were *region*, *baseline efficacy value* (depending on the rating scale), and *treatment* (*study* was also included in the short-term analysis). The treatment differences observed in each study were assessed informally to check for any qualita-

Table 3. Criteria for Remission of Anxiety Disorders[a]

| Disorder | Criteria |
|---|---|
| Panic disorder | |
| Short-term studies | No. of panic attacks = 0<br>CGI-Severity of Illness score = 1 |
| Long-term studies | No. of panic attacks = 0,<br>HAM-A score ≤ 7,<br>MSPS fear score ≤ 1, and<br>MSPS avoidance score = 0<br>CGI-Severity of Illness score = 1<br>Sheehan Disability Scale score < 5 |
| Social anxiety disorder | |
| Short- and long-term studies | LSAS total score ≤ 30<br>CGI-Severity of Illness score = 1 |
| Long-term study only | Sheehan Disability Scale score < 5 |
| Obsessive-compulsive disorder | |
| Short- and long-term studies | YBOCS total score ≤ 8<br>CGI-Severity of Illness score = 1 |
| Posttraumatic stress disorder | |
| Short-term studies | CAPS-2 total score < 20<br>CGI-Severity of Illness score = 1 |
| Generalized anxiety disorder | |
| Short- and long-term studies | HAM-A score ≤ 7<br>CGI-Severity of Illness score = 1 |
| Long-term study only | Sheehan Disability Scale score < 5 |

[a]Data from Ballenger.[3,18,40]
Abbreviations: CAPS-2 = Clinician Administered PTSD Scale version 2, CGI = Clinical Global Impressions scale, HAM-A = Hamilton Rating Scale for Anxiety, LSAS = Liebowitz Social Anxiety Scale, MSPS = Marks-Sheehan Phobia Scale, PTSD = posttraumatic stress disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

tive interaction, but the interaction between study and treatment was not routinely included in the model.

Main effects were tested using 2-tailed significance levels of 5%; interactions were tested at the 10% level. The odds ratios for differences in remission rates between paroxetine and placebo were calculated (along with their associated 95% CIs) for pooled data at each visit interval.

In order to assess the proportion of patients in remission according to all 3 criteria, i.e., disorder-specific, global (CGI-S), and functional (SDS), a combined assessment was conducted, where data were available. This combined assessment is a more stringent measure than are the individual measures alone. These data are presented descriptively for each indication. No formal statistical analysis was performed on the combined criteria as it had been decided at the outset to focus on the individual remission criteria. Additional analysis of the combined data would have implications for significance levels since it would constitute repeated testing of related data.

The results of the short- and long-term studies are summarized both in descriptive tables of percentage remission and as the odds ratio of remission during paroxetine treatment relative to placebo. In the short-term studies, the odds ratios were calculated using the data from the last postbaseline observation for each patient (last visit), and thus reflect a short-term ITT effect. For the long-term studies, the overall outcome at the last visit for each patient was assessed.

## RESULTS

Baseline demographics for the patients included in the panic disorder, social anxiety disorder, OCD, PTSD, and GAD short- and long-term studies are summarized in Table 4. Paroxetine and placebo treatment groups were well matched with respect to demographic variables.

### Panic Disorder

***Short-term studies.*** Data from a total of 772 patients included in the 4 randomized, double-blind, placebo-controlled panic disorder studies (references 21–23 and data on file [study 223], GlaxoSmithKline, Research Triangle Park, N.C.) were included in the analysis. The remission rates achieved using disorder-specific (no panic attacks) and global (CGI-S) criteria, odds ratios of remission for paroxetine versus placebo, and the associated significance levels are presented in Table 5.

Results indicate that following 8 to 12 weeks of therapy, the number of patients randomly assigned to paroxetine who experienced remission (i.e., no panic attacks in the previous 2–3 weeks), was statistically significantly greater than for those randomly assigned to placebo (35.3% vs. 22.4%; OR = 1.80, 95% CI = 1.26 to 2.57, p = .001). In addition, the number of patients receiving paroxetine who achieved a CGI-S score of 1, representing those patients judged to be "normal, not at all ill," was also statistically significantly higher than for placebo (24.6% vs. 10.0%; OR = 3.16, 95% CI = 2.05 to 4.88, p < .001). These data extend the results observed in the individual panic disorder studies, further showing that paroxetine is effective in the short-term treatment of panic disorder and produces a moderate number of largely recovered patients.

***Long-term studies.*** Data from a total of 209 patients included in 2 long-term, randomized, double-blind, placebo-controlled panic disorder studies[35,36] were also analyzed. One of these studies (study 228)[36] was an extension of a short-term study,[23] and the other was a relapse prevention study (study 222).[35] A statistically significant interaction between study and treatment was identified in the SDS score analysis, and so the data for the 2 long-term studies were analyzed separately. The remission rates achieved using each individual remission criterion, odds ratios for paroxetine versus placebo, and the associated significance levels for the 2 studies are reported in Table 6.

