A Controlled, Prospective, 1-Year Trial of Citalopram in the Treatment of Panic Disorder

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Background: The objective of this study was to evaluate the efficacy and tolerability of citalopram in the long-term treatment of adult outpatients with panic disorder with or without agoraphobia.

Method: Patients in this double-blind, parallel-group trial were assigned to 1 of 3 fixed dosage ranges of citalopram (10 or 15 mg/day, 20 or 30 mg/day, or 40 or 60 mg/day), 1 dosage range of clomipramine (60 or 90 mg/day), or placebo. After the completed 8-week acute treatment period, the eligible patients could continue the treatment for up to 1 year. Of the 475 patients who were randomly assigned for the short-term trial, 279 agreed to continue double-blind treatment at their assigned doses. The primary efficacy measure used was the Clinical Anxiety Scale panic attack item, and the response was defined as no panic attacks (score of 0 or 1). The other key measures used were the Physician's Global Improvement Scale, the Patient's Global Improvement Scale, and the Hamilton Rating Scale for Anxiety (HAM-A).

Results: In all drug-treated groups, except the group receiving the lowest citalopram dose, the treatment outcome was generally better than with placebo. As determined by a life table analysis of response, the probability of response during the 12 months was significantly greater with all treatment regimens than with placebo ($p < .05$), with citalopram 20 or 30 mg/day demonstrating the best response. Panic attacks tended to disappear in all patients remaining in the study until the end of follow-up. Analysis of the difference in the number of patients in different treatment groups remaining in the study (perhaps the best measure of long-term efficacy) also demonstrated that the patients treated with citalopram in dosage ranges of 20 or 30 mg/day and 40 or 60 mg/day had better response than placebo-treated patients ($p < .0002$ and $p < .004$, respectively). HAM-A and Global Improvement Scale scores also showed that patients treated with active drug showed greater improvement than placebo-treated patients. All treatment groups showed no new or exceptional adverse event clusters.

Conclusion: Citalopram in the dosage range of 20 to 60 mg/day is effective, well tolerated, and safe in the long-term treatment of patients who have panic disorder.

(J Clin Psychiatry 1998;59:528–534)

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Supported by H. Lundbeck A/S, Copenhagen, Denmark.

The authors thank all of the investigators in Finland, the Netherlands, Sweden, and the United Kingdom who contributed to this investigation and Mr. Vagn Pedersen for his valuable work in the preparation of this manuscript.

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Panic disorder, like other anxiety disorders, is a heterogeneous group of psychiatric symptoms characterized by fears and worries, nervousness, spells of terror or panic, and several physical symptoms. Unpredictable recurrence of new panic attacks can cause fear leading to severe avoidance behavior and anticipatory anxiety. In addition to severe concurrent disorders such as major depression and suicidal ideation,[1,2] panic disorder has been found to be a serious societal health problem.[3] Studies of maintenance drug treatments in panic disorder are scarce and are often in the form of naturalistic follow-ups after acute treatment trials. Approximately 75% of panic disorder patients with agoraphobia relapsed within 6 months of discontinuing imipramine treatment, but patients continuing with half of the original dose demonstrated a high therapeutic response throughout the 1-year maintenance period.[4]

Noyes et al.[5] reinterviewed their panic patients on average 2.5 years after ending a clinical trial with imipramine. More than 80% were found to be symptomatic at follow-up, but fewer than 50% reported panic attacks and fewer than 40% reported phobic avoidance during the 3 months before the interview. Over 60% of the patients were still taking medication of some kind, but the outcome did not differ substantially from that of the nonmedicated patients. In the Cross-National Collaborative Panic Study of alprazolam and imipramine, some of the patients were followed over 4 years.[6] One fifth of the

patients had a severe, chronic course, but nearly one third remained improved 4 years after the clinical trial. However, 50% of all patients showed recurrent or mild chronic symptoms. This finding shows that panic disorder is a heterogeneous disorder and that the course of treatment will be favorable in a subgroup of patients. In a 6-year follow-up study, 73% of patients were in full or partial remission (67% received antipanic medication), but a substantial proportion showed other psychiatric symptoms, such as major depression, phobic symptoms, or alcohol abuse.[2] Further, it has recently been found that patients with comorbid Axis I disorders are at risk to commit suicide.[7] These findings accentuate the importance of assessment and follow-up of overall psychopathology in patients with panic disorder.

