Efficacy of Paroxetine for Relapse Prevention in Social Anxiety Disorder

A 24-Week Study

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Background: The efficacy of selective serotonin reuptake inhibitors in the acute treatment of social anxiety disorder (social phobia) is well established.

Objective: To evaluate whether the efficacy of paroxetine hydrochloride in this disorder is maintained in the long term.

Methods: This was a placebo-controlled multicenter study comprising a single-blind acute treatment phase (12 weeks) and a randomized, double-blind maintenance treatment phase (24 weeks) for patients who had responded to paroxetine during the acute phase. Four hundred thirty-seven adult patients with social anxiety disorder (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria, code 300.23) entered the acute phase, and 323 continued into the maintenance phase (162 paroxetine and 161 placebo). The principal outcome measure was the proportion of patients relapsing during the maintenance phase.

Results: Two hundred fifty-seven patients completed the study (136 paroxetine-treated and 121 placebo-treated patients). Significantly fewer patients relapsed in the paroxetine group than in the placebo group (14% vs 39%; odds ratio, 0.24; 95% confidence interval, 0.14-0.43; \( P < .001 \)). At the end of the study, a significantly greater proportion of patients in the paroxetine group showed improvement as shown on the Clinical Global Impression global improvement rating compared with the placebo group (78% vs 51%; odds ratio, 3.66; 95% confidence interval, 2.22-6.04; \( P < .001 \)). Compared with placebo, paroxetine treatment significantly (\( P < .001 \)) improved the symptoms of social anxiety as shown on the Liebowitz Social Anxiety Scale, Social Phobia Inventory, Sheehan Disability Scale, Symptom Checklist-90 score, and EuroQol visual analogue scale, indicating decreased disability and increased well-being. Paroxetine was well tolerated.

Conclusion: Paroxetine is an effective long-term treatment for social anxiety disorder.

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Social anxiety disorder (social phobia) is characterized by fear of social situations involving performance or interaction. Fears may be limited to a few specific situations, such as eating or writing in front of others, or may be related to more generalized social interactions, such as dating or talking to colleagues. The disorder causes significant disability and substantially disrupts quality of life. It often has a serious negative effect on academic achievement and career development. Patients with social anxiety disorder also frequently have comorbid psychiatric disorders, such as depression and substance abuse disorders, further exacerbating the functional impairment.

Social anxiety disorder affects up to 13% of individuals at some point in their life. Persons with this condition may abuse alcohol or other drugs or contemplate suicide to escape the distressing effects of this condition. These data highlight the importance of recognizing and effectively treating social anxiety disorder.

In addition to cognitive behavioral therapies, several pharmacotherapies have been used for the treatment of social anxiety disorders, including monoamine oxidase inhibitors (eg, brofaromine, phenelzine sulfate, and moclobemide)\(^{11,12} \); \( \beta \)-blockers (eg, atenolol)\(^{12} \); benzodiazepines (eg, clonazepam)\(^{13} \); and selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine hydrochloride, fluvoxamine maleate, and sertraline hydrochloride).\(^{14-16} \) The SSRIs, however, have been recommended as first-line treatment for social anxiety disorder by virtue of their efficacy and tolerability.\(^{14-16} \) The efficacy of paroxetine in the acute treatment of social anxiety disorder...
has been clearly demonstrated in four 12-week, randomized, placebo-controlled studies involving 953 patients, and paroxetine is the first and only SSRI indicated for the treatment of this disorder. Similarly, the efficacy of sertraline and fluvoxamine in treating social anxiety disorder is evident from results of short-term studies (10-12 weeks). However, as social anxiety disorder is a chronic, disabling condition, the International Consensus Group on Depression and Anxiety has recommended that medication should be continued for a minimum of 12 months for treatment to have maximum benefit. Despite such expert recommendations, little work on the efficacy and tolerability of maintenance pharmacotherapy in social anxiety disorder has been conducted to date. A recent 20-week placebo-controlled study of sertraline (50-200 mg/d) in 204 patients showed the superiority of the SSRI over placebo in the treatment of social anxiety.

