Paroxetine Response and Tolerability Among Ethnic Minority Patients With Mood or Anxiety Disorders: A Pooled Analysis

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Background: Because of the poor quality of mental health care received by minorities, analyses documenting comparable response to and tolerability of medications for anxiety and depression in large samples of minority and majority populations could increase the willingness of providers and patients to use medications in minority populations.

Method: A pooled analysis of 14,875 adults who participated in 104 double-blind, placebo-controlled paroxetine clinical trials investigating major depression, panic disorder, generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or premenstrual dysphoric disorder from March 1984 through March 2002. An intent-to-treat analysis with last observation carried forward used the Clinical Global Impressions (CGI) scale to measure dichotomous outcome, classified as either response (CGI score of 1 or 2) or more complete response (CGI score of 1) ("full response"). Minority group differences were examined using logistic regression for the entire sample and repeated for those with major depression. Adverse events greater than 5% and twice the rate of placebo were descriptively tabulated. Finally, a survival analysis examined group differences in speed of onset of response.

Results: Hispanic and Asian subjects had a slightly lower response rate, while Asians had the highest rates and Hispanics had the lowest rates of "full response." The more consistent Hispanic outcome differences appeared to be due to a higher placebo response rate. There was no treatment by minority group interaction for depressed patients. Speed of response and adverse effects were similar across groups.

Conclusions: There were few consistent differences in medication response and tolerability. These findings may serve to counteract the greater rate of negative attitudes toward medication use among minorities and reinforce the value of medications used to treat anxiety and depression in minorities.

(J Clin Psychiatry 2005;66:1228–1233)

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Dr. Roy-Byrne's time for literature review, data interpretation, and writing of this paper was supported by National Institute of Mental Health (NIMH) grant #1 K24 MH065324, "Treating Anxiety in Public Sector Medical Settings."

Dr. Roy-Byrne has received grant/research support from GlaxoSmithKline, Pfizer, and Forest and serves on the speakers or advisory boards of GlaxoSmithKline, Forest, Eli Lilly, Wyeth, Shire, Roche, Cephalon, and Pfizer. Dr. Perera was an employee of GlaxoSmithKline at the time of authorship. Dr. Pitts is an employee of GlaxoSmithKline Pharmaceuticals. Ms. Christi is an employee of and a major stock shareholder in GlaxoSmithKline.

We acknowledge Kevin Kane, M.Sc., for providing statistical assistance.

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Recent population-based studies[1,2] show that the quality of psychiatric care for minorities with mood and anxiety disorders in the United States is poor. This has been best demonstrated for black and Hispanic populations, in which rates of very liberally defined "quality" pharmacotherapy or psychotherapy are significantly lower than in the majority population.[1,2] These differences do not appear to be entirely explained by differences in access to services, because the same findings have been observed in insured populations.[3] Similar studies[4,5] also suggest that Asian Americans are less likely to use mental health services compared with white Americans[4] and that, among those who use services, severity of illness is much higher, suggesting a marked delay in obtaining care.[5] These differences in mental health care mirror similar minority differences in care for other medical illnesses and contribute to the "chasm" in quality of care that has resulted in significant health care disparities outlined in a recent report from the Institute of Medicine.[6]

Perhaps reflecting similar social, psychological, or political factors, the recent Minority Supplement to the Surgeon General's Report on Mental Health[5] has documented a surprising and shocking absence of minorities in published NIMH-funded clinical trials, in which less than 7% of subjects were identified as minorities and no separate analyses of this admittedly small group were

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performed. Similarly, there are no published analyses of large clinical trials in depression or anxiety that examine potential similarities and differences in minority response to medication.

Separate analysis of minority subject response to psychiatric medications is important not just because of the mental health care disparities cited above, but because there are both biological and cultural bases for possible differences in medication response and side effects. In particular, there are clearly documented minority group differences in the distribution of genetic polymorphisms that control the metabolic enzymes and cellular proteins that determine, respectively, the pharmacokinetics and pharmacodynamics of different medications.[7] Although these differences produce only "average" variations in kinetics and dynamics, the dissimilarities could contribute to therapeutic or side effect profiles that vary from the norm. Because Hispanic populations constitute an ethnic group composed of multiple races, additional intra-Hispanic differences, related to the proportion of American Indian, black, and European ancestry, may further complicate results in this group. Secondly, there are multiple cultural factors including stigma, racism, stereotyping, belief systems, and attitudes toward and preferences for treatment, all of which could contribute to variation of response.[8–11]