Several classes of drugs have been found to be effective in the treatment of panic disorder: tricyclic antidepressants, monoamine oxidase inhibitors, high-potency benzodiazepines, and selective serotonin reuptake inhibitors (SSRIs). The consistent outcome of several new controlled trials is that SSRI drugs are efficient and well tolerated in the short-term treatment of panic disorder.[8,9–13] They are considered to be superior to alprazolam and imipramine[14] and are suggested as first-choice treatments.[15] There have been few long-term studies with SSRI agents in panic disorder, but paroxetine has been demonstrated to be efficacious at a minimum effective therapeutic dosage of 40 mg/day.[16]

Citalopram is one of the most potent and the most selective of the SSRIs.[17] Citalopram has a well-established antidepressive action, and it has been reported to have antiobsessive properties.[18] The antidepressant efficacy and favorable adverse event profile have been well established in a series of open and controlled trials. Meta-analyses of trials have shown that the minimum effective dosage is 20 mg/day, but if required, the dosage can be increased to 60 mg/day.[19]

The therapeutic efficacy of citalopram in panic disorder was first suggested by Humble and Wistedt[20] and supported by another open pilot trial.[21] In both of these trials, a once-daily dose of 40 mg was most often used. The latter pilot trial preceded a large dose-finding trial that was recently reported.[22] The results of this 8-week dose-finding trial showed that citalopram was effective in the management of panic disorder and was statistically superior to placebo and similar to clomipramine in efficacy, at dosages between 20 mg/day and 60 mg/day.

To establish whether efficacy is maintained or even improved with further long-term treatment, a trial was performed by continuing eligible patients from the 8-week dose-finding study in a double-blind fashion for up to 1 year. In the continuation study, monitoring of the clinical safety and tolerability of long-term treatment with citalopram in panic disorder patients was also performed. The current report describes the safety and efficacy of citalopram in this continuation study.

METHOD

Subjects

Patients who completed the 8-week short-term study[22] were eligible to enter this dose-finding, double-blind, placebo- and clomipramine-controlled long-term trial with treatment for up to 1 year (total time from start of 8-week study). In addition to completing the short-term period, patients were included who, according to the investigator's judgment, would be expected to benefit from continued treatment. The study followed the ethical guidelines laid down by the Declaration of Helsinki (with amendments) and was approved by the local ethical committee of each participating center. Informed consent was obtained from each participating subject, who retained the right to withdraw from the study for any reason at any time.

The study population consisted of patients of either sex, aged between 18 and 65 years, who were diagnosed with panic disorder, with or without agoraphobia, according to DSM-III-R classification.[23] They had to be free from severe depressive symptoms, with a score of less than 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS).[24]

The exclusion criteria included pregnancy or intention to become pregnant, depression, organic brain disease, neurologic disease, drug and/or alcohol abuse during the past year, other severe psychiatric or somatic disorders, orthostatic hypotension, and hypersensitivity to test preparations. No concomitant psychotropic drugs were allowed.

Patient Disposition

Of the 475 patients (143 men and 332 women with mean age of 38 years and range of 18 to 63 years) who were included by 22 centers in 4 countries in the short-term trial, 279 agreed to take part in the continuation phase and 91 stopped at week 8. Also, 105 patients were excluded already during the short-term trial mainly due to early dropout.[22] Of the continuing 279 patients, 179 completed the 12-month treatment period. The efficacy analysis population consisted of 258 patients. Eighteen of the patients completing the 12-month treatment period and 3 who did not complete 12 months of treatment had to be excluded from the efficacy analysis because of the use of concomitant psychotropic agents.