1. Disorder-specific. In study 222[35] at the long-term baseline (point of randomization), no patients randomly assigned to paroxetine were in remission according to the disorder-specific criterion (no panic attacks, HAM-A score ≤ 7, MSPS fear score of ≤ 1, and MSPS avoidance score of 0) compared with 3.5% of those randomly assigned to placebo. At the last visit, the proportion of patients maintained on paroxetine treatment who were in

**Table 4. Demographic Summaries for Short-Term (8–12 weeks) and Long-Term (6–12 months) Studies (pooled data) of Paroxetine for Anxiety Disorders**

| | Panic Disorder[a] | | Social Anxiety Disorder[b] | | Obsessive-Compulsive Disorder[c] | | Posttraumatic Stress Disorder,[d] ST | Generalized Anxiety Disorder[e] | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | ST | LT | ST | LT | ST | LT | | ST | LT |
| Intent-to-treat safety population, N | | | | | | | | | |
| Paroxetine | 452 | 110 | 496 | 162 | 528 | 68 | 676 | 735 | 274 |
| Placebo | 320 | 99 | 329 | 161 | 262 | 70 | 504 | 529 | 287 |
| Female, % | | | | | | | | | |
| Paroxetine | 64.4 | 64.5 | 44.6 | 60.5 | 39.0 | 35.3 | 64.8 | 61.5 | 62.8 |
| Placebo | 65.6 | 58.6 | 46.5 | 60.2 | 40.8 | 34.3 | 62.3 | 62.8 | 64.8 |
| Age, y | | | | | | | | | |
| Paroxetine | | | | | | | | | |
| Mean | 36.5 | 35.1 | 36.8 | 38.1 | 39.7 | 41.2 | 41.3 | 41.8 | 43.0 |
| Range | 19–74 | 19–66 | 18–70 | 19–66 | 16–77 | 18–67 | 18–75 | 18–78 | 20–79 |
| Placebo | | | | | | | | | |
| Mean | 36.8 | 38.2 | 36.5 | 38.2 | 39.2 | 43.9 | 40.1 | 42.5 | 43.7 |
| Range | 18–67 | 19–62 | 18–85 | 18–71 | 16–74 | 20–75 | 18–78 | 18–80 | 18–78 |

[a]Data from references 21–23, 35, 36, and data on file (study 223), GlaxoSmithKline, Research Triangle Park, N.C.
[b]Data from references 24, 25, 26, and 37.
[c]Data from references 27, 28, 38, and data on file (studies 118, 127), GlaxoSmithKline, Research Triangle Park, N.C.
[d]Data from references 29, 30, and 31.
[e]Data from references 32, 33, 34, and 39.
Abbreviations: LT = long-term studies, ST = short-term studies.

remission by this criterion was 17.6%, whereas none of the patients switched to placebo were in remission.

At the beginning of the extension phase in study 228,[36] no patients receiving either paroxetine or placebo were in remission. However, by the last visit, a higher, although not significant, proportion of paroxetine patients were in remission (25.5%) compared with placebo patients (9.7%) using the disorder-specific criterion (OR = 3.20, 95% CI = 0.82 to 12.46, p = .094).

2. Global. At the long-term baseline of study 222, 28.1% of paroxetine-treated patients and 35.1% of placebo-treated patients were in remission according to the criterion of a CGI-S score of 1. At last visit, the proportion of patients maintained on paroxetine treatment considered to be in remission was 42.4%, compared with 43.2% of placebo-maintained patients (OR = 0.97, 95% CI = 0.38 to 2.50, p = .95).

At the beginning of the extension phase in study 228,[36] 36.7% of patients maintained on paroxetine treatment and 15.5% of patients receiving placebo were in remission according to the criterion of a CGI-S score of 1. At the last visit in this study, the proportion of patients considered to be "normal, not at all ill" (CGI-S score = 1) was 38.2% for patients maintained on paroxetine treatment compared with 37.8% of those who continued to receive placebo (OR = 1.02, 95% CI = 0.47 to 2.22, p = .96).

3. Functional improvement. At the long-term baseline of study 222,[35] 82.9% of patients randomly assigned to paroxetine and 74.1% patients randomly assigned to placebo were in remission according to the criterion of a total SDS score of < 5. However, at the last visit in this study, there was no separation between paroxetine and placebo, with more than 60% of patients in both treatment groups achieving remission (73.2% vs. 66.0%; OR = 1.42, 95% CI = 0.54 to 3.70, p = .48).