The purpose of this analysis is to elucidate possible reasons for poor quality of care in minorities by evaluating possible differences between white, black, Hispanic, and Asian subjects in selective serotonin reuptake inhibitor (SSRI) drugs' speed of onset and degree of therapeutic effects and side effects, using the large paroxetine clinical trial database for mood and anxiety disorders. Because there is substantial ethno-racial variability involving the cytochrome P450 2D6 (CYP2D6) enzyme system, paroxetine, which is both a substrate and an inhibitor of this system, is a particularly appropriate agent to study. Similarities in response and side effects could counter clinician bias or stereotyping that might assume that minority patients, who often have a greater burden of chronic stressors, would be less responsive to medication treatments or might be more likely to experience side effects. Elucidation of the time course of response profile could enhance the clinical practice of clinicians with this patient population. Use of a clinical trial design, with its consistent "disease management" approach to the conduct of assessment, patient education, and treatment, would presumably eliminate many, but not all, of the clinical practice variations that might be affected by cultural factors and impact quality of care. In so doing, a model for the optimal outcome in minority patients could be provided, assuming the best possible "usual care" circumstances. In this analysis, the term *minority* refers to nonwhite populations in the European and North American countries where the vast majority (97%) of these studies were done.

METHOD

Subjects

Subjects were the 14,875 adults (data on file, GlaxoSmithKline) aged greater than or equal to 18 years who were randomly assigned to either paroxetine (N = 10,054) or placebo (N = 4821) in 104 paroxetine clinical trials to investigate the efficacy and safety of the drug for major depression (N = 7603); various anxiety disorders including panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder (N = 6156); and premenstrual dysphoric disorder (PMDD) (N = 1116). The studies pooled for these analyses were conducted, from March 1984 through March 2002, in various international settings: Europe (64%), North America (33%), South America (2%), and Africa (1%). Of these, 57% were flexible-dose studies, while 43% employed a fixed-dose design. Active controls were used in 55% of the studies and placebo controls in 35%, with a combination of active and placebo controls in the remaining trials. The dataset comprised 37% men, and the ages ranged from 18 to 98 years (mean = 42.3 years, SD = 14.1 years).

Ethno-racial identity was self-reported using predetermined categories that did not permit Hispanic subjects to designate an additional racial group if they checked "Hispanic." Furthermore, the terms available depended on the study era: earlier studies used the terms *Negroid* and *Mongoloid* instead of *black* and *Asian*, and later studies included an "other" category, which some Hispanic patients may have used. Of the group, 89% were white (N = 13,250), while the remainder were black (N = 610), Hispanic (N = 415), and Asian (N = 131). There were an additional 469 subjects for whom the race was unknown or did not fall into clearly defined categories (i.e., designated as "other" in later studies).

Subjects were enrolled for studies by a combination of advertisements and recruitment from clinic populations available to the investigator, and a large number of sites and investigators across the United States and Europe participated. For efficacy analyses, only clinical trials that employed the Clinical Global Impressions (CGI) scale were included. Forty-six trials enrolling 12,197 subjects met this criterion.

Procedure

All included trials were double-blind, placebo-controlled studies of at least 6 weeks in length. Both fixed and variable doses of paroxetine between 10 and 40 mg were employed in different studies. Some studies contained another active drug comparator as well as placebo. Because the measurement of efficacy varied in different studies depending on the condition in question (e.g., Hamilton Rating Scale for Depression for major depression, Hamilton Rating Scale for Anxiety for GAD, Liebowitz

Table 1. Treatment Response and Full Response by Ethno-Racial Group in Patients With Mood or Anxiety Disorders