Mean age of the efficacy analysis population was 39 years (range, 18–61 years) comprising 68 males and 190 females who all were white. There were no major differences between treatment groups. One hundred patients withdrew prematurely from the study, and the summary of withdrawals is shown in Table 1.

Study Design and Assessments

The study was designed as a blinded optional continuation for up to 1 year of a randomized, double-blind, placebo- and clomipramine-controlled short-term trial in

Table 1. Summary of Premature Discontinuation by Reason During Continuation Treatment (Month 2 to Month 12)

	Placebo (N = 41)		Citalopram 10 or 15 mg/d (N = 56)		Citalopram 20 or 30 mg/d (N = 63)		Citalopram 40 or 60 mg/d (N = 58)		Clomipramine 60 or 90 mg/d (N = 61)	
Reason for Withdrawal	N	%	N	%	N	%	N	%	N	%
Did not show up	0	0	3	5	0	0	2	3	4	7
Refused continued treatment	3	7	2	4	2	3	3	5	1	2
Study criteria not met	1	2	0	0	0	0	1	2	1	2
Ineffective[a]	6	15	3	5	2	3	4	7	5	8
Improvement/recovery	3	7	3	5	2	3	3	5	3	5
Noncompliance	1	2	2	4	2	3	0	0	0	0
Adverse events	1	2	4	7	3	5	1	2	4	7
Other reasons	3	7	7	13	3	5	4	7	8	13
Total	18	44	24	43	14	22	18	31	26	43
Remaining in trial at end of month 12[b]	23	13	32	18	49	27	40	22	35	20

[a]p = .04, Fisher exact test for overall difference between placebo and citalopram groups.
[b]Percentages are of the total number of patients remaining at the end of month 12.

which patients were randomly assigned to 1 of 5 treatment groups: citalopram 10 or 15 mg/day, 20 or 30 mg/day, or 40 or 60 mg/day; clomipramine 60 or 90 mg/day; or placebo.[22] Patients completing the 8-week short-term phase of the study were continued on their previously assigned dose. As in the short-term study, of the group that took citalopram 10 or 15 mg/day, about 40% of the patients took 10 mg/day, and in the groups that received 20 or 30 mg/day and 40 or 60 mg/day, between 50% and 60% received the lower dosage.[22] Assessments were made after 3, 6, 9, and 12 months of treatment.

The response to treatment was defined as no panic attacks in the week prior to assessment as measured by the Clinical Anxiety Scale (CAS) panic attack item.[25] The panic attack item from the CAS is scored from 0 to 4, and response is defined as no panic attacks (score = 0: no episodic sudden increase in the level of anxiety; or score = 1: episodic slight increases in the level of anxiety that are only precipitated by definite events or activities). The other efficacy measures were the overall improvement measured by the Physician's Global Improvement Scale (PHYGIS), which is investigator-rated, and the Patient's Global Improvement Scale (PATGIS), which is patient-rated.[26] Moreover, the general psychological well-being was scored by the Hamilton Rating Scale for Anxiety (HAM-A),[27,28] and depression was evaluated by the MADRS.[24]

Safety and tolerability assessments included vital signs (blood pressure and pulse rate), weight, hematology, and clinical chemistry tests. Adverse events, either observed by the investigator or reported by the patient after being asked an open question, were coded according to World Health Organization (WHO) terminology and recorded. Any concomitant medications were recorded et each visit.