The present study was conducted to assess the effectiveness of paroxetine maintenance treatment in the prevention of relapse in patients with social anxiety disorder and included a single-blind acute treatment phase (12 weeks), followed by a randomized, double-blind, maintenance treatment phase (24 weeks).

METHODS

PARTICIPANTS

Outpatients were recruited from 43 clinics in 10 countries (Belgium, Brazil, Canada, France, Ireland, Italy, the Netherlands, South Africa, Spain, and the United Kingdom).

Eligible patients were aged at least 18 years and had a primary diagnosis of social anxiety disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV], code 300.23), as assessed by psychiatrists and other qualified health care professionals who received training using the Mini-International Neuropsychiatric Interview for DSM-IV. No attempt was made to categorize patients as having generalized vs nongeneralized social anxiety disorder. Those older than 65 years had to be able to tolerate a paroxetine starting dosage of at least 20 mg/d and to be without renal or hepatic impairment. Patients were excluded from the study if they had any Axis I disorder other than generalized anxiety disorder or agoraphobia (such as major depression, obsessive-compulsive disorder, or body dysmorphic disorder) during the 6 months before screening, a primary diagnosis of panic disorder during the previous 6 months, or a history of schizophrenia or bipolar affective disorder. Substance abuse (during the previous 3 months) or dependence (during the previous 6 months) according to DSM-IV criteria also excluded patients from the study. Concomitant therapy with β-adrenergic blockers, monoamine oxidase inhibitors, benzodiazepines, or other psychoactive medication (except chloral hydrate) or psychotropic or antidepressant therapy within 14 days of baseline (4 weeks for fluoxetine and monamine oxidase inhibitors) also precluded patients from entering the study. Patients who had previously received a therapeutic dosage of an SSRI for social anxiety disorder for an adequate duration to achieve a clinical response (equivalent to fluoxetine 20-40 mg/d for 5 months) or who had received paroxetine for any indication but had not responded were also prevented from participating in the study.

Patients who satisfied the selection criteria but whose Clinical Global Impression (CGI) severity of illness score decreased by at least 2 points during the acute treatment phase, resulting in a final score of 3 or less, could enter the 24-week double-blind treatment phase. The CGI severity of illness scale rates the absolute severity of a patient’s illness and does not involve reference to a baseline score.

Randomization occurred at the end of the single-blind treatment phase (week 12). A computer-generated randomization list was used to randomize patients in a 1:1 ratio to receive either paroxetine or placebo. Each investigator and center was allocated a block of consecutively numbered treatment packs, which were dispensed in strict sequential order. The paroxetine and placebo capsules were identical in appearance and packaged to maintain blinding in all phases of the study. Eligible patients were identified throughout the study by their study and patient numbers allocated at the screening visit.

Responders at week 12 then continued with paroxetine or gradually switched to placebo for a further 24 weeks, depending on their randomization. Patients receiving paroxetine were to remain at the same dosage level as that of week 12. However, a single dosage reduction was permitted in the event of adverse experiences.

Patients receiving placebo were dispensed medication to reduce their paroxetine dosage gradually during a 3-week down-titration period, depending on their level of medication at week 12, and then received placebo for the remainder of the study. The daily dosage was reduced by 10 mg each week to 20 mg/d and was maintained at this dosage until week 15, after which...
all patients randomized to placebo received placebo medication for the remainder of the study (Figure 1).

A 3-week down-titration period was also used for all patients on completion of the trial or on early withdrawal from the study. Down-titration periods will be referred to as such and will not be numbered by week.

Patients who completed the study attended the clinic on up to 15 occasions during 36 weeks after screening for assessments of safety and efficacy.

ASSESSMENTS

The primary efficacy end point was the proportion of patients relapsing during the maintenance phase. Relapse was defined as an increase of at least 2 points from the CGI severity of illness score recorded at week 12 (end point of the acute phase), resulting in a score of 4 or higher, or withdrawal because of lack of efficacy.