At the beginning of the extension phase in study 228,[36] 50.7% of patients maintained on paroxetine treatment and 51.3% of patients receiving placebo met the SDS criterion for remission. At the last visit in this study, the proportion of patients achieving functional normality (SDS score < 5) was significantly greater for patients maintained on paroxetine treatment compared with those who continued to receive placebo (77.6% vs. 52.3%; OR = 4.22; 95% CI = 1.76 to 10.1, p = .001).

4. Combined criteria analysis. The proportion of patients achieving remission when all 3 criteria were combined (a stringent definition of remission)[3,11,18,42] was determined for study 228.[36] In the last visit analysis, more than double the number of patients maintained on paroxetine treatment were considered in remission using these combined criteria, including disorder-specific, global, and functional criteria, compared with patients treated with placebo (19.1% vs. 3.2%, respectively) (Figure 1).

When compared with the short-term data, the long-term studies suggest that continued treatment with paroxetine leads to a significantly greater proportion of patients achieving remission of panic disorder over time. This is an important new finding, i.e., treating patients who have only partially responded after short-term treatment (2–3 months) for longer periods leads to more patients achieving full remission from their psychiatric disorder.

## Social Anxiety Disorder

***Short-term studies.*** Data from over 800 patients included in 3 short-term, randomized, double-blind,

**Table 5. Percentage Remission and Odds Ratio of Remission at Last Visit for Paroxetine Versus Placebo in Anxiety Disorders: Short-Term (8–12 weeks) Studies (pooled LOCF data)**

| Criterion | Paroxetine, % | Placebo, % | OR | 95% CI | p Value |
|---|---|---|---|---|---|
| Disorder-specific[a] | | | | | |
| No panic attacks | | | | | |
| Panic disorder[b] | 35.3 | 22.4 | 1.80 | 1.26 to 2.57 | .001 |
| LSAS score ≤ 30 | | | | | |
| Social anxiety disorder[c] | 26.5 | 15.2 | 1.95 | 1.35 to 2.82 | .0004 |
| YBOCS score ≤ 8 | | | | | |
| Obsessive-compulsive disorder[d] | 13.6 | 6.9 | 2.21 | 1.28 to 3.82 | .004 |
| CAPS-2 score < 20 | | | | | |
| Posttraumatic stress disorder[e] | 31.2 | 16.3 | 2.29 | 1.68 to 3.12 | < .001 |
| HAM-A score ≤ 7 | | | | | |
| Generalized anxiety disorder[f] | 35.2 | 25.1 | 1.70 | 1.3 to 2.2 | < .001 |
| Global | | | | | |
| CGI-S score = 1[g] | | | | | |
| Panic disorder | 24.6 | 10.0 | 3.16 | 2.05 to 4.88 | < .001 |
| Social anxiety disorder | 13.0 | 5.9 | 3.26 | 1.72 to 6.19 | .0003 |
| Obsessive-compulsive disorder | 2.8 | 1.5 | 1.79 | 0.58 to 5.50 | .3 |
| Posttraumatic stress disorder | 13.4 | 6.7 | 2.20 | 1.4 to 3.3 | < .001 |
| Generalized anxiety disorder | 16.9 | 10.6 | 1.70 | 1.2 to 2.4 | .003 |

[a]Odds ratio for remission based on logistic regression analysis including study, baseline efficacy value, and treatment as variables.
[b]Data from references 21–23 and data on file (study 223), GlaxoSmithKline, Research Triangle Park, N.C.
[c]Data from references 24, 25, and 26.
[d]Data from references 27, 28, and data on file (study 118), GlaxoSmithKline, Research Triangle Park, N.C.
[e]Data from references 29, 30, and 31.
[f]Data from references 32, 33, and 34.
[g]Odds ratio for remission based on logistic regression analysis including study and treatment as variables.
Abbreviations: CAPS-2 = Clinician Administered PTSD Scale version 2, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, LSAS = Liebowitz Social Anxiety Scale, PTSD = posttraumatic stress disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

placebo-controlled social anxiety disorder studies[24–26] were included in the analysis. The remission rates achieved using disorder-specific (LSAS) and global (CGI-S) criteria, odds ratios of remission for paroxetine versus placebo, and the associated significance levels are shown in Table 5.

After 12 weeks of treatment, the proportion of patients randomly assigned to receive paroxetine achieving an LSAS total score of ≤ 30 was statistically significantly greater than for those randomly assigned to placebo (26.5% vs. 15.2%; OR = 1.95, 95% CI = 1.35 to 2.82, p = .0004). Likewise, the proportion of patients receiving paroxetine who achieved remission by the criterion of a CGI-S score of 1 was also significantly higher than for placebo-treated patients (13.0% vs. 5.9%; OR = 3.26; 95% CI = 1.72 to 6.19, p = .0003). These results supplement the findings reported from the individual social anxiety disorder studies and further demonstrate that paroxetine is effective in bringing a moderate number of patients into remission from the symptoms of social anxiety disorder, even after only 12 weeks of treatment.