Statistical Methods

Efficacy was assessed on both the efficacy analysis (N = 258) and completer (N = 161) populations. Analysis of both populations gave largely similar results. Efficacy was determined using total scores, and the difference between baseline and the score on treatment, for both primary and secondary efficacy parameters. The primary efficacy parameter was treatment success, defined as no panic attacks (score of 0 or 1 on the CAS panic attack item). The Fisher exact test was applied to test for significance of differences between citalopram treatment groups and placebo. Secondary parameters were tested by means of the ANCOVA model. Curves for the cumulative response rates in the treatment groups have been constructed using the actuarial method and have been compared pairwise using the log-rank test. The overall retention of patients in the trial was analyzed by Kaplan-Meier curves and the Cox proportional hazards model, where the treatment groups were compared first as a whole and then pairwise.

Crude incidence rates of adverse events were calculated at baseline and thereafter for the safety population (all patients included in the continuation phase). Global assessments of adverse events were compared between treatment groups using the Fisher exact test.

RESULTS

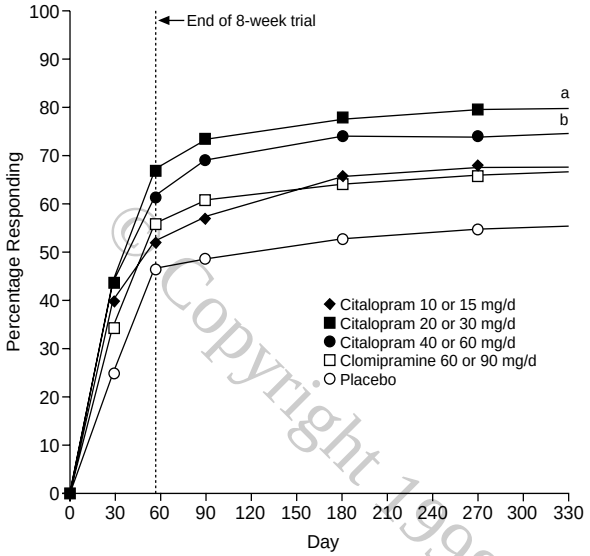
Patients

The withdrawal analysis showed that the proportion of patients who discontinued before month 12 owing to ineffectiveness was significantly higher in the placebo group than in the citalopram groups (Table 1).

Efficacy

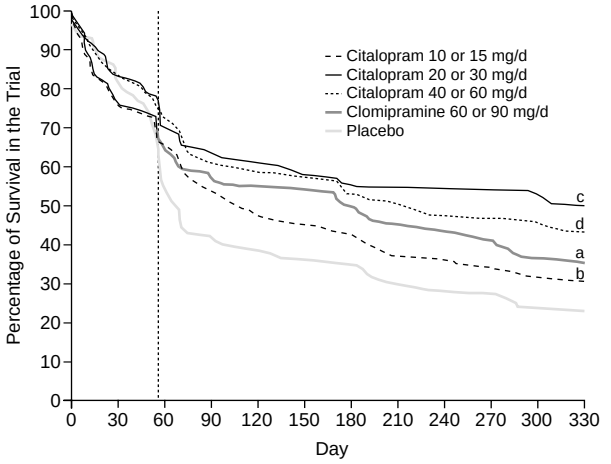
The cumulative response rates for the original intent-to-treat population for the whole 12-month trial period as measured with the CAS panic attack item are presented in Figure 1. The citalopram dose groups receiving 20 or 30 mg/day and 40 or 60 mg/day showed highly significantly

Figure 1. Cumulative Response Rates, Defined With Clinical Anxiety Scale Panic Attack Item, for the Original Intent-to-Treat Population*



*Response defined as no panic attacks. Dotted vertical line indicates the end of the short-term trial.
[a]Citalopram 20 or 30 mg/day vs. placebo, p = .001.
[b]Citalopram 40 or 60 mg/day vs. placebo, p = .003.