The secondary efficacy end points were time to relapse; percentage of improvers, as assessed by a CGI improvement score of “much improved” or “very much improved” at week 36; mean change in Liebowitz Social Anxiety Scale (LSAS) score from week 12 to week 36; and mean change in Social Phobia Inventory score from week 12 to week 36 (trial end point).

Assessments using the CGI improvement scale, LSAS, and Social Phobia Inventory were made at baseline; at weeks 1, 2, 3, 4, 8, 12, and 16 during the acute phase of the study; and at weeks 16, 20, 24, 28, 32, and 36 during the 24-week maintenance treatment phase. In addition, an evaluation using the Sheehan Disability Scale was made at each visit.

Symptom Checklist-90 (SCL-90) and EuroQol (EQ-5D) questionnaires were completed at baseline, at week 12 (end of the acute phase), and during the maintenance phase at weeks 24 and 36 (study end point). The SCL-90 is a psychiatric symptom checklist, while the EQ-5D provides a measure of quality of life by assessing mobility; presence of depressive symptoms, presence of pain or discomfort; ability for self-care; and performance of usual activities.

Hamilton Depression Rating Scale assessments were performed at baseline, at the end of the acute phase (week 12), and at the end of the study (week 36) to evaluate the presence of depressive symptoms.

To assess tolerability, adverse events were monitored throughout the study by asking patients nonleading questions, such as “Have you felt different in any way since your last visit?” A full physical examination, including the determination of biochemical and hematological variables, was performed at the screening visit and at the end of the study.

STATISTICAL ANALYSES

Assuming that 40% of patients continued into the long-term phase, 386 randomized patients were required to give 90% power (at $\alpha = .05$) to detect a difference between maintenance phase relapse rates of 25% and 50%. Assuming a 15% dropout rate (at phase 386 randomized patients were required to give 90% power to detect a difference between discontinuation rates of 25% and 50%). Assuming that 40% of patients continued into the long-term phase, 386 randomized patients would be required to give 90% power to detect a difference between discontinuation rates of 25% and 50%.

Paroxetine and placebo were compared using 2-tailed tests; statistical significance was set at $P \leq .05$. Categorical efficacy end points were analyzed by logistic regression; continuous variables were subjected to analysis of variance.

For the primary efficacy variable and the secondary efficacy variables relating to relapse, withdrawals, and CGI improvers, the proportion of relapsers was analyzed using logistic regression (PROC LOGISTIC in SAS; SAS Institute Inc). The change from double-blind baseline in LSAS, Social Phobia Inventory, and Sheehan Disability Scale scores was analyzed using parametric analysis of variance (PROC GLM in SAS Institute Inc). The proportion of patients withdrawing from the study because of lack of efficacy in each treatment group was compared using a $x^2$ test (PROC FREQ in SAS Institute Inc). For time to relapse, comparisons of survival times between treatment groups during the 24-week double-blind treatment phase were made using a nonparametric log-rank test (PROC LIFETEST in SAS Institute Inc).

All the data collected from the EQ-5D were compiled. The overall score of the SCL-90 and EQ-5D at the end of the 24-week double-blind treatment phase was not analyzed using analysis of covariance as planned, as the data did not meet the required distributional assumptions for the analysis. Nonparametric analysis (Wilcoxon rank sum test with nonparametric confidence intervals [CIs]) was conducted on changes in SCL-90 scores at week 36.

Summary statistics for EQ-5D utility scores were tabulated for the 12-week single-blind baseline and change from single-blind baseline and for the double-blind baseline and change from double-blind baseline. No formal hypothesis testing was performed on the EQ-5D utility scores. Tabulations of patient numbers and percentages for the EQ-5D health profile were produced at weeks 12, 24, and 36.

To distinguish between the effect of paroxetine on social anxiety and depressive symptoms, analyses of treatment effect were adjusted for the effect of baseline Hamilton Depression Rating Scale score. Analyses were also adjusted for treatment center.

There were no substantial differences in the methods used to recruit patients across sites. Investigators from all sites received identical training in the Mini-International Neuropsychiatric Interview and LSAS before initiation of the study. The consistency of rating across sites was addressed by means of the inclusion of the site as a covariate in the analysis.

