EFFECT OF CONCURRENT ANXIETY ON RESPONSE TO SERTRALINE AND IMIPRAMINE IN PATIENTS WITH CHRONIC DEPRESSION

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Anxiety commonly complicates the clinical presentation of depression and has been associated with poorer long-term outcome, but little information is available on the clinical correlates, and comparative effect on treatment response, of subsyndromic or secondary anxiety. Patients diagnosed with chronic major or double depression were randomized to 12 weeks of double-blind treatment with either sertraline or imipramine in a 2:1 ratio. A high anxiety subgroup was operationally defined by a HAM-D anxiety/somatization factor score ≥ 7. The effect of study treatment was measured utilizing the HAM-D, CGI, HAM-D anxiety/somatization factor, as well as a quality of life measure (Q-LES-Q) and a measure of psychosocial functioning (the MOS-SF-36). Two hundred nine patients were treated with imipramine and 426 patients were treated with sertraline. Thirty-six percent of the total met criteria for the high anxiety subgroup. According to Kaplan-Meier probability estimates, patients with significant concurrent anxiety symptoms were more likely to respond by 12 weeks (66.4%) than those without significant anxiety symptoms (54.2%). There was no significant difference in response rates for sertraline vs. imipramine. Both drugs were effective at treating high baseline levels of anxiety, with 60% of sertraline patients and 58% of imipramine patients having 50% or greater reduction from baseline in HAM-D anxiety/somatization factor scores, and only 4.6% and 9.9%, respectively, reporting treatment-emergent worsening in anxiety at study endpoint. Despite the chronicity of depressive illness, acute treatment with both sertraline and imipramine significantly improved psychosocial and quality of life measures. High baseline levels of anxiety did not reduce overall antidepressant response but did somewhat delay the onset of response to sertraline or imipramine in patients with chronic depression. Depression and Anxiety 13:18–27, 2001.

Key words: *sertraline; imipramine; anxiety; depression; antidepressive agents*

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Contract grant sponsor: Pfizer, Inc.

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Received for publication 27 March 2000; Accepted 27 September 2000

INTRODUCTION

Major depression and dysthymic disorder are both widely recognized as carrying a high risk of co-occurrence with an anxiety disorder. In the National Comorbidity Survey, a concurrent (12-month prevalence) diagnosis of anxiety was made in 51% of patients suffering from major depression [Kessler et al., 1996]. Anxiety comorbidity rates for *chronic* major depression are not well-documented, but for dysthymic disorder a large community survey found a rate of 42% [Weissman et al., 1988]. Among psychiatric patients, anxiety comorbidity in dysthymia has been reported to range from 45 to 70% [Sanderson et al., 1990; Klein et al., 1988; Mezzich et al., 1994; Markowitz et al., 1992].

Research consistently finds depression and anxiety disorder comorbidity to be associated with higher severity of illness [Grunhaus et al., 1988; Hecht et al., 1990; Coryell et al., 1992; Joffe et al., 1993; Fawcett, 1997], increased suicide risk [Fawcett, 1997], poorer functioning [Hecht et al., 1990; Lydiard, 1991], more help-seeking and treatment [Clayton et al., 1991; Vollrath and Angst, 1989] but poorer response to treatment [Grunhaus et al., 1988; Joffe et al., 1993; VanValkenburg et al., 1984; Dew et al., 1997], and poorer long-term outcome [Schapira et al., 1972; Emmanuel et al., 1998].

We were interested in examining the clinical correlates and effect on outcome of subsyndromic or secondary anxiety in patients with a primary diagnosis of chronic major depression and/or dysthymia. Anxious depression has existed for decades as a clinically recognized depressive subtype, but prevalence estimates are uncertain due to the lack of consensus criteria that operationally define the minimum severity of concurrent anxiety. Mixed anxiety-depression has, in the past, been considered as a candidate Axis I diagnosis in DSM-IV [Zinbarg et al., 1994].

The conduct of a large double-blind study that compared the efficacy of sertraline and imipramine in the treatment of chronic major and double-depression provided us with the opportunity to examine the clinical and psychosocial correlates of depression in patients presenting with high concurrent levels of symptomatic (but subsyndromic or secondary) anxiety. It also permitted us to examine the differential effect of high baseline levels of anxiety on both depressive symptom and psychosocial outcome, as well as the effectiveness of the respective antidepressants in treating the presenting symptoms of anxiety.

METHOD

Entry criteria and study methodology have been described in detail in previous publications [Rush et al., 1998; Keller et al., 1998] but will be briefly summarized here.