Figure 2. Retention of Patients in the Study as Shown by Cumulative Survival Curves*



*Dotted vertical line indicates the end of the short-term trial.
[a]Clomipramine vs. placebo, p < .065.
[b]Citalopram 10 or 15 mg/day vs. placebo, p < .25.
[c]Citalopram 20 or 30 mg/day vs. placebo, p < .0002.
[d]Citalopram 40 or 60 mg/day vs. placebo, p < .004.

better response than patients receiving placebo (p = .001 and p = .003, respectively). Also, low-dose citalopram and clomipramine showed some gain (p < .05). The gains seemed to level off between months 6 and 9, with no further improvement. The optimal dose of citalopram appeared to be 20 or 30 mg/day.

The same order of the treatment groups can be seen in Figure 2, where the retention of the patients in the trial is shown. The highest percentage of patients was retained in the group receiving citalopram 20 or 30 mg/day followed by the group receiving citalopram 40 or 60 mg/day. When compared with the placebo group, the differences were highly significant (p < .0002 and p < .004, respectively). The clomipramine group and the group receiving citalopram 10 or 15 mg/day did not differ significantly from the placebo group. This result clearly shows that the best acceptability of treatment by the patients was in the medium-dose–range citalopram group.

At the end of the 1-year treatment period, almost all of the patients who remained in the study, regardless of treatment, were free from panic attacks when measured with the CAS panic attack item. The CAS panic attack item results analyzed by visit month showed significant differences compared with the placebo group at month 3 for groups receiving citalopram 20 or 30 mg/day, 40 or 60 mg/day, and the clomipramine group, and for the citalopram high-dose group at month 6.

The PHYGIS and PATGIS results are shown in Table 2. There was a significant difference between active and placebo groups at various times throughout the 12-month period on these measures. The outcome of the other efficacy assessments (HAM-A and MADRS) were generally comparable to the PHYGIS and the PATGIS results. Month 3 and month 6 assessments showed greater gains from active treatment relative to placebo than those for either month 9 or month 12. Figure 3 shows the results of the HAM-A during the 12-month study period. The relative efficacy of placebo improved after the month 6 assessment. At month 6, all of the active medication groups were significantly superior to placebo. Groups receiving citalopram 20 or 30 mg/day and 40 or 60 mg/day and the clomipramine group were significantly superior to the placebo group also at month 3, but at endpoint the difference was nonsignificant. However, for item 3, "fears," significant differences compared with the placebo group were seen in all citalopram dose groups (p = .046, .006, .030, respectively, for the low-, medium-, and high-dose groups). Comparison of the clomipramine group with the placebo group did not reach the level of statistical significance (p = .109).

Tolerability and Safety

As shown in Table 1, a total of 13 patients discontinued owing to adverse events, 8 of these received citalopram, 4 received clomipramine, and 1 received placebo.

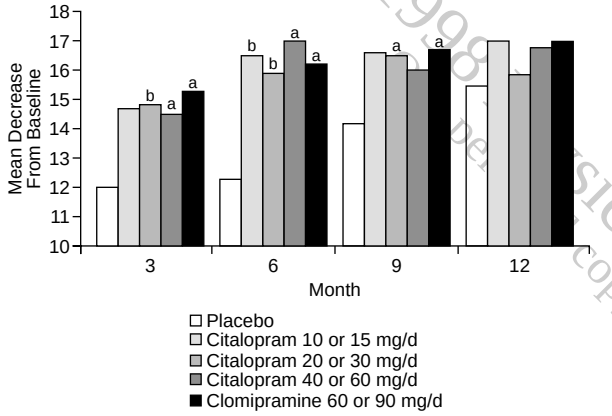
All patients in the study reported at least 1 adverse event. The pattern of previously unreported events showed no clustering in any particular treatment group. In this continuation phase, the incidence of headache was still higher in the citalopram and the placebo groups than in the clomipramine group, whereas tremor and dry

Table 2. Percentage of Response Rates of PHYGIS and PATGIS and Respective p Values When Compared With Placebo at Each Assessment Point*

