A Double-Blind, Multicenter Study in Primary Care Comparing Paroxetine and Clomipramine in Patients With Depression and Associated Anxiety

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Background: 60%–90% of patients with a primary diagnosis of depression also experience symptoms of anxiety, and such patients have a poorer prognosis than those with uncomplicated depression. The serotonin selective reuptake inhibitors have demonstrated efficacy in the treatment of both depression and certain anxiety states. Furthermore, in a meta-analysis of the paroxetine clinical trial database of 2963 patients in whom depression predominated, there was a concomitant reduction in the Hamilton Rating Scale for Depression anxiety factor. The purpose of the present study was to prospectively compare the efficacy of paroxetine and clomipramine in patients specifically selected for coexisting depression and anxiety.

Method: This was a 12-week, double-blind, parallel-group trial comparing paroxetine 20–40 mg/day with clomipramine 75–150 mg/day in 1002 patients with a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20 and a Clinical Anxiety Score (CAS) ≥ 11 after a 3–7 day placebo run-in period.

Results: Both paroxetine and clomipramine reduced the MADRS and CAS ratings at 2, 6, and 12 weeks and at endpoint, with no significant differences between treatment groups at any time point. CGI severity of illness and global improvement ratings were also similar throughout the trial; however, there was a statistically significant difference in the CGI efficacy index at 6 weeks and at endpoint, favoring paroxetine ($p = .015$ and $p = .015$, respectively). Paroxetine resulted in fewer treatment-emergent adverse experiences and related withdrawals than clomipramine ($p = .025$ and $p = .008$, respectively). The number of serious adverse experiences was not significantly different in the paroxetine group compared with the clomipramine group (14 [2.8%] vs. 27 [5.4%]), but did approach statistical significance ($p = .056$). Anticholinergic-emergent adverse experiences were reported twice as frequently by patients in the clomipramine group as in the paroxetine group (36.1% vs. 18.6%).

Conclusion: There was no evidence of any significant difference in efficacy between paroxetine and clomipramine in patients with coexisting depression and anxiety. However, paroxetine was better tolerated as shown by total treatment-emergent adverse experiences, anticholinergic adverse experiences, and withdrawals due to adverse experiences.

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The coexistence of depression and anxiety is common in both primary care and psychiatric patients,[1,2] and it has been estimated that 60%–90% of patients with a primary diagnosis of depression also experience some symptoms of anxiety.[3] Conversely, patients in whom an anxiety disorder is the primary complaint—particularly those with multiple anxiety disorders—often have high levels of depression.[4,5]

Depressed patients with significant levels of anxiety have more severe depressive symptoms, have considerably more functional and psychosocial impairment, and, because their illness has a more chronic course, have a poorer outcome after treatment than depressed patients with low levels of anxiety.[1,5–8] Furthermore, patients with increased levels of psychic anxiety and panic attacks during a depression are more likely to commit suicide in the year following treatment.[9]

The pathogenesis of mood disorders is complex, and affective state is thought to be modulated through interactions between the monoamine neurotransmitters, particularly norepinephrine and serotonin (5-hydroxytryptamine, 5-HT).[10] Drugs that interact with the serotonergic neurotransmitter systems, for example the serotonin selective reuptake inhibitors (SSRIs) are effective antidepressants.[11,12] Moreover, during the early clinical trials of SSRIs in patients in whom the symptoms of depression predominated, it was noted that ratings for anxiety also improved during treatment.[13,14]

The SSRI paroxetine is a potent and highly effective antidepressant that has a more favorable side effect profile than the traditional tricyclic antidepressants.[12,15–17] An analysis of the worldwide clinical trial database on paroxetine convincingly demonstrated that paroxetine improved both depressive and anxious symptomatology ratings on the Hamilton Rating Scale for Depression.[18] Furthermore, the results of a prospective comparative study of the efficacy and tolerability of paroxetine and amitriptyline in relation to depression with associated anxiety in 505 primary care patients have recently been briefly reported.[19] Amitriptyline (an antidepressant with acknowledged anxiolytic properties) and paroxetine did not differentiate in respect to changes in depression and anxiety ratings.

We have prospectively conducted a large, multicenter, comparative study of the efficacy, safety, and tolerability of paroxetine versus the tricyclic antidepressant clomipramine in a population of more than 1000 patients with depressive disorder and significant associated anxiety.