***Long-term study.*** This analysis comprised data from a total of 323 patients included in 1 long-term, randomized, double-blind, placebo-controlled social anxiety disorder relapse prevention study.[37] The remission rates achieved using each individual remission criterion, odds ratios for paroxetine versus placebo, and the associated significance levels are shown in Table 6.

1. Disorder-specific. At the long-term baseline (point of randomization), 34.6% of patients randomly assigned to paroxetine and 37.9% of patients randomly assigned to placebo were in remission according to the criterion of an LSAS score of ≤ 30. At the last visit, the proportion of patients maintained on paroxetine treatment who were in remission was 48.4%, whereas the remission rate in those switched to placebo was 32.7%, a significant difference (OR = 3.05, 95% CI = 1.75 to 5.31, p < .001).

2. Global. At the long-term baseline, similar proportions of patients randomly assigned to paroxetine or placebo were in remission according to the criterion of a CGI-S score of 1 (10.5% vs. 18.0%, respectively). Again at the last visit, the proportion of patients in remission maintained on paroxetine treatment compared with those switched to placebo was 33.1% and 12.0%, respectively (OR = 3.73, 95% CI = 2.07 to 6.71, p < .001).

3. Functional improvement. At the long-term baseline, similar proportions of patients randomly assigned to paroxetine or placebo were in remission according to the criterion of a total SDS score of < 5 (28.4% vs. 29.2%, respectively). At the last visit, the proportion of patients achieving functional normality (SDS score < 5) was significantly greater in patients maintained on paroxetine treatment than for patients switched to placebo (44.9% vs. 26.4%; OR = 3.77, 95% CI = 2.06 to 6.96, p < .001).

4. Combined criteria analysis. When all 3 criteria were combined at the last visit analysis, more than 3 times

**Table 6. Percentage Remission and Odds Ratio of Remission at Baseline[a] and Last Visit for Paroxetine Versus Placebo: Long-Term (6–12 months) Studies (LOCF)**

| | Paroxetine, % | | Placebo, % | | Statistic[c] | | |
|---|---|---|---|---|---|---|---|
| Criterion | Last Visit | Baseline | Last Visit | Baseline | OR | 95% CI | p Value |
| Disorder-specific | | | | | | | |
| Panic disorder[b] | | | | | | | |
| Study 222[d] | 17.6 | 0 | 0 | 3.5 | ND | ND | ND |
| Study 228[e] | 25.5 | 0 | 9.7 | 0 | 3.20[f] | 0.82 to 12.46 | .094 |
| LSAS score ≤ 30 | | | | | | | |
| Social anxiety disorder (study 595)[g] | 48.4 | 34.6 | 32.7 | 37.9 | 3.05[f] | 1.75 to 5.31 | < .001 |
| YBOCS score ≤ 8 | | | | | | | |
| Obsessive-compulsive disorder (studies 126 and 127 pooled)[h] | 36.8 | 15.3 | 17.1 | 13.3 | 3.04[f] | 1.35 to 6.86 | .007 |
| HAM-A score ≤ 7 | | | | | | | |
| Generalized anxiety disorder (study 646)[i] | 73.0 | 44.5 | 34.4 | 50.9 | 6.4[j] | 4.3 to 9.4 | < .001 |
| Global | | | | | | | |
| CGI-S score = 1 | | | | | | | |
| Panic Disorder | | | | | | | |
| Study 222 | 42.4 | 28.1 | 43.2 | 35.1 | 0.97 | 0.38 to 2.50 | .95 |
| Study 228 | 38.2 | 36.7 | 37.8 | 15.5 | 1.02[k] | 0.47 to 2.22 | .96 |
| Social anxiety disorder (study 595) | 33.1 | 10.5 | 12.0 | 18.0 | 3.73[k] | 2.07 to 6.71 | < .001 |
| Obsessive-compulsive disorder (studies 126 and 127 pooled) | 8.8 | 1.4 | 7.1 | 1.4 | 1.23[k] | 0.35 to 4.24 | .75 |
| Generalized anxiety disorder (study 646) | 44.2 | 24.5 | 20.6 | 24.8 | 3.05[l] | 2.10 to 4.44 | < .001 |
| Functional | | | | | | | |
| SDS score < 5 | | | | | | | |
| Panic disorder | | | | | | | |
| Study 222 | 73.2 | 82.9 | 66.0 | 74.1 | 1.42[f] | 0.54 to 3.70 | .48 |
| Study 228 | 77.6 | 50.7 | 52.3 | 51.3 | 4.22[f] | 1.76 to 10.1 | .001 |
| Social anxiety disorder (study 595) | 44.9 | 28.4 | 26.4 | 29.2 | 3.77[f] | 2.06 to 6.96 | < .001 |
| Obsessive-compulsive disorder (studies 126 and 127 pooled) | ND | ND | ND | ND | ND | ND | ND |
| Generalized anxiety disorder (study 646) | 58.0 | 24.5 | 31.1 | 26.8 | 3.5[j] | 2.2 to 5.4 | < .001 |