		Treatment Group							
			Citalopram						
		Placebo	10 or 15 mg/d		20 or 30 mg/d		40 or 60 mg/d	Clomipramine	
Measurement	Assessment Point	Percent Change	Percent Change	p Value vs Placebo	Percent Change	p Value vs Placebo	Percent Change	p Value vs Placebo	Percent Change	p Value vs Placebo
PHYGIS	After 3 months	31	58	.016[a]	67	.001[a]	57	.025[a]	71	< .001[a]
	After 6 months	38	69	.079	76	.009[a]	75	.031[a]	65	.036[a]
	After 9 months	52	81	.432	84	.024[a]	86	.091	78	.071
	After 12 months	68	78	.476	83	.059	85	.016[a]	89	.023[a]
PATGIS	After 3 months	37	55	.037[a]	62	.004[a]	62	.052	64	.014[a]
	After 6 months	46	65	.146	78	.006[a]	74	.035[a]	74	.031[a]
	After 9 months	41	69	.215	89	.008[a]	75	.116	70	.063
	After 12 months	60	70	.394	88	.107	86	.019[a]	83	.046[a]

*All percent increases are increases from baseline in scores 9 or 10 on the PHYGIS or PATGIS. Abbreviations: PATGIS = Patient's Global Improvement Scales, PHYGIS = Physician's Global Improvement Scale.
[a]Statistically significant difference vs. placebo.

Figure 3. Decrease in Mean Hamilton Rating Scale for Anxiety (HAM-A) Scores From Baseline (Day 0)



[a]p < .05 vs. placebo.
[b]p < .01 vs. placebo.

mouth were significantly more frequent in the clomipramine group than in the citalopram groups. The reported adverse events that differed significantly (or approached significance) from each other or from placebo in the treatment groups are shown in Table 3. The statistical analysis is based on the combined 3 citalopram treatment groups. Very few patients discontinued treatment because of adverse events (see Table 1).

There were no clinically important changes in vital signs or laboratory values considered to be related to treatment with citalopram.

DISCUSSION

In the continuation period, the cumulative response rates as measured on the CAS panic attack item showed further increase and continued to be significantly higher in all active treatment groups compared with placebo. The measures of cumulative response rates and overall retention of patients in the trial clearly show the benefit of long-term treatment for panic disorder. Our findings were quite similar to those of the earlier controlled long-term trials, as the response rate in our study appeared high at the end of the long-term trial period irrespective of treatment regimen. In two 8-month placebo-controlled prospective trials comparing alprazolam, imipramine, and placebo,[29,30] the patients who remained in the trials showed equally good results at month 8 for the effect on panic attacks irrespective of treatment group, but for several other measures active treatment was superior to placebo.

Results for other efficacy parameters in this study showed a somewhat different pattern when compared with CAS results. Results of the PHYGIS and PATGIS show greater efficacy for citalopram in dosages between 20 and 60 mg/day and for clomipramine throughout the treatment period, either demonstrating statistical significance or a trend favoring active treatment. Our findings are therefore well in line with previous clinical trial results with panic disorder, that patients may no longer have panic attacks but may still suffer from other core symptoms,[31] which should be assessed in determining efficacy in considerations of response and remission. It has also been suggested that occurrence of panic attacks is not an ideal measure of treatment outcome in panic disorder with agoraphobia, as global improvement is more related to the reduction of avoidance than decrease in number of panic attacks.[32] Our HAM-A results compared with the CAS panic attack item results after 6 months reflected this difference, as only the group taking citalopram 40 or 60 mg/day differed significantly from the placebo group in the CAS panic attack item results, whereas all of the active treatment groups, including the group receiving the lowest citalopram dose, differed significantly from the placebo group when measured with the HAM-A scale. Moreover, all active treatments, including 10 or 15 mg/day of citalopram, had a significantly better effect on "fears" than placebo, reflecting a reduction in phobic anxiety.