METHOD

This was a randomized, double-blind, parallel-group study conducted at 121 centers in Canada, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, South Africa, and the United Kingdom. The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki, and the protocol and statement of informed consent was approved by an Ethics Committee at each center.

Entry Criteria

Patients of either sex in primary care facilities, aged 18–70 years with a diagnosis of depression (in Ireland the Ethics Committee required that this was a new episode) with associated anxiety and a total score of at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS)[20] (maximum possible is 60) and of at least 11 on the Clinical Anxiety Scale (CAS)[21] (maximum possible is 24), who were considered suitable for treatment with an antidepressant, were enrolled in the study after giving informed consent.

Patients were excluded from the study if they had any severe coexisting disease, any other comorbid psychiatric disorder (e.g., schizophrenia, dementia), or in centers in certain countries, clinically significant abnormalities in hematology or clinical chemistry. Women of childbearing potential who were not using adequate contraceptive measures or who were pregnant or lactating were also excluded. Furthermore, patients who posed a current suicidal risk or who were known to abuse alcohol or illicit drugs were not included in the study. Exclusion criteria relating to previous psychotropic medication included the use of depot neuroleptics in the previous 6 months; lithium or ECT in the past 8 weeks; oral neuroleptics in the previous 2 weeks; and anxiolytics, hypnotics, or β-blockers in the previous 7 days. In Irish centers, patients were also excluded if they had taken any antidepressant in the past 4 weeks, while in the remaining centers patients were not allowed to have received monoamine oxidase inhibitors in the previous 3 weeks, tri- or tetracyclic antidepressants in the past 7 days, or an SSRI in the previous 4 weeks. Patients who were currently receiving oral anticoagulants or Type IC antiarrhythmics or who had received any investigational compound in the past 3 months were also excluded.

Study Medication

Following screening, patients entered a 3- to 7-day placebo run-in phase, after which patients were randomly assigned on the basis of a computer-generated schedule in which treatments were balanced within blocks of consecutive patients to receive double-blind treatment with either paroxetine or clomipramine for 12 weeks.

Each patient took two capsules of active drug or placebo in the morning and evening. Patients in the paroxetine group took 20 mg each morning for the first 4 weeks of the study. According to the patient's clinical response, the dose could then be increased to 40 mg/day for the remainder of the study. In the clomipramine group, patients took 25 mg each evening for 3 days, then 50 mg each evening for 4 days, and then in the second and subsequent weeks 75 mg/day as a divided dose (25 mg in the morning and 50 mg in the evening). If a dose increase was considered necessary after 4 weeks, the dose was increased to 150 mg/day (50 mg in the morning, 100 mg in the evening). The only concurrent psychotropic medication permitted during active treatment was temazepam, up to 20 mg at night as a hypnotic, on an as needed basis.

Efficacy Assessments

After screening, clinical assessments were made at baseline and after 2, 4, 6, 8, and 12 weeks of active treatment. At each visit, MADRS, CAS, and Clinical Global Impressions (CGI)[22] scores were assessed. Compliance was also checked by a routine capsule count and any concurrent medication noted. Patients were asked a non-leading question to elicit details of treatment-emergent adverse experiences. Observed and spontane-

ously reported events were also noted, and sitting blood pressure and heart rate measured. The protocol required that patients with a serious adverse experience (any experience that is fatal, life-threatening, disabling, or incapacitating or results in hospitalization, prolongs a hospital stay, or is associated with congenital abnormality, carcinoma, or overdose) or noncompliance for more than 3 consecutive days were withdrawn from the study. At the 12-week visit, or earlier if the patient withdrew prematurely, a physical examination was also undertaken and urine samples were obtained for laboratory tests. In some centers, a protocol variation allowed for blood samples to be taken at the 12-week visit for laboratory tests; this occurred in countries where paroxetine had not been as extensively marketed in order to provide additional safety data.