[a]Defined as remission rates at the point of randomization following short-term, single-blind, or open-label paroxetine treatment and prior to double-blind, relapse prevention phase of the study, with the exception of study 228 where baseline is defined as the last measurement taken before the beginning of the extension phase.
[b]No panic attacks, HAM-A score ≤ 7, MSPS fear score ≤ 1, and MSPS avoidance score = 0.
[c]Comparison of percentages at last visit between paroxetine and placebo.
[d]Data from reference 35.
[e]Data from reference 36.
[f]Based on logistic regression analysis including baseline efficacy value and treatment as variables.
[g]Data from reference 37.
[h]Data from reference 38 and data on file (study 127), GlaxoSmithKline, Research Triangle Park, N.C.
[i]Data from reference 39.
[j]Based on logistic regression analysis including region, baseline efficacy value, and treatment as variables.
[k]Based on logistic regression analysis including treatment as a variable.
[l]Based on logistic regression analysis including region and treatment as variables.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, LSAS = Liebowitz Social Anxiety Scale, MSPS = Marks-Sheehan Phobia Scale, ND = not determined (because remission value for placebo = 0), SDS = Sheehan Disability Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

as many patients maintained on paroxetine treatment were considered to be in remission, compared with those switched to placebo (18.4% vs. 6.4%, respectively) (Figure 1).

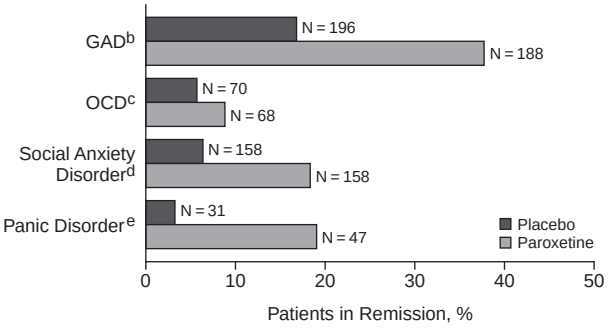
These results demonstrate that the efficacy of paroxetine in treating the symptoms of social anxiety disorder is maintained during long-term treatment, with a significantly greater proportion of patients receiving paroxetine displaying superiority over placebo across all criteria defining remission.

## Obsessive-Compulsive Disorder

***Short-term studies.*** Data from a total of 790 patients included in 3 randomized, double-blind, placebo-controlled, short-term OCD studies (references 27, 28, and data on file [study 118], GlaxoSmithKline, Research Triangle Park, N.C.) were included in the analysis. Table 5 displays the remission rates achieved using disorder-specific (YBOCS) and global (CGI-S) criteria, odds ratios of remission for paroxetine versus placebo, and the associated significance levels.

The pooled data at the end of the short-term treatment period showed that the proportion of patients randomly assigned to receive paroxetine achieving a YBOCS score of ≤ 8 was significantly greater compared with those randomly assigned to placebo (13.6% vs. 6.9%; OR = 2.21, 95% CI = 1.28 to 3.82, p = .004). The proportion of patients receiving paroxetine who achieved a CGI-S score of 1 was higher than for placebo, although not significantly so (2.8% vs. 1.5%; OR = 1.79; 95% CI = 0.58 to 5.50,

**Figure 1. Patients in Remission According to the Combined Remission Criteria Analyses at the Last Visit in Long-Term Studies With Paroxetine or Placebo Treatment for Anxiety Disorders[a]**




[a]Ns represent only those patients with data available.
[b]Data from reference 39.
[c]Data from reference 38 and data on file (study 127), GlaxoSmithKline, Research Triangle Park, N.C. Sheehan Disability Scale not performed in OCD studies.
[d]Data from reference 37 only.
[e]Data from reference 36.
Abbreviations: GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder.

p = .3). These findings confirm that paroxetine is effective treatment in OCD, with more than twice as many patients achieving remission after 12 weeks of therapy compared with those taking placebo.

***Long-term studies.*** A total of 138 patients from 2 identical long-term (12-month) OCD relapse prevention studies (reference 38 and data on file [study 127], GlaxoSmithKline, Research Triangle Park, N.C.) were included in the analysis. The remission rates achieved using each individual remission criterion, odds ratios for paroxetine versus placebo, and the associated significance levels are reported in Table 6.