Table 3. Adverse Events That Differed Significantly ($p < .05$) or Approached Significance ($p < .1$)

	Treatment Group											
			Citalopram						Clomipramine		p Value[a]	
	Placebo (N = 41)		0 or 15 mg/d (N = 56)		20 or 30 mg/d (N = 63)		60 or 90 mg/d (N = 58)		All (N = 177)		60 or 90 mg/d (N = 61)		Citalopram vs Clomipramine	Citalopram vs Placebo
Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%		
Increased sweating	3	7	8	14	17	27	14	24	39	22	18	30	.30	.03
Headache	l9	46	30	54	29	46	26	45	85	48	17	28	< .01	.86
Tremor	2	5	0	0	4	6	3	5	7	4	13	21	.00	.68
Dry mouth	12	29	14	25	13	21	14	24	41	23	25	41	.01	.42
Somnolence	2	5	9	16	8	13	8	14	25	14	15	25	.07	.12

[a]p Value from the Fisher exact test.

All follow-up or continuation studies present problems in the interpretation of the efficacy data, because the number of patients remaining in a treatment group is determined by many factors, including patients' subjective assessment of well-being (acceptability) resulting from treatment itself, active or otherwise. Investigators may tend to withdraw patients at early stages of the trial if the patients do not benefit at all. In addition, nonresponders tend to withdraw themselves from the study. It should be mentioned that in the present study only a few patients withdrew from the trial owing to complete recovery. Nonacceptability can be defined as total withdrawal from the study, which occurs when the patient or the clinician no longer believes that the drug effects are sufficient and/or that adverse events are tolerable. This occurrence means that the largest proportion of patients should remain in the most effective treatment group. This hypothesis is supported by this study. At month 12, the patients remaining in each treatment group reflected the results of the short-term trial, i.e., that citalopram 20 or 30 mg/day is the optimum treatment regimen, followed by citalopram 40 or 60 mg/day, clomipramine, citalopram 10 or 15 mg/day, and placebo. The effective dose range in panic disorder seems to be the same that is used in treatment of major depression. This finding is in contrast to results with paroxetine, which indicate that the minimum effective dose in treatment with panic disorder is 40 mg/day.[16]

The proportion of patients who discontinued treatment prematurely owing to ineffectiveness was significantly higher in the placebo group than in the citalopram groups and was greater than the proportion in any treatment group withdrawing owing to an adverse event. The finding that withdrawal from the continuation phase was more closely correlated with lack of efficacy than with adverse events supports the hypothesis that patients remaining in the study benefited from treatment. When compared with results of the large alprazolam second phase trial,[33] the early dropout rate, especially due to inefficacy, was clearly lower in our preceding short-term trial.[22] Thus, many of the problems of panic disorder trials discussed by Marks et al.,[34,35] which might bias the results, seem to have been avoided in this trial, as the dropout rate was more gradual and the overall retention in the trial was high, even in the placebo group.

It is not surprising that in a 12-month study many patients experienced some kind of adverse events. Some of these, including events such as acute infections, were reported although they are not drug related. In the preceding short-term trial,[22] some patients had sexual side effects such as anorgasmia, which seemed to be dose related and disappeared with long-term treatment. This finding is understandable in light of the fact that sexual side effects either disappear in long-term treatment or that the patients learn to manage better with them. Otherwise, the pattern of adverse events is similar to that in the short-term phase,[22] and tremor and dry mouth were still significantly more frequent in the clomipramine group than in the citalopram groups.

The results of this continuation study support the short-term evidence that citalopram in dosages of 20 to 60 mg/day and also clomipramine, 60 or 90 mg/day, are effective in the treatment of panic disorder with or without agoraphobia over a period of 1 year and indicate that the response rate improves beyond 2 months of treatment. The dose range of 20 or 30 mg/day was obviously the optimal range in the majority of patients. All 3 dose levels of citalopram and clomipramine were well tolerated over the treatment period of 1 year, reflecting the available safety data from previous long-term depression trials.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), imipramine (Tofranil and others), paroxetine (Paxil).

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