The primary efficacy parameters were the changes in the MADRS and CAS total scores at endpoint (the latest time point at which at least 70% of the patients remained in each treatment group). The secondary efficacy variables were the changes in the MADRS and CAS total scores at time points other than endpoint, the proportion of patients with at least a 50% reduction in MADRS and CAS total scores, the change from baseline in the CGI severity of illness scale (where 1 represents normal and 7 extremely ill), the score on CGI global improvement scale (on which 1 represents very much improved and 7 very much worse), and the CGI efficacy index. For the CGI efficacy index, clinical efficacy is assessed against side effects, and final scores can range from +2 to –2, where a positive score denotes overall benefit and a negative score indicates overall disadvantage. Secondary efficacy variables were assessed at Weeks 2, 6, and 12 and, for the proportion of patients with at least a 50% reduction from baseline in MADRS and CAS scores and the change from baseline in CGI severity of illness score, at endpoint also.

Statistical Methods

This study was designed to provide a 90% power to detect a difference of 2.4 points in the MADRS score, with a significance level of .05. Allowing for an attrition rate of 25%, it was planned that 1000 patients would be randomized to active treatment.

Endpoint data were generated from the last available on-treatment assessment for each patient. The endpoint for each analysis was taken as the visit at which at least 70% of the intent-to-treat population (randomized patients with at least one valid on-treatment efficacy assessment) remained. For the primary and secondary efficacy variables, a variable representing each country was constructed and examined for significance of treatment by country interaction ($p = .10$). Each variable was analyzed by analysis of variance (ANOVA) with a significance level of 5%. Each variable was also subjected to nonparametric tests to assess whether the results were independent of the method of analysis. The Cochran-Mantel-Haenszel chi-square test, adjusted for country, was used to analyze the proportions of patients with a 50% reduction in MADRS and CAS total scores. This test was also used to compare the incidence of emergent adverse experiences. The Fisher's exact test was used to compare the withdrawals due to adverse experiences and serious adverse experiences.

RESULTS

Treatment Groups

A total of 1098 patients entered the placebo run-in phase of the study, but 79 patients were withdrawn before randomization. The reasons for withdrawal included noncompliance (N = 17), patient improvement (N = 17), loss to follow-up (N = 14), significant adverse experiences (N = 9), protocol violation (N = 2), concurrent disease (N = 1), abnormal laboratory values (N = 2), and other miscellaneous reasons (N = 17). Therefore, 1019 patients were randomized; 513 to paroxetine and 506 to clomipramine. Seventeen of the randomized patients (13 paroxetine, 4 clomipramine) were excluded from the intent-to-treat population owing to the lack of any efficacy data after the initiation of active therapy.

The baseline characteristics of the 1002 patients (paroxetine, N = 500; clomipramine, N = 502) who formed the intent-to-treat population are presented in Tables 1 and 2. Those characteristics were similar in the two treatment groups. Approximately three quarters of the patients were female, with a mean age of 42.6 years, and more than 95% were white. The majority had had their depression for less than 6 months, with just under half having already received treatment, principally with benzodiazepines and/or standard antidepressants. Three hundred and ninety-one patients (78%) assigned to paroxetine and 376 patients (75%) assigned to clomipramine who met the entry criteria of the study and received at least 6 weeks of medication were included in the per-protocol analyses.

One hundred and three patients (21%) randomly assigned to paroxetine and 142 (28%) randomly assigned to clomipramine withdrew prematurely from the study. The majority of withdrawals occurred between 2 and 8 weeks of active treatment. The reasons for patient withdrawal are presented in Table 3.

Efficacy

The dose of paroxetine was increased from an initial level of 20 mg daily to a maximum of 40 mg daily, and for clomipramine the dose was titrated upward from 25 mg daily to the lower dose level of 75 mg daily and thereafter to a maximum of 150 mg daily if required. Approximately 60% of patients in both treatment groups remained on the lower dose level (paroxetine 20 mg, clomipramine 75 mg), with 41% of paroxetine patients and 33% of clomi-

Table 1. Demographic Characteristics of Intent-to-Treat Population

Characteristic	Paroxetine (N = 500)	Clomipramine (N = 502)
Sex (N, %)		
Male	128 (25.6%)	138 (27.5%)
Female	372 (74.4%)	364 (72.5%)
Age (y)		
Range	18–71	18–70
Mean	43.3	42.0
Race (N, %)		
White	476 (95.2%)	479 (95.4%)
Other[a]	24 (4.8%)	23 (4.6%)
Weight[b] (kg)		
Mean ± SD	68.7 ± 15.5	69.1 ± (15.3)

[a]Other includes black, Asian, Hispanic, other.
[b]Due to missing data, N = 492 for paroxetine group and N = 494 for clomipramine group.