Significant heterogeneity between centers was observed, and subsequent analyses were conducted to investigate this interaction. The analysis of the primary efficacy variable revealed a significant center group by treatment interaction effect (ie, the magnitude of the difference between the treatment groups was not consistent between center groups). However, further analysis confirmed that this interaction did not compromise the overall significant treatment effect found for the primary efficacy variable. The analysis of the data from Canada, Europe, and South Africa and the analysis for the patients from Brazil both showed a significant treatment effect in favor of paroxetine use, confirming the initial result.

Results are presented for the intention-to-treat population, which included all patients who received at least 1 dose of randomized treatment and had 1 valid efficacy assessment during the maintenance phase of the study. Primary inferences were based on the intention-to-treat last observation carried forward end point.

![Figure 1. Study design.](https://archpsyc.jamanetwork.com/)
STUDY POPULATION

Four hundred eighty-three patients were screened for eligibility, and 437 entered the acute single-blind phase of the study, of which 435 were included in the intention-to-treat population. The patient population was recruited from 10 treatment centers; the largest number of patients was recruited by a center in Brazil (32 in the paroxetine group and 33 in the placebo group) and the smallest from a center in Ireland (2 in the paroxetine group and 1 in the placebo group).

Of the 437 patients who entered the single-blind phase, 323 continued into the double-blind maintenance phase of the study. Of these, 162 were randomized to receive paroxetine and 161 were to receive placebo (Figure 2). The reasons for patient withdrawals during the single-blind phase were adverse events, lack of efficacy, deviation from protocol, lost to follow-up, and other.

The mean±SD daily dosage of paroxetine for all patients completing the 12-week single-blind phase (n=377) was 37.21±10.91 mg. At the start of the 24-week, double-blind, randomized phase, the mean±SD daily dosage for patients taking paroxetine who completed the randomized phase (n=136) was 36.54±11.31 mg.

The treatment groups were well matched with regard to baseline patient characteristics at the start of the double-blind maintenance phase (week 12) (Table 1).

Of the 323 patients continuing into the double-blind maintenance phase of the study, 257 (136 paroxetine-treated [84%] and 121 placebo-treated [75%] patients) completed the study. Sixty-six patients withdrew (26 paroxetine-treated [16%] and 40 placebo-treated [25%] patients) (Figure 2).

RESULTS

Table 1. Demographic Data of Intention-to-Treat Population at the Double-blind Baseline*  

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Paroxetine Hydrochloride Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>(n = 162)</td>
<td>(n = 161)</td>
</tr>
<tr>
<td>Male</td>
<td>77 (47.5)</td>
<td>85 (52.8)</td>
</tr>
<tr>
<td>Female</td>
<td>85 (52.5)</td>
<td>76 (47.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>158 (97.5)</td>
<td>159 (98.8)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.5)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>38.1 (11.7)</td>
<td>38.2 (11.2)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>37.0 (11.5)</td>
<td>37.0 (11.5)</td>
</tr>
<tr>
<td>Baseline psychiatric assessments</td>
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</tr>
<tr>
<td>at week 12, mean (SE)</td>
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<td></td>
</tr>
<tr>
<td>Clinical Global Impression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of illness</td>
<td>2.3 (0.05)</td>
<td>2.2 (0.06)</td>
</tr>
<tr>
<td>Improvement</td>
<td>1.7 (0.05)</td>
<td>1.8 (0.05)</td>
</tr>
<tr>
<td>Liebowitz Social Anxiety Scale</td>
<td>42.3 (1.80)</td>
<td>38.6 (1.79)</td>
</tr>
<tr>
<td>Social Phobia Inventory</td>
<td>21.7 (0.88)</td>
<td>20.7 (0.81)</td>
</tr>
<tr>
<td>Sheehan Disability Scale</td>
<td>7.6 (0.42)</td>
<td>7.1 (0.40)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated.