PATIENTS

Six hundred thirty-five men and women between the ages of 21 and 65 who gave informed consent were enrolled in this multicenter study. Patients were diagnosed by using the Structured Clinical Interview for DSM-III-R (SCID) as having one of two *primary* diagnoses: either chronic major depression (n = 294) or chronic dysthymic disorder with a concurrent major depression ("double depression"; n = 341). Individuals were excluded from study entry if they met DSM-III-R criteria for any other *primary* Axis I disorder, including any Axis I anxiety disorder. Patients were also excluded if they suffered any clinically significant acute or unstable medical condition.

STUDY DESIGN

After a 1-week, single-blind placebo run-in, patients were randomized to 12 weeks of double-blind treatment with either sertraline (in a flexibly titrated dose in the range of 50– 200 mg per day) or imipramine (in a flexibly titrated dose in the range of 50– 300 mg per day). Owing to power considerations concerning subsequent maintenance phase treatment, randomization was performed in a 2:1 ratio for sertraline and imipramine, respectively. Sertraline treatment was initiated at 50 mg per day for the first 3 weeks, with flexible titration thereafter in the range of 50– 200 mg per day based on therapeutic response and tolerability. Imipramine treatment was initiated at 50 mg per day for the first week, with titration by 50 mg per week thereafter to a final dose in the range of 50– 300 mg per day based on therapeutic response and tolerability.

Patients participated in clinic visits at screening, baseline, and at weeks 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12. At screening and baseline, demographic characteristics were recorded and patients were assessed for depressive and anxiety symptoms by using the 24-item Hamilton Rating Scale for Depression [HAM-D; Hamilton, 1960]. To be included in the study, a total HAM-D score of ≤ 18 was required after a 1-week, single-blind placebo run-in.

The Clinical Global Impression (CGI) was noted at all visits by study physicians [Guy, 1976]. The HAM-D was utilized to assess the satisfactory therapeutic response and remission rates at weeks 1, 2, 4, 6, 8, 10, and 12.

ASSESSMENTS

The SCID-P [Structured Clinical Interview for DSM-III-R with Psychotic Screen; Spitzer et al., 1989] administered by trained raters was utilized at baseline to identify the presence of chronic major depression or double depression, other psychiatric disorders, and the occurrence of psychiatric exclusion criteria. A physician-rated CGI and trained-rater-administered HAM-D assessed depressive symptoms and overall severity at baseline and weeks 1, 2, 4, 6, 8, 10, and 12 of the study.

The presence and severity of concurrent anxiety symptoms were measured at weeks 1, 2, 4, 6, 8, 10, and 12 utilizing the anxiety/somatization factor of the 24-item HAM-D, administered by trained raters. The six-item HAM-D anxiety/somatization factor has been utilized widely in clinical studies to measure anxiety symptoms and their severity [Cleary and Guy, 1975; Tollefson et al., 1994; Dunbar and Fuell, 1992]. Psychosocial (MOS-SF-36) and quality of life (Q-LES-Q) measures were assessed at baseline and weeks 4 and 12.

DEFINITION OF SIGNIFICANT CONCURRENT ANXIETY

As operationally defined in previous studies, clinically significant concurrent anxiety was defined as a score of ≥ 7 on the six-item HAM-D anxiety/somatization factor [Tollefson et al., 1994; Schwab et al., 1972], which includes HAM-D items numbered 10–13, 15, and 17. This definition is consistent with the distribution of the HAM-D anxiety/somatization factor score in our sample (mean = 5.97; sd = 1.99; median = 6.0).

DEFINITION OF REMISSION AND RESPONSE

To ensure that the HAM-D anxiety/somatization factor score would not confound results, we defined a "satisfactory therapeutic response" to be at least a 50% reduction from baseline in the adjusted 18-item HAM-D total score (i.e., excluding the six anxiety/somatization factor items described above). Also required to meet satisfactory therapeutic response criteria were a CGI-improvement score of 1 or 2 (very much or much improved), and a CGI severity score ≤ 3 (mildly ill). "Remission" was defined as an adjusted 18-item HAM-D total score of ≤ 7 (again, excluding the six anxiety/somatization factor items described above) and a CGI-Improvement score of 1 (very much improved).

STATISTICAL ANALYSIS

Demographic and baseline characteristics were compared across patient groups with Mantel-Haenszel chi-square tests for categorical measures, Mantel-Haenszel mean-score chi-square tests with stratified midranks for ordinal categorical measures, and analysis of variance (ANOVA) for continuous measures. All comparisons included an adjustment for investigator site, depression type (chronic vs. double), and treatment group. The two anxiety groups (with and without significant concurrent anxiety symptoms) were compared for differences in response and remission at endpoint using a Mantel-Haenszel chi-square test stratifying over investigator site, treatment group, and depression type (referred to as the intent-to-treat analysis). Endpoint for each parameter was defined as the last observation available per patient. Within anxiety groups, treatment groups were compared for response rates by using similar methods. If warranted, the interaction between treatment and anxiety group was tested with a logistic regression model which adjusted for investigator site and depression type.