1. Disorder-specific. At the long-term baseline (point of randomization), 15.3% of patients randomly assigned to receive paroxetine and 13.3% of patients randomly assigned to placebo were in remission according to the disorder-specific criterion of a YBOCS score of ≤ 8. At the last visit, the proportion of patients in remission was significantly higher in those who continued paroxetine treatment compared with those patients switched to placebo (36.8% vs. 17.1%; OR = 3.04, 95% CI = 1.35 to 6.86; p = .007).

2. Global. At the long-term baseline, 1.4% of patients randomly assigned to paroxetine and 1.4% of patients randomly assigned to placebo had achieved remission according to the criterion of a CGI-S score of 1. With further treatment (6 months), the proportion of patients in remission who continued paroxetine treatment compared with those patients switched to placebo was 8.8% and 7.1%, respectively (OR = 1.23, 95% CI = 0.35 to 4.24, p = .75).

3. Combined criteria analysis. As the SDS rating scale was not included in these studies, the proportion of patients achieving remission by combined YBOCS and CGI-S criteria was analyzed. In total, 8.8% of patients maintained on paroxetine treatment and 5.7% of those switched to placebo were in remission according to the combined measurements (Figure 1).

## Posttraumatic Stress Disorder

***Short-term studies.*** Data from a total of 1180 patients included in 3 large, randomized, double-blind, placebo-controlled, short-term PTSD studies[29–31] were included in the analysis. The remission rates achieved using disorder-specific (CAPS-2) and global (CGI-S) criteria, odds ratios of remission for paroxetine versus placebo, and the associated significance levels are displayed in Table 5.

The proportion of patients treated with paroxetine who achieved a CAPS-2 total score of < 20 was statistically significantly greater than for patients taking placebo following 12 weeks of treatment (31.2% vs. 16.3%; OR = 2.29, 95% CI = 1.68 to 3.12, p < .001). Likewise, the proportion of patients receiving paroxetine who achieved a CGI-S score of 1 was also significantly higher than for placebo (13.4% vs. 6.7%; OR = 2.20, 95% CI = 1.4 to 3.3, p < .001). These results supplement the findings from the 3 individual short-term PTSD studies and demonstrate that paroxetine is effective in bringing a significant proportion of patients to remission even after only 12 weeks of therapy.

## Generalized Anxiety Disorder

***Short-term studies.*** Data from a total of 1254 patients from 3 large, short-term (8-week), randomized, double-blind, placebo-controlled, GAD studies[32–34] were included in the analysis. The remission rates achieved using disorder-specific (HAM-A) and global (CGI-S) criteria, odds ratios of remission for paroxetine versus placebo, and the associated significance levels are shown in Table 5.

Following 8 weeks of treatment, a significantly higher proportion of patients randomly assigned to receive paroxetine achieved remission (according to the criterion of a HAM-A total score of ≤ 7) compared with those randomly assigned to placebo (35.2% vs. 25.1%; OR = 1.7, 95% CI = 1.3 to 2.2, p < .001). Furthermore, the number of patients receiving paroxetine who achieved a CGI-S score of 1 was also significantly higher than for placebo (16.9% vs. 10.6%; OR = 1.7, 95% CI = 1.2 to 2.4, p = .003). These findings underline the previous findings that paroxetine is an effective treatment for GAD, with a significant proportion of patients achieving remission after only 8 weeks of therapy.

***Long-term study.*** This analysis included data from a total of 561 patients from 1 randomized, double-blind, placebo-controlled, long-term GAD relapse prevention

study.[39] The remission rates achieved using each individual remission criterion, odds ratios for paroxetine versus placebo, and the associated significance levels are shown in Table 6; remission rates using the combined criteria are shown in Figure 1.

1. Disorder-specific. An equivalent proportion of patients randomly assigned to paroxetine or placebo treatment were in remission according to the criterion of a HAM-A score of ≤ 7 at the long-term baseline (point of randomization, 44.5% vs. 50.9%, respectively). At the last visit, the remission rate in patients maintained on paroxetine treatment was significantly greater at 73.0% compared with 34.4% for those patients switched to placebo for the 24-week double-blind period (OR = 6.4, 95% CI = 4.3 to 9.4, $p < .001$).

2. Global. At the long-term baseline, similar proportions of patients randomly assigned to paroxetine or placebo had achieved remission using the criterion of a CGI-S score of 1 (24.5% vs. 24.8%, respectively). However, at the last visit, the remission rate in patients maintained on paroxetine treatment was significantly higher at 44.2%, compared with 20.6% in those patients switched to placebo (OR = 3.05, 95% CI = 2.10 to 4.44, $p < .001$).