There were 26 withdrawals (8 in the paroxetine group and 18 in the placebo group) because of lack of efficacy, which is discussed further in the next subsection. Withdrawals because of adverse events were more common in the placebo group (8 [5%]) than in the paroxetine group (3 [2%]). Further reasons for withdrawal included deviation from protocol (4 paroxetine-treated [3%] and 7 placebo-treated [4%] patients), lost to follow-up (6 paroxetine-treated [4%] and 3 placebo-treated [2%] patients), and other (5 paroxetine-treated [3%] and 4 placebo-treated [3%] patients). This last group comprised patients who moved away, those who withdrew consent, and those suspected of being pregnant.

Efficacy

Significantly fewer patients relapsed in the paroxetine group than in the placebo group (14% vs 39%; odds ratio, 0.24; 95% CI, 0.14-0.43; P<.001). The odds of patients relapsing were 2.78 times greater in the placebo group compared with the paroxetine group.

Withdrawal because of relapse was more common in the placebo group than in the paroxetine group (18 [11%] vs 8 [5%]).

Paroxetine was also significantly superior to placebo in terms of time to relapse. Comparison of survival times between the 2 treatment groups using a nonparametric log-rank test gave an estimated hazard ratio of 3.29 (95% CI, 2.80-3.78; P<.001) (Figure 3). This means that the estimated probability of relapse at any particular time was 3.29 times greater for placebo-treated patients than for paroxetine-treated patients. The survival function calculation did not include down-titration data. The last paroxetine-treated patient relapsed 168 days after randomization, and the last placebo-treated patient relapsed 181 days after randomization (Figure 2). Last on-treatment measures for the paroxetine and placebo groups were comparable, 192 days and 190 days, respectively.

Figure 2. Profile of the randomized maintenance phase of the trial.
A significantly greater proportion of patients in the paroxetine group were “much improved” or “very much improved” on the CGI improvement scale at the end of the study compared with the placebo group (78% vs 51%; odds ratio, 3.66; 95% CI, 2.22-6.04; P<.001) (Figure 4).

Liebowitz Social Anxiety Scale, Social Phobia Inventory, and Sheehan Disability Scale assessments revealed significantly greater improvement with paroxetine than with placebo during maintenance treatment (P<.001 for all) (Table 2).

At study baseline, the mean Hamilton Depression Rating Scale score was 6.5 and fell during acute treatment with paroxetine to 4.1 at week 12 (end of acute treatment phase). From week 12 to the study end point (week 36), there was a slight further reduction in these scores of 0.08 points in the paroxetine group and 0.83 points in the placebo group (Table 2). These data confirm that patients were experiencing only minimal depressive symptoms throughout the study.

There was marked improvement in median SCL-90 score (−38.1) from baseline to the end of the acute phase, with only headache (11%) in the paroxetine group and 23% of male patients), nausea (24%), headache (20%), somnolence (17%), insomnia (17%), and sweating (11%). Dizziness occurred in 6% of patients.

The prevalence of adverse effects during the 24-week maintenance phase was markedly lower than during the acute treatment phase, with only headache (11%) in the paroxetine group and headache (16%) and dizziness (15%) in the placebo group occurring in 10% or more of the patients. The prevalence of dizziness in the paroxetine group was 6%.

During the double-blind treatment phase, 23% of patients in the paroxetine group had a significant weight increase (≥7%) compared with 9% in the placebo group; however, similar proportions of patients in the paroxetine and placebo groups (3% and 4%, respectively) had significant weight decrease. No patients from either group withdrew from the study as a result of weight gain or loss.

There were no unexpected findings regarding adverse events, and there were no clinically relevant changes in biochemical or hematological results or in vital signs.

Few patients experienced serious adverse events: 4 patients during the acute single-blind phase (unintended pregnancy, trauma, emotional lability, and kidney pain) and 6 patients during the maintenance phase (2 unintended pregnancies and 1 abortion in the paroxetine group; and 1 unintended pregnancy, 1 pulmonary embolus, and 1 withdrawal syndrome in the placebo group). None of the serious adverse events were considered to be related to study medication. No patients died.