Table 2. Baseline Psychiatric Characteristics of Intent-to-Treat Population*

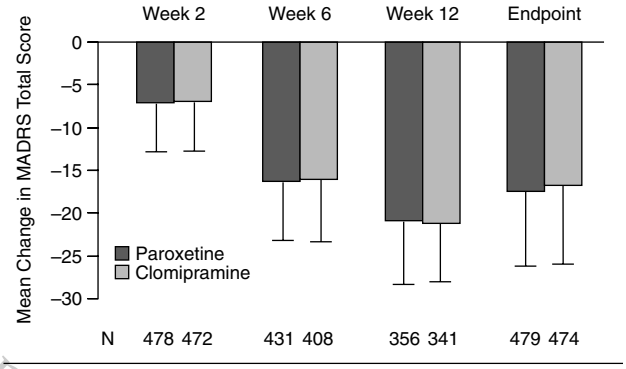
Characteristic	Paroxetine (N = 500)	Clomipramine (N = 502)
Duration of present depressive episode[a] (N, %)		
≤ 6 mo	357 (71.5%)	375 (74.8%)
> 6 mo	142 (28.5%)	126 (25.2%)
Previous treatment for current episode (N, %)		
Any	233 (46.6%)	221 (44.0%)
Benzodiazepines	165 (33.0%)	153 (30.5%)
Standard antidepressants	86 (17.2%)	88 (17.5%)
Previous history of depression	291 (58.2%)	278 (55.4%)
MADRS score (mean ± SD)	29.7 ± 5.4	29.1 ± 5.5
CAS score (mean ± SD)	15.2 ± 2.6	15.2 ± 2.8
CGI severity of illness score (mean ± SD)	4.6 ± 0.8	4.6 ± 0.8

*Abbreviations: CAS = Clinical Anxiety Scale; CGI = Clinical Global Impressions Scale; MADRS = Montgomery-Asberg Depression Rating Scale.
[a]One patient in each group had missing data.

Table 3. Reasons for Withdrawal (Intent-to-Treat Population)

Reason	Paroxetine (N = 500) N	Paroxetine (N = 500) %	Clomipramine (N = 502) N	Clomipramine (N = 502) %
Lack of efficacy/relapse	12	2.4	8	1.6
Lack of efficacy + adverse events	16	3.2	16	3.2
Significant adverse events	41	8.2	69	13.7
Lack of patient compliance	13	2.6	16	3.2
Patient lost to follow-up	7	1.4	13	2.6
Patient improvement	5	1.0	10	2.0
Protocol violation	0	0	4	0.8
Other	9	1.8	6	1.2
Total	103	20.6	142	28.3

Figure 1. Reduction in Mean MADRS Total Score at 2-, 6-, and 12-Week Assessment and Endpoint in the Intent-to-Treat Population



pramine patients receiving the higher dose level. A small percentage of clomipramine patients (6%) did not complete the up-titration phase.

The endpoint in this study, at which at least 70% of the patients remained in each treatment group, was Week 8.

Both paroxetine and clomipramine reduced the mean MADRS total score in the intent-to-treat population at Weeks 2, 6, and 12 (Figure 1). There were no statistically significant differences between the two groups at any time point. At the endpoint there was a mean ± SD reduction from baseline of 17.3 ± 8.7 in the paroxetine group, compared with 16.5 ± 9.4 in the clomipramine group (Table 4). The treatment differences at endpoint adjusted for country in both the intent-to-treat and per-protocol analyses were not significant (p = .17 and .70, respectively).

Efficacy was also assessed by using the mean change from baseline in the CAS total score (Figure 2). Both paroxetine and clomipramine reduced the mean CAS total score in the intent-to-treat population over the 12-week treatment period, and there were no statistically significant differences between the two groups at any time point. At the endpoint, there was a mean reduction from baseline of 8.1 ± 4.7 in the paroxetine group compared with 8.0 ± 5.1 in the clomipramine group (Table 4). The treatment difference at endpoint adjusted for country was not significant (p = .58), nor was the per-protocol analysis (p = .49).