Kaplan-Meier survival estimates and logrank tests were utilized in the intent-to-treat sample to test the null hypothesis that concurrent anxiety does not affect the length of time to reach adequate therapeutic response. Anxiety groups and treatments within an anxiety group were compared by using an unstratified logrank test. The relationship between time to response or time to remission and the baseline HAM-D anxiety/somatization factor was evaluated using a Cox proportional hazards regression model, which included terms for investigator site, treatment, depression type, 18-item baseline HAM-D total score (excluding the 6 items that comprise the anxiety/somatization factor), and the baseline HAM-D anxiety/somatization factor score. The interaction of treatment with depression type, and the HAM-D anxiety/somatization score with treatment, depression type, and time to response (< 6 weeks vs. ≥ 6 weeks) were evaluated for model inclusion.

For the high anxiety subgroup, change from baseline in the HAM-D anxiety/somatization factor score and continuous psychosocial outcomes were analyzed by using an analysis of covariance (ANCOVA) model with effects for treatment group, investigator site, depression type, and baseline value. Comparisons of incidence of adverse events, severe adverse events, attrition due to adverse events, and attrition for all causes were tested by using an unadjusted chi-square test, or a Fisher's Exact test, depending on sample size.

It is important to note that our objective in the current study was to test for differences between anxiety or treatment groups in an exploratory "hypothesis generating" manner, rather than to test a specific set of a priori hypotheses. Therefore, the *P*-values reported here are best interpreted as descriptive tools that identify differences between groups, rather than confirm hypotheses that such differences exist.

RESULTS

Of the 635 study patients, 209 were treated with imipramine and 426 were treated with sertraline. Demographic and clinical variables were similar for both types of chronic depression. The two depressive diagnosis subtypes were combined for the purposes of the analysis in the present investigation.

The success of the randomization procedure was reflected in the fact that there were no significant baseline differences between the two treatment groups in the key clinical measures, including baseline CGI severity score, the HAM-D total score (both the unadjusted as well as the 18-item non-anxiety HAM-D adjusted score) and the 6-item HAM-D anxiety/somatization factor score.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH AND WITHOUT CONCURRENT ANXIETY

Two hundred twenty-nine study patients (36.1%) had significant concurrent anxiety symptoms at baseline as defined by a HAM-D anxiety/somatization factor score ≥7. Neither the prevalence nor the degree of concurrent anxiety symptoms differed by depression diagnosis or by treatment group. As can be seen, there were few baseline differences in any of the demographic, clinical history, or comorbidity variables summarized in Table 1, with the most notable exception being a significantly lower college graduation rate in patients with concurrent anxiety at baseline. Since college graduation may be affected by age of onset of depression, we looked to see if level of anxiety had a different impact on graduation rates for patients with early or late (over age 21) onset of depression. For patients reporting early depression onset, the subgroup with significant concurrent anxiety reported particularly low rates of college completion compared to their non-anxious counterparts (24% vs. 40%, $P < 0.006$). The trend was similar for late onset depression (32% vs. 46%; $P < 0.017$).

As can be seen in Table 2, there are statistically significant, but clinically very modest, differences in baseline CGI-severity and HAM-D severity scores (even after factoring out higher levels of anxiety in the latter measure). The HAM-D anxiety/somatization factor, by definition, was higher in the concurrent anxiety group. An analysis by gender found women to have a higher baseline HAM-D anxiety/somatization factor score than men (6.05 ± 2.0 vs. 5.85 ± 2.1; F = 4.04, df = 1, 623; $P = 0.045$).

EFFECT OF BASELINE ANXIETY ON DEPRESSION TREATMENT RESPONSE

In these chronically depressed patients, the Kaplan-Meier estimated probability of at least a satisfactory therapeutic response at 12 weeks of treatment was 66.4% (95% CI; 59.7– 73.0) for those with significant anxiety and 54.2% (95% CI; 49.0– 59.5) for patients without significant anxiety. The intent-to-treat analyses confirmed these findings. Response rates at endpoint were better for depressed patients with significant

TABLE 1. Demographic and clinical characteristics of patients by baseline anxiety level