3. Functional improvement. As with the other 2 criteria discussed above, similar proportions of patients randomly assigned to the paroxetine or placebo treatment groups were in remission at the long-term baseline according to the criterion of a total SDS score of < 5 (24.5% vs. 26.8%, respectively). However, at the last study visit, the proportion of patients in remission in the paroxetine group was almost double that of those patients switched to placebo (58.0% vs. 31.1%; OR = 3.5, 95% CI = 2.2 to 5.4, $p < .001$), again a significant comparison.

4. Combined criteria analysis. When the proportion of patients in remission by all 3 criteria was assessed, 37.8% of patients maintained on paroxetine treatment versus 16.8% of those switched to placebo met this most stringent criterion of remission at the last visit (Figure 1).

These results emphasize the benefit of continuing paroxetine treatment beyond an initial 8-week period in order to allow a significantly greater proportion of patients to reach full recovery in GAD.

### Overview

These analyses provide even more rigorous support that paroxetine is efficacious in the treatment of each of the anxiety disorders under investigation. Specifically, a significant proportion of patients achieved remission (i.e., wellness, asymptomatic status, functional normality) across the range of anxiety disorders studied during both short- and long-term treatment with paroxetine. After only 8 to 12 weeks of paroxetine treatment, a statistically significant proportion of patients achieved remission from their disorder. Although the remission rates vary across the anxiety disorders, a greater proportion of patients achieved full recovery following longer-term treatment than following short-term treatment. This supports the view that longer-term treatment of anxiety disorders with paroxetine is required to maximize response. It is generally recommended that treatment continue for at least 6 months and frequently for 12 to 18 months in the various anxiety disorders.[7,9–11] An important research question is whether even longer-term treatment (i.e., longer than 12 months) would enable an even greater proportion of patients to achieve remission of their symptoms.

Most now agree that full remission and functional recovery have become the primary goals of treatment. This ideally requires that a patient meets all of the remission criteria for a given anxiety disorder. The results of the combined analysis of disorder-specific, global (CGI-S score = 1), and functional improvement (SDS score < 5) criteria showed that a significant proportion of patients with each anxiety disorder can be considered in remission following paroxetine treatment (Figure 1).

## DISCUSSION

In the past, clinical studies of drug therapies for anxiety disorders have generally focused on short-term improvements in the severity of clinical symptoms and have rarely evaluated the proportion of patients achieving remission from their symptoms and recovery from the syndrome itself. However, a significant proportion of treatment "responders" still have subsyndromal symptoms. Therefore, stopping treatment after a patient has responded but has not yet fully recovered has been shown to result in increased relapse rates, impaired functioning, and increased utilization of health care resources. Patients with major depressive disorder who are maintained on treatment until they achieve remission have fewer relapses and recurrences of their condition,[46] and it is assumed that the same is true for the anxiety disorders. With the availability of newer antidepressants with superior efficacy and tolerability, there is a consensus among clinical psychiatrists that treatment goals should now be set beyond the attainment of a clinical response. Remission—which is perhaps most accurately defined as resolution of both clinical symptoms and any functional impairment caused by the anxiety disorder or as a return to "normal"—is now the primary goal of therapy in routine clinical practice.

The SSRI paroxetine is in the unique position of having an extensive clinical studies database for both the short- and long-term treatment of the entire range of anxiety disorders—panic disorder, social anxiety disorder, OCD, PTSD (short-term treatment only), and GAD. This comprehensive review has retrospectively analyzed the ability of paroxetine to treat patients to remission using stringent remission criteria for each of the anxiety disorders,[1] and it demonstrates the ability of paroxetine to im-

prove anxiety symptoms in a significant proportion of patients to the point that they can be considered asymptomatic, normal, or "well." This is all the more notable considering that most of these patients have been suffering from their condition for many years before seeking treatment. For example, a GAD patient will typically suffer from symptoms for 5 to 10 years before diagnosis and treatment,[10] OCD patients even longer,[47] and the average duration of illness for a patient with social anxiety disorder is 20 years.[48]

The odds ratios of achieving remission while receiving paroxetine treatment were always higher and were significantly higher in the majority of trials for those patients receiving placebo (short-term) or being switched to placebo (long-term relapse prevention studies), using disorder-specific, global, and functional criteria across the range of anxiety disorders studied. Although the combined criteria comparisons were not statistically compared, they consistently favored the drug group. Compared with the other anxiety disorders, OCD had the lowest rates of remission, particularly in the short-term studies, and this may reflect the recognized fact that OCD often requires higher dosages and longer periods of pharmacotherapy to maximize benefit[33] and that response rates are lower than for the other anxiety disorders.[3] This analysis suggests a recovery rate of generally only 10% to 15%, which is consistent with previous trials. Only in the long-term study was the rate higher (36.8% for the YBOCS score ≤ 8 criterion).