The number of patients with at least a 50% reduction in MADRS total score was also analyzed. At Week 2, approximately 15% of patients from both treatment groups had at least a 50% reduction in MADRS total score, and the proportion of patients increased over the treatment period. For those patients who completed 12 weeks of treatment, 301 (84.6%) of 356 paroxetine-treated patients and 284 (83.3%) of 341 clomipramine-treated patients had responded. The results at endpoint in the intent-to-treat population are presented in Table 5. There were no significant differences between the treatment groups at any time point.

Similarly, the number of patients with at least a 50% reduction in the CAS total score was analyzed over the 12-week treatment period. At endpoint, 61.4% of the paroxetine group and 60.1% of the clomipramine group had a

Figure 2. Reduction in Mean CAS Total Score at 2-, 6-, and 12-Week Assessment and Endpoint in the Intent-to-Treat Population

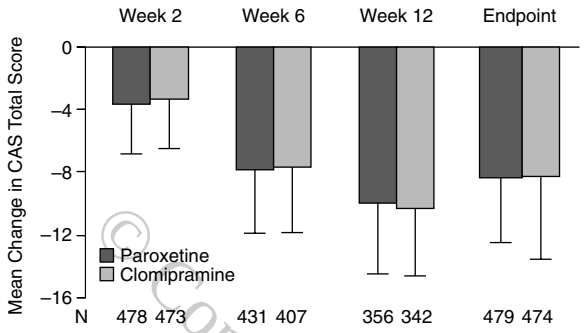


Table 4. Changes in Primary Efficacy Variables at Endpoint in Intent-to-Treat Population

	Paroxetine		Clomipramine	
Score	N	Mean (SD)	N	Mean (SD)
MADRS total				
Baseline	493	29.7 (5.4)	498	29.1 (5.5)
Mean change	479[a]	–17.3 (8.7)	474[a]	–16.5 (9.4)
CAS total				
Baseline	493	15.2 (2.6)	498	15.2 (2.8)
Mean change	479[a]	–8.1 (4.7)	474[a]	–8.0 (5.1)

[a]Due to intermittent missing data points, the number of patients providing a valid endpoint assessment is reduced.

Table 5. Changes in Secondary Efficacy Variables at Endpoint in Intent-To-Treat Population

Variable	Paroxetine (N = 479)[a]	Clomipramine (N = 474)[a]	p Value
Patients with a ≥ 50% reduction in total MADRS (N, %)	328 (68.5%)	317 (66.9%)	.587
Patients with a ≥ 50% reduction in total CAS (N, %)	294 (61.4%)	285 (60.1%)	.785
Mean change from baseline (SD) in CGI-severity	–2.0 (1.4)	–2.0 (1.4)	.972
Mean score (SD) for CGI-efficacy	1.1 (0.9)	1.0 (1.0)	.015
Mean score (SD) for CGI-global improvement	2.1 (1.2)	2.1 (1.2)	.942

[a]Due to intermittent missing data points, the number of patients providing a valid endpoint assessment is reduced.

Table 6. Summary of Adverse Experiences (AE) Occurring in Patients in Either Treatment Group (Intent-to-Treat Population)*

Adverse Experience	Paroxetine (N = 500)	Clomipramine (N = 502)	p Value
Patients with at least one treatment-emergent AE	334 (66.8%)	368 (73.3%)	.025
Anticholinergic-emergent AE	93 (18.6%)	181(36.1%)	NT
Severe emergent AE	76 (15.2%)	100 (19.9%)	NT
Serious emergent AE (including deaths)[a]	14 (2.8%)	27 (5.4%)	.056
Withdrawals due to AE	54 (10.8%)	84 (16.7%)	.008
AE considered to be treatment-related	69 (13.8%)	92 (18.3%)	NT

*NT = statistical difference not tested.
[a]Serious adverse experience = any experience that was fatal, life-threatening, disabling, or incapacitating or resulted in hospitalization, prolonged a hospital stay, or was associated with congenital abnormality, carcinoma, or overdose.

reduction of at least 50% in the CAS total score (p = .79) (Table 5). For those patients who completed 12 weeks of treatment, 263 (73.9%) of 356 paroxetine-treated patients and 265 (77.5%) of 342 clomipramine-treated patients had a reduction in the total score of at least 50%. Again, there were no statistically significant differences between the two treatment groups.