	Response			Full Response		
Ethno-Racial Group	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
All disease groups						
White (N = 10,108)	2.1	2.0 to 2.3	< .001	2.0	1.8 to 2.2	< .001
Black (N = 547)	2.1	1.5 to 3.0	< .001	1.6	1.1 to 2.4	.016
Hispanic (N = 361)	1.1	0.7 to 1.7	.554	0.9	0.6 to 1.5	.780
Asian (N = 112)	1.1	0.5 to 2.4	.743	2.7	1.0 to 2.0	.061
Depression subjects only						
White (N = 3990)	2.0	1.7 to 2.2	< .001	1.9	1.7 to 2.3	< .001
Black (N = 244)	1.8	1.1 to 3.1	.027	1.5	0.8 to 2.7	.167
Hispanic (N = 157)	1.3	0.7 to 2.5	.397	1.3	0.6 to 2.7	.507
Asian (N = 41)	1.3	0.4 to 4.6	.637	4.0	0.9 to 18.2	.743
Anxiety subjects only[a]						
White (N = 6118)	2.2	2.0 to 2.5	< .001	2.0	1.8 to 2.3	< .001
Black (N = 303)	2.5	1.5 to 4.0	< .001	1.7	1.0 to 2.8	.046
Hispanic (N = 204)	1.0	0.6 to 1.8	.871	0.8	0.4 to 1.4	.376
Asian (N = 71)	1.1	0.4 to 2.9	.840	2.2	0.5 to 9.0	.282

[a]Premenstrual dysphoric disorder has been categorized for analysis as an anxiety disorder.

Social Anxiety Scale for social anxiety disorder), we have employed the CGI scale for this pooled analysis of all studies, since it is the only scale common to all the studies. It is also well regarded as a standard of efficacy evaluation with clear-cut guidelines for response (CGI score of 1 or 2).

Because there is no accepted CGI measure of full response, we decided to use a CGI score of 1 to define a more complete response, which we have termed here *full response*. Use of a CGI score of 1 to define a subtype of response has been suggested previously,[12] although these authors acknowledge that it often produces groups that still have residual symptomatology and are not really "remitted." Side effects were measured by recording the spontaneous report of patients to a general open-ended inquiry about any new effects since the previous assessment. All side effects that occurred during randomized treatment were included.

Analysis

The overall strategy was to perform a pooled analysis, combining raw data from the variety of different studies carried out over the years, and completing analyses as outlined by Thase.[13] An intent-to-treat analysis was executed using the last CGI assessment completed (last observation carried forward) up to a maximum of 12 weeks after randomization. In order to provide data that are most clinically interpretable, rates of response (CGI = 1 or 2) or full response (CGI = 1) rather than group mean values were compared.

To separate the effects of treatment group and minority status, a logistic regression was performed. A treatment by minority group interaction, with a 10% α level, was used to test whether there was a difference in drug-placebo response by minority group. Analyses were done for the entire group and then separately for the largest homogeneous group, that of patients with a diagnosis of major depression, and for the remaining heterogeneous group of mostly anxiety disorder patients (also including PMDD patients). Finally, a survival analysis using a log-logistic model was used to examine speed of onset in the most homogeneous group (patients with major depression). Common adverse events greater than 5% and twice the rate of placebo for any minority cohort were recorded so that rates could be compared by visual inspection.

RESULTS

There were 11,416 subjects with CGI assessments in the required time period, although 288 of these were included in the "missing" or "other" minority category. Figure 1 depicts the percent values for both response and full response in the entire group. The odds ratios for the odds of having response to treatment and full response are shown in Table 1 for each of the ethno-racial groups. There is a significant treatment by ethno-racial group interaction for both response (p = .014) and full response (p = .012). The odds of responding for all disease groups appear to be lower for Asian and Hispanic subjects than the odds for white and black subjects. Conversely, for the full response outcome, Asian subjects (but not Hispanic subjects) have the best odds of achieving full response compared to the other ethno-racial groups. Hispanic subjects have the lowest odds of achieving full response, consistent with their lower odds of achieving response.

Figure 2 depicts the same data as Figure 1 for only those subjects with major depression, and Table 1 contains the corresponding odds ratios for relative response and full response rates. Interestingly, the treatment by ethno-racial group interaction is no longer significant, for either response (p = .62) or full response (p = .44), although the odds of responding are still numerically and consistently lower in Hispanic and black subjects across both response levels. For the other more heterogeneous subgroup of patients with anxiety disorders (Figure 3), the

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Figure 1. Response to Treatment by Ethno-Racial Group in Patients With Mood or Anxiety Disorders (all patients)