Patient variable	Depression with significant anxiety (N = 229)	Depression without significant anxiety (N = 406)	*P*-value
Female, %	65.1%	61.8%	0.176
Race, %			0.054
White, %	88.7%	92.1%	
Other, %	11.4%	7.9%	
Age, yrs, m ± SD	41.6 ± 10.6	40.8 ± 9.7	0.398
Marital status, %			0.542
Married/cohabiting, %	43.9%	39.5%	
Never married, %	21.9%	27.6%	
Divorced/separated, %	31.6%	30.9%	
Widowed, %	2.6%	2.0%	
Education			
At least high school graduate, %	94.3%	97.0%	0.372
At least college graduate, %	28.6%	43.4%	0.001
Age at onset of Major Depression, yrs, m ± SD	24.8 ± 12.1	24.9 ± 12.0	0.719
Age at onset of Dysthymia, yrs, m ± SD	17.3 ± 13.2	16.7 ± 13.1	0.433
No. prior episodes of Depression, m ± SD	1.6 ± 2.1	1.8 ± 2.1	0.866
Patients with 2 or more prev. episdoes, %	37.7%	43.1%	0.624
History of comorbid anxiety disorder, %			
Panic disorder, %	9.2%	5.9%	0.079
Social phobia, %	11.4%	12.4%	0.615
GAD, %	7.0%	4.2%	0.276
Any anxiety disorder, %	25.8%	23.2%	0.561
History of comorbid personality disorder, %			
Cluster A, %	9.2%	7.7%	0.678
Cluster B, %	10.9%	12.4%	0.467
Cluster C, %	37.1%	40.1%	0.888
History of alcohol abuse, %	26.2%	30.9%	0.096
History of substance abuse, %	30.6%	37.0%	0.047
Prior treatment with antidepressants			
Adequate treatment, %[a]	21.5%	19.7%	0.513
Prior psychotherapy, %	53.7%	61.9%	0.096

[a] *Adequate treatment defined as 150 mg or more of imipramine (or its equivalent) for at least 1 month.*

TABLE 2. Baseline clinical and psychosocial characteristics of patients by baseline anxiety level

Patient variable	Depression with significant anxiety (N = 229)	Depression without significant anxiety (N = 406)	*P* -value
HAM-D total score, m ± SD	27.7 ± 5.6[a]	23.6 ± 4.1	<0.001
18-item, non-anxiety adjusted HAM-D score, m ± SD	19.7 ± 5.0[a]	18.8 ± 3.9	0.048
6-item HAM-D anxiety factor score, m ± SD	8.1 ± 1.4	4.8 ± 1.2	<0.001
CGI-severity score, m ± SD	4.3 ± 0.6	4.1 ± 0.5	0.019
GAF score, m ± SD	52.4 ± 7.1	53.2 ± 7.5	0.177
Q-LES-Q score, m ± SD	51.2 ± 9.9	54.7 ± 9.8	<0.001
Number of hours worked per week, m ± SD	25.4 ± 21.2	28.6 ± 20.7	0.105
SF-36 general health, m ± SD	56.7 ± 22.2	66.9 ± 19.3	<0.001
SF-36 social functioning, m ± SD	45.9 ± 25.5	51.9 ± 26.3	0.030
SF-36 role limitation emotional, m ± SD	20.3 ± 29.3	20.1 ± 29.6	0.656
SF-36 role limitation physical, m ± SD	51.5 ± 42.0	70.4 ± 37.7	<0.001

[a]*Group differences are a result of the definition of significant concurrent anxiety, based on the six-item Ham-D anxiety factor.*

anxiety (60.3%) than those without (48.4%; $\chi^2 = 5.066$, df = 1, $P = 0.024$). The intent-to-treat remission rate was 42.4% for those with significant concurrent anxiety and 29.8% for patients without significant anxiety ($\chi^2 = 5.45$, df = 1, $P = 0.020$).

A significant interaction was found between time-to-response and baseline HAM-D anxiety/somatization factor in this sample (proportional hazards model $\chi^2 = 4.516$, df = 1, $P = 0.034$). Those with significant anxiety were less likely to achieve a satisfactory therapeutic response until they had received at least 6 weeks of treatment. However, after 6 weeks of treatment, those with significant anxiety symptoms were more likely to respond than patients without significant anxiety symptoms. This effect is unrelated to the baseline depressive symptom severity based on the remaining 18 non-anxiety HAM-D items or the dose of sertraline or imipramine received at endpoint.

DRUG DIFFERENCES AND RESPONSE TO TREATMENT

In depressed patients with significant concurrent anxiety, the Kaplan-Meier estimated probability of achieving at least a satisfactory therapeutic response for patients at 12 weeks of treatment was 64.2% (95% CI = 56.0– 72.4) for sertraline and 70.3% (95% CI = 59.1– 81.4) for imipramine (logrank $\chi^2 = 0.151$, df = 1, $P = 0.698$). Intent-to-treat analyses also were consistent with Kaplan-Meier estimated probability of response rates.

However, chronically depressed patients treated with sertraline who had significant concurrent anxiety symptoms were more likely to achieve full remission (42.5%) at endpoint than those without anxiety (28.0%; $\chi^2 = 6.07$, df = 1, $P = 0.014$). No significant within-group difference was observed for imipramine (although no treatment by anxiety interaction effect was observed).

EFFICACY OF SERTRALINE AND IMIPRAMINE IN TREATING HIGH BASELINE ANXIETY

In the high anxiety subgroup, sertraline treatment yielded a reduction from baseline of 4.31 ± 2.61 points in the HAM-D anxiety/somatization factor compared to a reduction of 3.76 ± 2.95 points on imipramine (F = 2.72; df = 1, 217; $P = 0.10$).