Patients in both groups in the intent-to-treat population improved when assessed by using each of the three parts of the CGI scale (Table 5). There were no statistically significant differences between the means of the treatment groups at any time point with respect to severity of illness and global improvement, but there were statistically significant differences between the means of the treatment groups in efficacy index scores in favor of paroxetine at Week 6 (treatment difference, paroxetine vs. clomipramine = 0.13, p = .015) and endpoint (treatment difference, paroxetine vs. clomipramine = 0.15, p = .015).

Tolerability

Treatment-emergent adverse experiences were reported by 66.8% of patients treated with paroxetine and 73.3% treated with clomipramine (p = .025) (Table 6). The body systems most frequently affected in both groups were the digestive system and the nervous system. The most common emergent experiences in the paroxetine group were nausea, headache, and dry mouth, while in the clomipramine group, patients most frequently reported dry mouth, nausea, and constipation. Adverse experiences occurring in > 10% of patients in either group are presented in Table 7. Anticholinergic-emergent experiences were reported twice as frequently by patients in the clomipramine group as in the paroxetine group (36.1% vs. 18.6%) (statistical analysis not carried out) (Table 6).

Serious emergent adverse experiences were reported in almost twice as many patients in the clomipramine group compared with the paroxetine group (paroxetine, N = 14 [2.8%]; clomipramine, N = 27 [5.4%]). This difference approached statistical significance (p = .056). The most common serious adverse experience was suicidal thoughts (paroxetine, N = 5; clomipramine, N = 11). In the paroxetine group, 4 patients had serious adverse experiences that were considered to be probably related to the study drug (syncope, N = 2; anxiety, N = 1; anxiety, migraine, and vomiting, N = 1). All of these adverse experiences resolved on hospitalization and/or drug withdrawal. In the clomipramine group, 8 patients had experiences that were assessed as being both serious and probably related to the study drug (suicidal thoughts, N = 3; sweating and tachycardia, N = 1; confusion, N = 1; dizziness,

Table 7. Treatment-Emergent Adverse Experiences Occurring in > 10% of Patients in Either Treatment Group (Intent-to-Treat Population)*

Adverse Experience	Paroxetine (N = 500)	Clomipramine (N = 502)
Nausea	95 (19%)	76 (15%)
Headache	69 (14%)	58 (12%)
Dry mouth	65 (13%)	146 (29%)
Tremor	51 (10%)	63 (13%)
Sweating	40 (8%)	53 (11%)
Sexual dysfunction[a] (includes impotence and abnormal ejaculation)	16 (13%)	10 (7%)
Constipation	39 (8%)	66 (13%)

*Statistical difference between the groups for individual adverse experiences was not tested.
[a]Gender-specific event; % calculated on the basis of the male population.

N = 1; anxiety, nausea, depression, dizziness, and tachycardia, N = 1; diarrhea, N = 1). In 5 of the patients, these episodes resolved on drug withdrawal and/or treatment.

Overall, 10.8% of paroxetine-treated patients and 16.7% of clomipramine-treated patients withdrew because of adverse experiences; the difference was significant (p = .008) (Table 6).

A total of 4 patients in the paroxetine group took a drug overdose of the study drug alone (N = 1), the study drug in combination with other drugs (N = 2), and temazepam only (N = 1). In the cases where paroxetine was involved, all patients made an uneventful recovery. In the clomipramine group, 9 patients took a drug overdose of clomipramine alone (N = 3) or combined with other agents (N = 6). In those cases involving clomipramine, the condition of 3 of the patients (2 of whom took clomipramine alone) was life-threatening, while another died (the details of this patient are described below in the section on deaths).

Two deaths occurred during the study; 1 patient in the clomipramine group died of lung cancer, while 1 patient in the paroxetine group committed suicide (not with the study drug). A further patient in the clomipramine group died more than 14 days after withdrawal from the study, following an overdose of clomipramine and benzodiazepines and its complications.

During the study, mean changes in vital signs were generally small and considered to be clinically nonsignificant. A detailed evaluation of laboratory tests failed to indicate any findings of clinical significance in either treatment group.