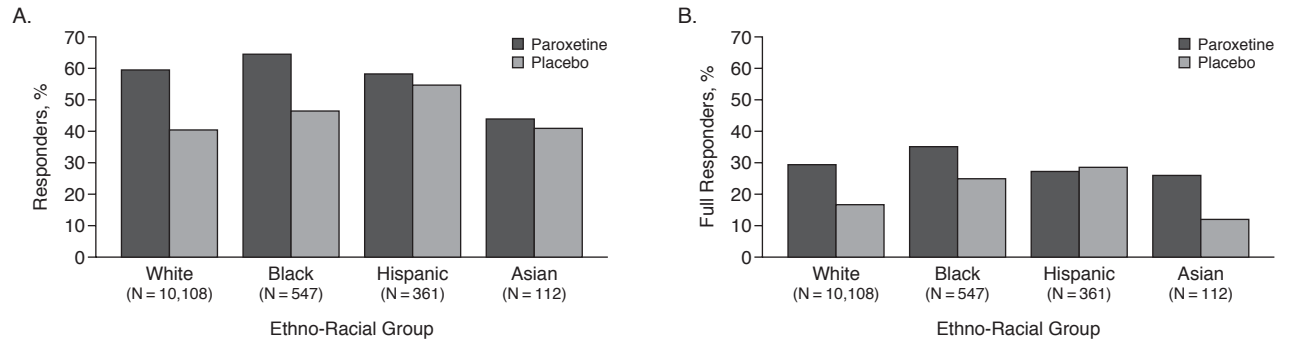


Figure 2. Response to Treatment by Ethno-Racial Group in Patients With Major Depression

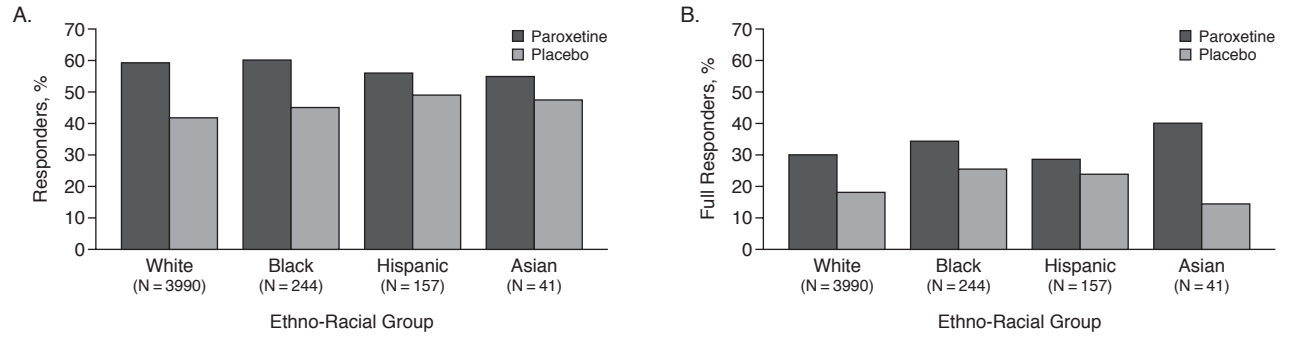
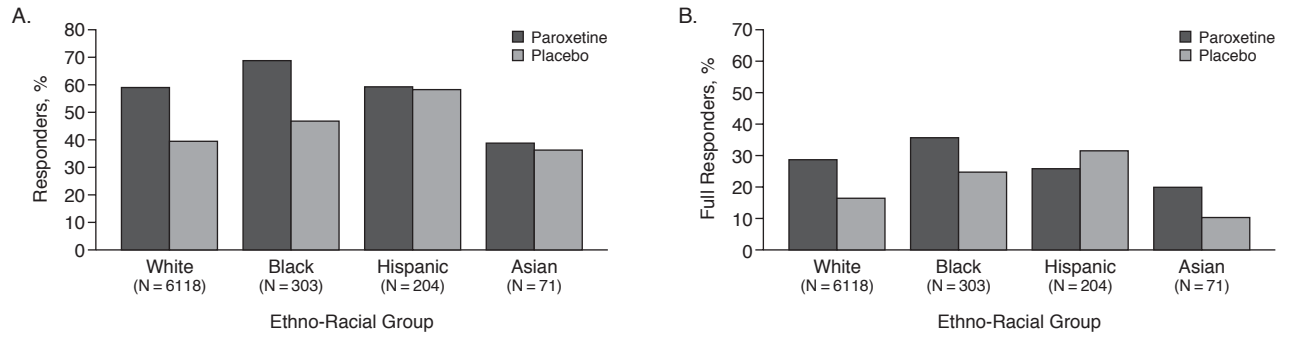


Figure 3. Response to Treatment by Ethno-Racial Group in Patients With Anxiety Disorders[a]



[a]For the purpose of analysis, premenstrual dysphoric disorder is considered an anxiety disorder.

treatment by ethno-racial group interactions were significant for both response ($p = .033$) and full response ($p = .019$). Table 1 shows that odds of responding in this group appear to be lower for both Hispanic and Asian subjects, although for the full response outcome, only Hispanic patients appear to have lower odds of achieving full response.