When patients were continued on paroxetine treatment in longer-term studies, remission rates were maintained and usually improved beyond the rates seen after short-term treatment. Furthermore, most of the long-term studies included in this analysis incorporated endpoints to assess the proportion of patients achieving functional normality in the realms of their family, work, and social lives (total SDS score < 5). Resolution of functional impairment is probably one of the most effective measures for documenting complete recovery or remission.[19,49] For panic disorder (study 228), social anxiety disorder, and GAD, a significant proportion (44.9%–77.6%) of paroxetine-treated patients achieved remission according to this functionality criterion. We utilized multiple criteria for remission in this study to maximize the use of this rich and unique dataset. The disorder-specific criteria in social anxiety disorder (LSAS score ≤ 30), OCD (YBOCS score ≤ 8), PTSD (CAPS-2 score < 20), and even GAD (HAM-A score ≤ 7) could well be considered remission criteria by themselves since they all estimate the symptom level of a normal population. The panic disorder criterion of no panic attacks for 2 to 3 weeks would be a less reliable criterion for multiple reasons that have been argued for years.[50,51] The use of a CGI-S rating again could be utilized on its own in that it represents someone who is "normal, not at all ill." Similarly, the criterion of an SDS score of < 5 has itself been shown to correspond to that of a normal population. The combination of criteria is perhaps best conceptually because it requires the patient to be symptomatically and functionally "normal," although this combination is certainly stringent.

As with all clinical analyses, there are limitations to the study designs. With the exception of the PTSD studies, the clinical trials included in these analyses excluded patients with other significant comorbid psychiatric conditions. This may lessen the generalizability of these results to clinical practice, where patients presenting with individual anxiety disorders as "pure" conditions comprise only a small minority of patients. However, the efficacy of paroxetine demonstrated across the range of anxiety disorders studied strongly suggests that paroxetine would also be effective in assisting patients with comorbid anxiety conditions to achieve remission. In clinical practice, many patients with anxiety disorders present with comorbid depression. This has been taken into account in published remission criteria that included measurement of depressive symptoms using the Hamilton Rating Scale for Depression (HAM-D).[18] As previously noted, the majority of studies included in these analyses (PTSD studies being the exception) excluded patients with comorbid depression, and therefore inclusion of the HAM-D remission criterion was inappropriate.

A possible shortcoming of pooled analyses is the potential for results from any particularly large, individual study to influence the overall data. However, the significant differences in remission rates for paroxetine compared with placebo were also confirmed by the use of multiple remission criteria and combined criteria.

It would be important to compare the results obtained in this analysis with remission data for the other SSRIs in the treatment of anxiety disorders; however, there is a paucity of published data in this area. Recently, a pooled analysis of the remission rates observed in two 6-month studies of the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine in patients with GAD was conducted.[52] The primary remission criterion used was attainment of a HAM-A total score of ≤ 7, similar to the criteria reported here. However, functional remission (SDS total score < 5) was not included in the venlafaxine analysis. At the end of the study, a significantly greater proportion of patients receiving venlafaxine had achieved remission by the HAM-A criterion compared with placebo (43% vs. 19%, $p < .001$).[52]

In our analysis, using the same HAM-A criterion, the remission rates observed with long-term paroxetine treatment of patients with GAD (paroxetine 73% vs. placebo 34%, $p < .001$) compare favorably with those reported for venlafaxine. However, these studies differed in their design, and to date there have been no direct head-to-head comparisons of paroxetine and venlafaxine in any of the anxiety disorders.

In conclusion, this analysis has shown that short- and long-term treatment with paroxetine results in a significantly greater proportion of patients attaining remission (using strictly defined, clinically relevant criteria) compared with placebo across the entire spectrum of anxiety disorders (panic disorder, social anxiety disorder, OCD, PTSD, and GAD). These results, taken in conjunction with the proven antidepressant activity of this agent, provide the rationale for paroxetine (and perhaps other SSRIs) being considered an effective treatment for both "pure" and comorbid anxiety disorders. These results are particularly important considering the high rates of comorbidity seen in patients with these conditions.

Perhaps the most clinically important finding of this analysis is the significantly greater proportion of patients achieving remission with longer-term (2–12 months) paroxetine treatment compared with placebo. It was only in OCD that an increase compared with placebo was not observed. These data and others strongly suggest a significant change in clinical thinking and strategy for patients with anxiety disorders. It now seems clear that rather than switching medications in partial responders, serious consideration should be given to maintaining them on the same treatment for a longer period of time (total of 3–12 months). Since not all (or in some cases not even the majority of) patients achieve remission even with 6 to 12 months of treatment, research needs to be performed to determine predictors of response. These predictors would then assist the clinician in deciding which patients to treat for longer with the same antidepressant and which patients need to receive a different treatment.

*Drug names:* alprazolam (Xanax and others), clomipramine (Anafranil and others), paroxetine (Paxil and others), venlafaxine (Effexor).

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