Figure 1 summarizes the effect of each study treatment on change-from-baseline in levels of anxiety in the subgroup of anxious depressives. Improvement was defined as ≤ 50% reduction from baseline in the HAM-D anxiety/somatization factor score. Worsening was defined as any endpoint HAM-D anxiety/somatization factor score that was higher than baseline. As can be seen, when the criterion was used, the majority of patients in each treatment group showed significant anxiolytic benefit, while only a small minority reported treatment-emergent worsening of anxiety during the course of the study.

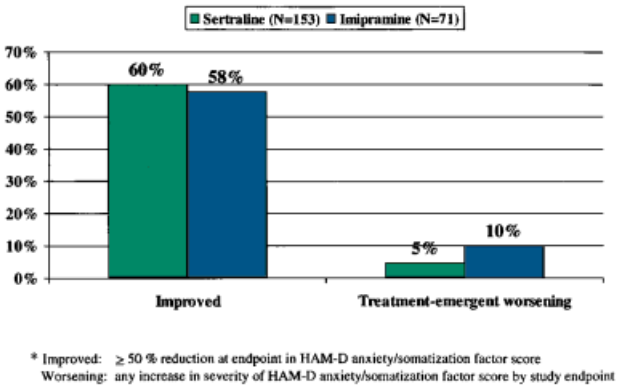

Figure 1. Endpoint effect of study treatment on the HAM-D anxiety factor in subgroup of patients with high concurrent anxiety.

EFFICACY OF STUDY TREATMENT IN IMPROVING PSYCHOSOCIAL FUNCTIONING AND QUALITY OF LIFE

As noted in Table 2, patients with high concurrent anxiety were found to have significantly lower levels of psychosocial functioning and quality of life, as measured, respectively, by the SF-36 and the Q-LES-Q, than patients without significant concurrent anxiety. Figure 2 summarizes the effect of study treatment on psychosocial functioning, comparing endpoint values for patients with high concurrent anxiety who remitted, as well as those who achieved a satisfactory therapeutic response, to a normative community sample. As can be seen, acute treatment led to substantial improvement that, for remitters, fully returned them to levels of psychosocial functioning equal to what has been reported in the community. Note that for the purposes of this analysis both treatment groups have been combined. There were no statistically significant between-drug differences in the improvement observed in psychosocial function, with the exception that sertraline treatment was associated with a significantly greater improvement than imipramine in the SF-36 Role Limitation, Emotional factor (*change score* of 65.1 ± 38.4 vs. 39.3 ± 37.5; F = 5.23; df = 1, 83; $P \leq 0.025$) for patients who achieved remission.

Figure 3 shows the effect of study treatment on the Q-LES-Q total score for patients with high concurrent anxiety. A similar pattern of improvement in perceived quality of life was achieved, with patients categorized as remitters reporting the greatest improvement. For both response categories, satisfactory response and remission, sertraline treatment was associated with a significantly greater enhancement in perceived quality of life. For patients who achieved a satisfactory therapeutic response, mean change-from-baseline in the Q-LES-Q total score was 18.9 ± 10.6 vs. 11.6 ± 11.7 for sertraline and imipramine, respectively (F = 4.99; df = 1,31; $P = 0.033$). For patients who achieved a remission, mean change-from-baseline in the Q-LES-Q total score was 24.6 ± 12.6 vs. 19.2 ± 16.8 for sertraline and imipramine, respectively (F = 4.04; df = 1,84; $P = 0.048$).

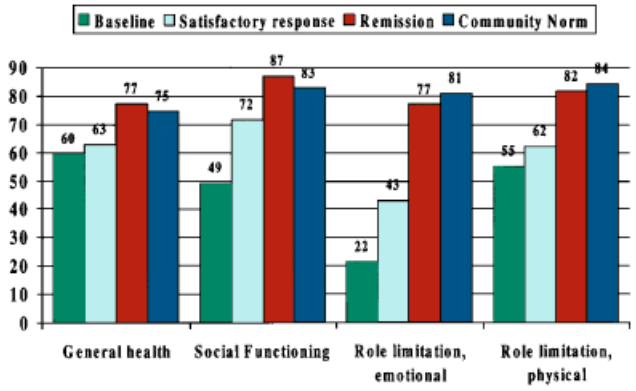

Figure 2. Effect of study treatment on MOS Short Form-36 scores by response category, compared to normative functioning in the community, for chronically depressed patients with high concurrent anxiety.

