The Pharmacologic Treatment of Anxiety and Depression in African Americans

Considerations for the General Practitioner

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A growing pool of recent research points to the importance of ethnicity in psychopharmacologic management of depression and anxiety disorders, with sometimes profound implications for efficacy and safety. Such research has provided provocative findings that illustrate important interethnic pharmacogenetic, pharmacokinetic, and pharmacodynamic differences, especially for African Americans. We did a systematic literature review of psychopharmacologic treatment considerations among African Americans with anxiety and mood disturbance seen by primary care physicians, who provide most psychopharmacologic treatment. The findings commonly point to a greater percentage of "poor metabolizers" among African Americans compared with Euro-Americans. General treatment considerations include greater attention to adverse effects and better clinical response and poorer compliance for a given dose, potential need for lower starting doses and slower increases, use of plasma drug levels if available, determination of past responses to a similar drug, and integration of pharmacogenetic information into an overall socioculturally and ethnically sensitive approach to assessment and treatment.

Arch Fam Med. 1997;6:371-375

The Epidemiological Catchment Area Study has determined that the lifetime prevalence of any mental disorder in the United States is 33%.[1] More than half of the patients with mental disorders are treated by primary care physicians, and fewer than 20% receive treatment in specialized mental health settings.[2] This is especially true for anxiety and depression, which are among the most common of the mental disorders treated.[2] Family physicians treat about 90% of anxiety disorders.[3] Surveys of outpatients in primary care settings show that 6% to 8% suffer from a major depressive disorder[4] that often is associated with high levels of medical utilization.[5] This pattern of health care delivery is also true of African American patients.[6]

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Although these disorders are treatable, they can be difficult to manage and may require attention to many patient variables, including interethnic pharmacogenetic, pharmacokinetic, and pharmacodynamic differences. When primary care physicians refer their patients to mental health specialists, as many as half of the patients do not complete the referral.[7,8] Because primary care physicians treat most of these patients, primary care physicians must understand how these variables modulate treatment outcome.

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There has been an emerging interest in the study of the relations between mental disorders, ethnic and cultural influences, and subsequent pharmacologic treatment interventions. Although considerably more study of ethnic differences and pharmacologic treatment have been accomplished with nonpsychoactive medications,[9] recent research

developments in psychopharmacology disclose important ethnobiological differences in response to a number of different psychotropic compounds.[10-13] Pharmacokinetic properties of psychotropic and nonpsychotropic compounds share similar metabolic pathways.[14,15] Consistent with this finding, it is not surprising that ethnic differences also have been reported to occur with psychoactive compounds. Historically, most comparative studies that showed pharmacokinetic and pharmacogenetic differences compared Asian, Hispanic, and European populations. Yet, the importance of understanding the contrast with African Americans is clear considering that this group is prescribed a greater volume of sedating compounds[16] and is at greater risk for being given more severe diagnoses despite no greater prevalence rate of psychiatric disorders when standardized diagnostic systems are used.[17,18]

We studied ethnic-related factors that should be considered in pharmacotherapy for anxiety and mood disorders in African American patients, and we suggest some general considerations for the use of psychotropic compounds in African American populations. Although a significant percentage of interethnic differences will be genetically determined, additional sociocultural influences such as nutritional status, diet, smoking behavior, alcohol consumption, and illicit or prescribed drug use may singularly or collectively modify a medication effect.

GENETIC BASIS FOR PHARMACOKINETIC DIFFERENCES

Most psychotropic drugs are metabolized by one of the hepatic cytochrome P-450 isoenzymes.[19] Genetic polymorphism in the functional expression of these isoenzymes underlies the well-documented individual variability in drug metabolism.[20,21] Of primary concern is the subpopulation who are "poor metabolizers," which results in higher plasma drug levels and, in turn, greater incidence of adverse effects.[19] Two of the most often encountered P-450 isozymes are IID6 (debrisoquine hydroxylase) and IIC19 (mephenytoin hydroxylase) and they also are polymorphic in nature.[22] The IID6 isoenzyme is responsible for the metabolism of many tricyclic antidepressants (TCAs), selective serotonergic reuptake inhibitors (SSRIs), and most antipsychotics.[23] Although only 2.9% to 10% of Euro-Americans are IID6-mediated poor metabolizers, a recent study by Kalow[24] suggests that as many as 33% of African Americans have a "gene alteration" in this isoenzyme that results in a slower metabolic rate. Thus, if this finding is observed to be consistently true, the metabolism of TCAs, SSRIs, and antipsychotics may be notably reduced in up to one third of African American patients. The IIC19 isoenzyme is involved in the metabolism of diazepam and the demethylation of the tertiary TCAs.[25] Although only 3% of Euro-Americans are IIC19 poor metabolizers, about 18% to 22% of African Americans are IIC19 poor metabolizers, suggesting a slower rate of metabolism of some benzodiazepines and tertiary TCAs in a higher proportion of African Americans. However, no evidence exists of genetic polymorphism in the 3A4 isoenzyme, which metabolizes benzodiazepines such as alprazolam, triazolam, and midazolam and some TCAs. Unfortunately, understanding the frequency of interethnic genetic variations probably is insufficient to resolve problems of multiple allelism and heterozygosity. Although understanding of specific polymorphism is important, it accounts for only a portion of interethnic differences.[26]

In summary, research on differences in liver metabolism, specifically the P-450 subsystems, of common psychotropic drugs comparing African Americans and Euro-Americans indicates higher frequency of poor metabolism in African Americans, which has clinical implications suggesting the need for more cautious prescribing patterns for anxiolytics, antipsychotics, and most antidepressants.