DISCUSSION

In depressed patients with anxiety, who have a poor clinical picture and prognosis and who are at increased risk of suicide, it is important to treat both sets of symptoms. At present, patients are generally managed by targeting therapy at the predominant symptom. Although there is an increasing tendency to use the newer generation of antidepressants in this role, particularly in North America, in many parts of the world, including Europe, the tricyclic antidepressants and/or benzodiazepines are still used as frontline drugs.[23–26] The problem of dependence with benzodiazepines is well recognized, and furthermore in mixed anxiety and depression, these drugs have no effect on the underlying depression.[26] While the tricyclic antidepressants appear to be effective in treating both depression and anxiety,[26] they cause a wide range of troublesome side effects.[27] There is clearly a need for a drug with both antidepressant and anxiolytic properties that causes minimal side effects.

In this double-blind clinical trial comparing the SSRI paroxetine with the tricyclic antidepressant clomipramine in a large patient population specially selected for the presence of depression and associated anxiety, there was no evidence of a significant difference in efficacy between paroxetine (20–40 mg/day) and the tricyclic antidepressant clomipramine (75–150 mg/day) for the treatment of the symptoms of both anxiety and depression. This result mirrors the analysis of the worldwide database on paroxetine[18] and the recent study comparing paroxetine and amitriptyline in a similar patient sample.[19] Overall, the only difference between the treatments was in the CGI efficacy index, for which a small (but statistically significant difference) favoring paroxetine was demonstrated at 6 weeks and at endpoint (p = .015 for both time points).

Although there were no significant differences between paroxetine and clomipramine in the treatment of the symptoms of both depression and anxiety, there were significantly more patients in the clomipramine group with at least one treatment-emergent adverse experience compared with the paroxetine group, and twice as many patients treated with clomipramine experienced treatment-emergent anticholinergic effects than did patients in the paroxetine group (36.1% and 18.6%, respectively). Furthermore, significantly more patients in the clomipramine group withdrew from the trial following adverse experiences than did patients treated with paroxetine (16.7% versus 10.8%, respectively). These findings are consistent with previous comparisons of paroxetine with clomipramine[28] and other traditional tricyclic compounds.[12,15,17] Comparisons between imipramine and nefazodone[29] or venlafaxine[30] have also shown a higher rate of attrition due to adverse events with the tricyclic antidepressant.

Depressed patients commonly experience suicidal thoughts, and the risk of suicide is increased in patients with concomitant anxiety.[9] A differential advantage of several SSRIs over the tricyclic antidepressants with respect to reducing suicidal thoughts has been previously reported.[31] Both groups of drugs also provide some protection against the emergence of suicidality. The toxicity of the tricyclic antidepressants in overdose is well known,

whereas after suicide attempts with the SSRIs, there are significantly fewer complications, particularly death. This is well illustrated in this study, in which patients attempting suicide with paroxetine made an uneventful recovery, whereas the condition of some patients in the clomipramine group became life-threatening and 1 died.

That suicidal thoughts were reported as a treatment-emergent adverse event in this study is anomalous. The emergence of suicidal thoughts in this patient population reflects the course of the depressive illness and suggests that either the patients were continuing unresponsive to treatment or the depression was poorly or partially treated. In retrospect, it would have been more appropriate for the incidence of suicidal thoughts to have been reported as an efficacy measure.

In summary, anxiety is commonly comorbid with depressive disorder, and often, when the depression resolves, anxiety can remain as a residual symptom.[32] Thus, it is important that both sets of symptoms are effectively treated when they coexist. To date, few comparative trials have been conducted in a patient population with coexisting depression and anxiety, particularly in the primary care setting. The current options for treating comorbid depression and anxiety, the tricyclic antidepressants or benzodiazepines, are less than optimal. The tricyclics are not well tolerated and have a low margin of safety, which can be problematical, particularly in the primary care setting. The benzodiazepines have the potential to induce dependence, and they lack efficacy in the treatment of depression. Furthermore, in the primary care setting, maintaining patient compliance can be difficult, and its improved tolerability profile may make paroxetine a valuable alternative for the treatment of patients with comorbid depression and anxiety.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil), nefazodone (Serzone), paroxetine (Paxil), temazepam (Restoril and others), venlafaxine (Effexor).

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