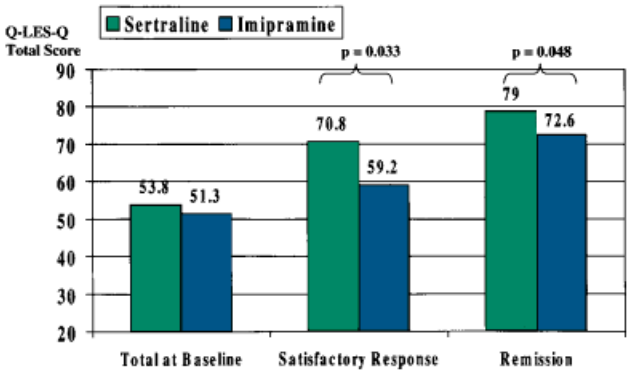

Figure 3. Effect of study treatment on the Q-LES-Q total score by response category for chronically depressed patients with high concurrent anxiety.

EFFECT OF CONCURRENT ANXIETY ON ADVERSE EVENTS AND STUDY DISCONTINUATION

The mean final dose was 141.0 mg (SD ± 59.4) for sertraline and 200.2 (SD ± 82.1) mg for imipramine. Table 3 summarizes the treatment-related adverse events observed for both sertraline and imipramine in patients in the high concurrent anxiety subgroup. Both drugs were fairly well tolerated, but there was only one adverse event that was significantly more frequent on sertraline (diarrhea) compared to eight adverse events reported significantly more frequently on imipramine (dry mouth, dizziness, sweating, constipation, tremor, micturition disorder, tachycardia, and flushing). No significant difference was observed in the incidence of treatment-emergent, treatment-related adverse events between high anxiety and low anxiety patients for the pooled treatment groups. A comparison of adverse events for high vs. low anxiety patients treated with sertraline, and high vs. low anxiety patients treated with imipramine identified only one statistically significant difference: 38.4% of low anxiety patients treated with sertraline reported dry mouth compared to 28.4% of high anxiety patients ($\chi^2 = 4.34$; df = 1; $P = 0.037$).

Reports of adverse events rated as severe were less frequent for sertraline compared to imipramine in both the low anxiety (13% vs. 20%, $\chi^2 = 3.50$; df = 1; $P = 0.062$) and the high anxiety (9% vs. 19%; $\chi^2 = 4.56$; df = 1; $P = 0.033$) subgroups.

Overall, 21% of patients with high anxiety discontinued prematurely from the study for *all* reasons, with no significant between-drug difference. There was no significant difference in study discontinuations for patients with high baseline anxiety (21%) compared with those

TABLE 3. Summary of treatment-related, treatment-emergent adverse events reported at a rate ≥ 10% in either treatment group for patients with high concurrent anxiety

Adverse event	Sertraline N = 155 (%)	Imipramine N = 74 (%)	*P*-value*
Headache	37	38	0.951
Mouth dry	28	80	0.001
Insomnia	28	20	0.224
Nausea	27	18	0.114
Diarrhea	26	3	0.001
Sedation	19	28	0.098
Dizziness	14	39	0.001
Sweating increased	14	30	0.005
Dyspepsia	14	23	0.098
Sexual dysfunction[a]	12	11	0.751
Fatigue	11	12	0.790
Nervousness	11	14	0.576
Constipation	9	35	0.001
Tremor	7	27	0.001
Anxiety	7	11	0.341
Loss of appetite	5	11	0.088
Micturition disorder	3	16	0.001
Tachycardia	2	12	0.001
Flushing	1	11	0.001

**P-value based on unadjusted chi-squared test, except for loss of appetite, tachycardia, and flushing, that were based on Fisher's exact test.*
[a]Sexual dysfunction includes delayed ejaculation, anorgasmia, impotence, and decreased libido.

with low baseline anxiety (19%; $\chi^2 = 0.282$, df = 1, $P = 0.596$). However, low anxiety patients treated with imipramine discontinued from the study at a higher rate (28%) than low anxiety patients treated with sertraline (15%; $\chi^2 = 10.406$, df = 1, $P < 0.001$).

DISCUSSION

THE EFFECT OF CONCURRENT ANXIETY ON ANTIDEPRESSANT RESPONSE

The results of the current study found a higher response rate for patients presenting *with* current subsyndromic or secondary anxiety than for patients who presented with chronic depression without notable concurrent anxiety. At endpoint, 60.3% of patients presenting with an anxious depression responded, compared to 48.4% of patients without concurrent anxiety ($\chi^2 = 5.066$, df = 1, $P = 0.024$). The intent-to-treat remission rate (based on stringent criteria) revealed a parallel result, with a 42.4% remission rate for patients presenting with an anxious depression, and 29.8% for non-anxious patients ($\chi^2 = 5.45$, df = 1, $P = 0.20$). For patients with anxious depression, there was no significant difference in response rates for sertraline compared to imipramine.