Finally, Figure 4 depicts survival curves indicating the time to first response in the entire group of patients separated by ethno-racial group status. There is no treatment by ethno-racial group interaction for rapidity of response (treatment by cohort interaction, $p = .74$), although the figure suggests some trend for a slower response onset in black and Asian subjects. This same treatment by cohort interaction was similarly nonsignificant for the separate subgroups of patients with depression ($p = .71$) and anxiety ($p = .46$).

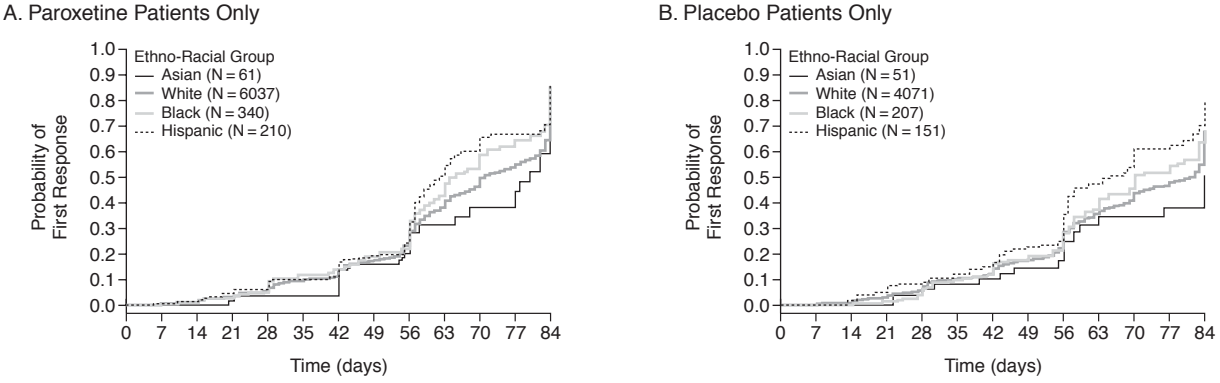
Table 2 lists common adverse events that occurred in at least 5% of patients at a rate twice that of placebo by the different minority cohorts. Of these, insomnia is the only event to show a statistical difference between minority cohorts due to a higher rate observed in the Asian sub-

Table 2. Common Adverse Events by Ethno-Racial Group in Patients With Mood or Anxiety Disorders[a]

Adverse Event	Black[b] (N = 393)	Hispanic[b] (N = 261)	Asian[b] (N = 77)	White[b] (N = 8987)	Interaction Test p Value
Constipation	5.6	7.7	7.8	8.5	.269
Decreased appetite	6.1	10.0	10.4	5.2	.368
Dry mouth	14.0	10.3	11.7	12.2	.216
Nausea	19.8	16.5	24.7	21.9	.814
Anxiety	5.3	4.6	2.6	4.7	.243
Dizziness	10.9	13.8	15.6	10.9	.780
Insomnia	10.4	10.3	20.8	14.1	.057
Libido decreased	4.6	3.8	2.6	5.8	.336
Somnolence	19.1	22.6	19.5	15.4	.676
Tremor	6.4	6.1	5.2	7.5	.622
Sweating	5.1	3.4	6.5	8.1	.923
Abnormal ejaculation[c]	11.7	12.0	7.7	16.7	.508
Impotence[c]	5.1	3.6	2.6	5.7	.617

[a]Adverse events that occurred in at least 5% of patients at a rate twice that of placebo.
[b]Values shown in percents.
[c]Analyses carried out in male subjects only.

Figure 4. Time to First Response to Treatment by Ethno-Racial Group in Patients With Mood or Anxiety Disorders (all indications)



jects. Otherwise, no discernible pattern can be observed, with ethno-racial groups having numerically small rates for some adverse events and somewhat larger rates for others.