ADVERSE EFFECTS

The most common adverse experiences occurring during the 12-week acute phase were abnormal ejaculation (26% of male patients), nausea (24%), headache (20%), somnolence (17%), insomnia (17%), and sweating (11%).
Paroxetine has proven efficacy in the acute treatment of social anxiety disorder. The primary objective of this study was to evaluate the efficacy of paroxetine as maintenance treatment following acute treatment for this disorder. This was assessed through the proportion of patients relapsing following the end of treatment. The secondary objective was to investigate the long-term safety of paroxetine in the treatment of social anxiety disorder.

This study confirms preliminary indications that the efficacy of paroxetine at the dosage initially required to obtain treatment response is maintained during continued treatment. The odds of relapse were 2.78 times greater for patients who discontinued treatment with paroxetine compared with those who continued receiving paroxetine for a further 24 weeks. The clinical relevance of this difference was reflected in the significant reduction in disease severity and improvement of symptoms in the patients who continued to receive paroxetine. The range of efficacy variables assessed in this study demonstrated a clinically important benefit of continued treatment with paroxetine in the management of social anxiety disorder. The mean LSAS score at baseline suggested moderate to severe manifestations of disorder, but fell to a level consistent with milder disorder after 12 weeks of treatment with paroxetine, and continued to fall further until the end of the study. Studies of short-term pharmacotherapy for social anxiety disorder may therefore underestimate the extent to which initial severe symptoms can improve over time.

A 20-week placebo-controlled study of sertraline (50-200 mg/d) was conducted in patients with generalized social phobia. At the intention-to-treat end point, significantly more patients receiving sertraline (53%) were considered responders according to their CGI improvement scores compared with those receiving placebo (29%). The present study confirms these results and indicates that SSRIs can be considered among the first-line treatments for social anxiety disorder.

The efficacy of paroxetine in reducing the symptoms of social anxiety was maintained over the long term, markedly reducing the risk of relapse. This is in agreement with the International Consensus Group on Depression and Anxiety, which recommends that medication should be continued for a minimum of 12 months, thus minimizing any risk of relapse. Reducing the risk of relapse should improve a patient’s capacity to build social and professional relationships, allowing him or her to lead a more productive and satisfying life. A corresponding improvement in quality of life, as indicated by significantly greater increase in EQ-5D scores with paroxetine treatment than with placebo, was recorded during the study.

Long-term treatment with paroxetine (up to 52 weeks) is well tolerated in patients with depression, obsessive-compulsive disorder, and panic disorder. The pattern of adverse experiences during this study is consistent with that reported in the long-term studies for other indications and confirms the favorable safety profile of paroxetine. In the double-blind treatment phase of this study, fewer patients in the paroxetine
group than in the placebo group withdrew because of adverse effects.

During this study, care was taken to down-titrate patients from paroxetine treatment on study completion, on early withdrawal, or when being switched to double-blind treatment with placebo. Dizziness was noted during the discontinuation periods but was infrequent and generally mild.

A possible limitation of the present study is that the study population was limited to patients with a primary diagnosis of social anxiety disorder according to DSM-IV criteria (code 300.23), and although agoraphobia without a history of panic disorder (code 300.22) was allowed if it was secondary or nonpredominant to social anxiety disorder, patients were excluded from the study if they had any Axis I disorders other than generalized anxiety disorder currently or diagnosed during the previous 6 months. This represents an exclusive population that is unlikely to be similar to that encountered by the physician during the course of his or her consultations. Similarly, on the topic of inclusion criteria, subdivision of the study population into those with generalized vs nongeneralized social anxiety might have been more informative.

It can be concluded that maintenance treatment with paroxetine is an effective and well-tolerated treatment for the prevention of relapse in social anxiety disorder. All efficacy variables in this study showed statistically significant differences compared with placebo, and there were no unexpected findings regarding adverse events, vital signs, or laboratory values. This study also supports earlier expert clinical recommendations to continue pharmacotherapy for an extended period beyond the early improvement achieved in the first 4 months of treatment. Although 24 weeks is a sufficient period from which to conclude that paroxetine is an effective maintenance treatment for social anxiety disorder, further long-term studies lasting a minimum of 52 weeks are required to confirm that paroxetine is effective in the long-term treatment of social anxiety disorder.

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REFERENCES