The results of the current study contrast with most but not all previous reports that have found concurrent anxiety to be associated with a lower antidepressant response rate [Grunhaus et al., 1988; Joffe et al., 1993; VanValkenburg et al., 1984]. The reasons for the more favorable outcome in the current study are uncertain but may relate to the longer duration of acute treatment (12 weeks) and the fairly aggressive dosing (mean final dose of sertraline, 141 mg; and imipramine, 200 mg). It also may relate to the decisions to define response in terms of a revised 18-item HAM-D total score that excluded anxiety items, but this is less likely since the anxiety/somatization factor also showed parallel improvement.

The only other SSRI that has been systematically assessed as to its efficacy in the anxious depression subtype is fluoxetine. Fava and colleagues [1997], in a large but uncontrolled study, reported that patients presenting with anxious depression responded modestly (but not statistically significantly) *less* well to fluoxetine than did non-anxious patients. These findings are consistent with a previous meta-analyses [Tollefson et al., 1994] of patients with major depression that also reported a modestly, but not significantly, lower response rate to fluoxetine in patients with anxious vs. non-anxious depression. Interestingly, the results of the meta-analysis found a higher proportion of patients among anxious depressives who achieved remission (38.3% vs. 29.5%, p = 0.013).

TIME COURSE OF ANTIDEPRESSANT RESPONSE

A significant interaction was found between time-to-response and baseline HAM-D anxiety/somatization factor in this sample ($\chi^2 = 4.516$, df = 1, $P = 0.034$). Those with significant anxiety were less likely to respond until they had received at least 6 weeks of treatment. However, after 6 weeks of treatment, those with significant anxiety symptoms were more likely to achieve a satisfactory therapeutic response than patients without significant anxiety symptoms. Since the overall response rate for the non-anxious subset of depressed patients was lower, the effect was to *raise* the median Kaplan-Meier time-to-response for the non-anxious group. This helps to explain the apparently paradoxical finding that anxious patients responded less frequently by 6 weeks but ended up having a shorter (8 weeks) overall median time-to-response than non-anxious patients (10 weeks).

EFFICACY OF STUDY TREATMENT IN REDUCING CONCURRENT ANXIETY

Conventional wisdom has long held that tricyclic antidepressants, by virtue of their sedating properties, might offer an advantage over SSRIs in the treatment of the anxiety component that is so frequently a clinical feature of major depression. Contrary to conventional wisdom, sertraline treatment produced levels of improvement in baseline anxiety symptomatology that was comparable to what was observed with imipramine treatment (Fig. 1), with only a very small minority of patients reporting worsening in anxiety by treatment endpoint.

These results are consistent with preliminary research that has found sertraline to have significant efficacy in reducing the somatic and psychic symptoms of anxiety associated with non-chronic forms of depression [Bisserbe et al., 1996; Sogaard et al., 1997; Moon et al., 1994]. These results are also consistent with a growing body of controlled research, suggesting that sertraline has potent anxiolytic effects across a variety of anxiety diagnoses, including panic disorder [Pohl et al., 1998; Londborg et al., 1998; Pollack et al., 1998], PTSD [Brady et al., 1998], social phobia [Lane, 1998], and OCD [Greist et al., 1995; Rasmussen et al., 1997].

There is evidence that other SSRIs offer similar anxiolytic benefit in patients presenting with anxious depression. Meta-analyses of venlafaxine [Rudolph et al., 1998], fluoxetine [Tollefson et al., 1994], and paroxetine [Dunbar and Fuell, 1992] found these medications to effectively treat the anxiety component of anxious depression. The rate of treatment-emergent anxiety appeared to be somewhat higher after venlafaxine treatment (24%) than the rate we observed after sertraline treatment in the current study (5%). Treatment-emergent anxiety/nervousness have been reported at a rate of approximately 15% for fluoxetine [Tollefson et al., 1994], which is consistent with other reports of treatment-emergent anxiety in the early weeks of fluoxetine [Smith et al., 1998; Aguglia et al., 1993].

Several of the SSRIs have been approved by the FDA for use in the treatment of anxiety disorders, including fluoxetine (OCD), sertraline (PTSD, panic disorder, and OCD), paroxetine (panic disorder, social phobia, and OCD), and venlafaxine (GAD). More approved anxiety disorder indications are likely to be forthcoming. It should be noted, though, that there is remarkably little prospective, controlled research that examines the efficacy of SSRIs (or any class of antidepressant) for the treatment of currently comorbid Axis I anxiety and depressive disorders, despite the high prevalence of such comorbidity.