DISCUSSION

This pooled analysis shows that, across a heterogeneous group of subjects with mood and anxiety disorders, certain minority groups seemed to differ in their drug-placebo responsivity to paroxetine. In particular, the odds of responding to drug compared with placebo were lower in Hispanic and Asian than in white and black subjects. However, the odds of achieving full response, while also comparatively lower in Hispanic subjects, were highest in Asian subjects. These findings of minority differences in response and full response appeared to be confined to the heterogeneous subgroup of patients with anxiety disorders and were not present in a more homogeneous group that contained only subjects with major depression.

Although these results are provocative and interesting, they may be limited by a number of factors: the small sample sizes of the ethnic minority groups compared with the white population, the multiple statistical tests performed, the absence of consistent results using both response and full response criteria, the absence of any effects in the more homogeneous major depression group, and the absence of a consistent pattern in many of the response differences observed (e.g., Figure 1 shows that Hispanic subject differences are due to a higher placebo response rate, while Asian subject differences are due to a lower drug response rate). However, it must be acknowledged that the results involving Hispanic subjects were quite consistent, with lower rates for both response and full response in both the larger analysis and the anxiety subgroup analysis, and rates remained numerically lower, though nonsignificant, in the depressed cohort. The absence of any clear minority group differences in time course of response and in side effect profile may also have been limited by sample size, especially for the very small Asian group (N = 131), for whom response appeared to be somewhat slower.

The one possibly valid effect, observed for both response and full response rates (but, most likely, only in the heterogeneous group of patients with anxiety disorders and PMDD and not with major depression), was an apparently higher placebo response rate in Hispanic subjects. This was especially evident in the anxiety subgroup. The reason for this is unclear, although 3 prior studies of Hispanic patients have reported this same phenomenon,[14–16] 1 involving Hispanic HIV-positive depressed patients living in New York City, 1 involving a group of depressed patients from Colombia, and 1 involving a very large duloxetine database with mixed Hispanic population. It is possible that rater differences in perception of minority subjects could have contributed to this difference, especially since the CGI is so rater-dependent and has few behavioral anchor points to facilitate clinical judgments, which are of necessity more "global." Additional subject characteristics (e.g., attitude toward physicians/researchers[8] or toward medication[17,18]) could also have contributed to this higher placebo response rate. Finally, the presence of an anxiety disorder itself may have interacted with the above factors to increase placebo response in these subjects, since this phenomenon is clearly more evident in the anxiety group. Given the presence of this finding in groups of Hispanic subjects from different geographical regions with presumed different racial composition, it is less likely that there is a biological explanation for this finding.

Although there is some evidence that Asians are more likely to be slow metabolizers of medications cleared via a CYP2D6 mechanism,[7,19,20] there was little evidence of any consistent side effect difference, save for the somewhat higher rate of insomnia, in this admittedly small group of Asian subjects. However, because only a proportion of Asian subjects might be "slow metabolizers," such effects would more likely be observed with maximal dosing rather than the wide dose ranges used in these studies. Again, the general inquiry method used in these studies for eliciting side effects is prone to differences in how various groups spontaneously report side effects and how thoroughly clinicians elicit them, and hence is less optimal for examining minority group side-effect differences.

Perhaps the most important point to be made about this analysis is that there is still a strikingly low number of minorities recruited as subjects in these studies. It is clear that, for this issue to be more completely and validly explored, a greater effort must be made to recruit more minority subjects for future clinical trials. In addition, rating methods should be optimized in order to overcome the numerous biases inherent in open-ended approaches (e.g., global ratings and general inquiries about side effects).

In conclusion, these findings document, on balance, comparable response to and tolerability of the SSRI paroxetine in various minority groups compared with white subjects. Studies have documented a more negative attitude toward taking medication in minority subjects with both depression and anxiety. Dissemination of information documenting response and tolerability in these groups similar to that observed in the white majority might serve to counteract negative attitudes and reinforce the value of using medications to treat the distress and impairment associated with mood and anxiety disorders in minority populations. Clearly, further study of this issue should be encouraged among clinical researchers as well as advocacy of clinical trial involvement among minority populations.

Drug names: duloxetine (Cymbalta), paroxetine (Paxil, Pexeva, and others).

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