CLINICAL AND PSYCHOSOCIAL CORRELATES OF CONCURRENT ANXIETY

It should be emphasized that the patients in the current investigation represent a convenience sample recruited for a treatment study. Therefore, though the sample size is relatively large, one cannot draw inferences concerning the clinical and psychosocial correlates of concurrent anxiety in patients suffering from chronic depression *in the community*. Several interesting findings deserve comment, though, that may be relevant for the subset of anxious depressive patients who are seeking treatment. First is the notable absence of significant clinical or demographic differences among the high vs. low anxiety subgroups of patients with chronic depression. As can be seen in Table 1, clinical features such as gender, age of depression onset, number of prior episodes, and other Axis I and Axis II comorbidity were not different for patients presenting with anxious vs. non-anxious depression. The most notable and consistent difference between the two subgroups of patients consisted of the significantly greater degree of psychosocial impairment and impairment in quality of life associated with the presence of concurrent anxiety (Table 2). Related to quality of life and issues of lost human capital, educational advancement was also notably impaired in the high anxiety subgroup. Interestingly, a preliminary sub-analysis of the high vs. low anxiety groups of patients with early vs. late onset depression suggests that the presence of concurrent anxiety contributes as much interference to educational advancement as age of onset.

EFFECT OF STUDY TREATMENT ON PSYCHOSOCIAL OUTCOME

If high concurrent levels of anxiety is associated with higher rates of baseline psychosocial impairment, just how effective is study treatment, not simply in causing symptomatic improvement in depression and anxiety, but also in returning patients to normative levels of psychosocial functioning? As can be seen in Figure 2, the subset of patients who achieved a remission at the end of acute treatment reported levels of functioning on the MOS-SF-36 that were equivalent to the community sample. This is a remarkable finding: despite a mean of more than 10 years of major depression, and more than 20 years of dysthymia, approximately 12 weeks of acute treatment not only yielded a remission of depression in approximately half of patients, but it also returned their psychosocial functioning to the levels reported for community samples [McHorney et al., 1994]. A corollary clinical conclusion should be noted: the majority of the psychosocial improvement occurred in patients who were able to achieve a remission in their depression. This finding underscores the negative psychosocial effects of relatively mild residual, subsyndromic levels of depressive symptoms. The clinical lesson appears to be that the physician should strive for a full remission. Whether continued treatment of patients who initially achieved a satisfactory response would consolidate their symptomatic improvement, as well as improvement in their psychosocial functioning, will be the subject of a later report.

A comparison of the effect of sertraline and imipramine on psychosocial measures found that, despite similar levels of symptomatic improvement at endpoint, sertraline treatment was associated with greater improvement in levels of psychosocial functioning (Fig. 2). These numerical advantages for sertraline only achieved statistical significance on the SF-36 Role Limitation, Emotional Factor among remitting patients. A similar advantage for sertraline was also observed (Fig. 3) for the quality of life measure, the Q-LES-Q.

TOLERABILITY OF STUDY TREATMENT

Is the presence of the anxious subtype of depression associated with a greater likelihood that antidepressant treatment will be poorly tolerated? Based on the results of the current study, the answer would appear to be no: rates of adverse events, including rates of severe adverse events, as well as the rate of discontinuation due to adverse events, were similar for both the high and the low anxiety subgroups. For sertraline, discontinuations due to adverse events were 6% and 8% for the non-anxious and anxious patients, respectively. These results are consistent with the findings of a previous meta-analysis [Tollefson et al., 1994] that found an equal discontinuation rate (of 15%) due to adverse events in anxious and non-anxious patients treated with fluoxetine.

The results of the current study suggest that sertraline may be better tolerated than imipramine in patients presenting with anxious depression. Overall, diarrhea was the only adverse event reported significantly more frequently with sertraline treatment (26%) than with imipramine treatment (3%; $P = 0.001$). In contrast, there were eight adverse events that were reported at a significantly higher rate on imipramine compared to sertraline (Table 3). Consistent with this, imipramine treatment was associated with a higher incidence of severe adverse event than sertraline, as well as a higher incidence of attrition due to adverse events. Again, these results are consistent with previously reported meta-analysis results that compared TCAs to fluoxetine, which found higher adverse event rates for the former [Tollefson et al., 1994].

CONCLUSIONS

We conclude with a note of caution concerning the current study results. Baseline anxiety status was defined using a 6-item HAM-D anxiety/somatization factor that, despite its previous validation and use [Cleary and Guy, 1975; Tollefson et al., 1994; Dunbar and Fuell, 1992], is still less satisfactory than the far more widely used, and validated, Hamilton anxiety rating scale. The current study results, thus qualified as exploratory, found that chronically depressed patients who presented with an anxious depression had a somewhat slower antidepressant response, but one that, at the end of 12 weeks of acute treatment, was significantly higher than was observed for non-anxious patients. For the high concurrent anxiety subgroups, sertraline and imipramine were comparable in treating both the depression, as well as the concurrent anxiety symptomatology. But sertraline appeared to have an advantage over imipramine in terms of both tolerability and perceived improvements in functioning and quality of life.

Acknowledgments. A special thanks is extended to Tara Edwards and Mukesh Patel for their assistance with this manuscript.

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