TRICYCLIC ANTIDEPRESSANTS

Studies involving psychopharmacologic responses to TCAs in African American populations only recently have received systematic investigation. The few studies that have been performed disclose important differences in the pharmacokinetics between African Americans and Euro-Americans.

Raskin et al[27] studied the differential effects of chlorpromazine hydrochloride and imipramine hydrochloride in 159 African American and 555 Euro-American inpatients. They used standard psychometric scales to assess the symptoms and the response to different medications administered. The study suggested that African Americans show more rapid improvement and that African American men were therapeutically more responsive to imipramine. The more rapid improvement among African American patients treated with TCAs is not an isolated finding. It is reasonable to suspect that this could be related to higher rates of poor metabolism in African Americans, resulting in higher plasma levels. Earlier large-scaled, multicentered studies[28,29] also showed "by chance" similar differences in the response rates in African American patients.

In the study by Zeigler et al,[30] no ethnic differences were found in the rate of demethylation of amitriptyline hydrochloride to nortriptyline hydrochloride or the steady-state plasma levels of amitriptyline. However, African American patients had significantly higher (50%) nortriptyline plasma levels compared with Euro-Americans. This difference (higher levels of secondary amine TCAs) is proposed as a plausible reason for the more rapid response to TCAs in African American patients.

In a retrospective medical chart review, Livingston et al[31] studied 125 psychiatric inpatients (102 Euro-Americans and 23 African Americans) treated with TCAs. African

Americans composed 18% of the sample, but of the 10 patients who experienced delirium, half were African American. The researchers concluded that delirium was notably more common in African American patients, older patients, and those with higher TCA plasma levels. However, it is unclear from the authors' summary of the data how race is notably related to delirium independent of age and plasma TCA levels.

In another retrospective medical chart review,[32] 19 patients who had overdosed on amitriptyline were studied. Subjects included were 13 Euro-American (5 men and 8 women) and 6 African American women. Results disclosed important ethnic differences in the level-dose ratio between African American and Euro-American women and higher plasma concentrations in African Americans.

In a study of indigenous African outpatients from Tanzania, the patients responded to clomipramine hydrochloride in much lower doses than those recommended in Western textbooks.[33] Yet, at the low-to-moderate dose of 125 mg of clomipramine hydrochloride, drowsiness and tremulousness were notable.

In conclusion, although these clinical reports suffer from some methodologic concerns, taken together, they consistently suggest that African Americans treated with TCAs will have higher plasma levels per dose, more adverse effects with equivalent plasma levels, and earlier onset of action than Euro-Americans. Adverse effects may be major reasons for patient noncompliance. Adverse effects and noncompliance may be minimized without compromise of efficacy by starting with lower doses of TCAs than generally recommended. Although the percentage of poor metabolizers among African Americans is higher than among Euro-Americans, a minority of patients is affected. Therefore, most African American patients probably will need traditional doses for effective treatment. Use of plasma TCA levels may be an especially helpful adjunct to clinical interview in identifying poor metabolizers, in determining when an adequate dose is being used, and in ascertaining whether there has been an adequate trial of the drug. Although monitoring of the electrocardiogram is recommended for all patients receiving TCAs, this may be especially important for African American populations, who may have a tendency to have higher plasma levels and may be more sensitive to the adverse cardiotoxic effects.

SEROTONERGIC ANTIDEPRESSANTS

A search of the recent literature yields no data on ethnic differences in the pharmacokinetic, pharmacodynamic, or pharmacotherapeutic effects of SSRIs in African American patients. Recent Food and Drug Administration approvals for new SSRIs and their popularity as alternatives to TCAs suggest a need for studies of ethnic variations in their biological activity. An important clue to the potential importance of such research is found in the review on metabolism of SSRIs by Preskorn,[34] who described a substantial inhibitory effect on the P-450 isoenzyme system. Fluoxetine hydrochloride and paroxetine at effective minimum doses had a profound inhibitory effect on the hepatic isoenzyme CYP2D6, with fluoxetine also inhibiting CYP3A4.[35,36] Both of these enzymes in the P-450 class are important in the hepatic metabolism of various drugs (eg, TCAs, some neuroleptics, β-blockers, alprazolam, and carbamazepine). Fluoxetine hydrochloride and paroxetine at the common dose of 20 mg/d cause a decrease in clearance of the TCA desipramine hydrochloride by about 80%. This pharmacologic effect of fluoxetine on desipramine is expressed in greater cognitive impairment and psychomotor functioning.[37] Another SSRI, sertraline hydrochloride, showed minimal (<30%) effect on the metabolism of desipramine. The effect of fluoxetine on CYP3A4 is relevant for the role of this enzyme in the metabolism of drugs such as alprazolam and carbamazepine.[37,38]

Considering that the SSRIs are metabolized by or inhibit the P-450 isoenzymes, and the genetic polymorphism of these enzymes in African Americans, we can predict at least some pharmacokinetic differences in a notable minority of African American patients. It is our clinical observation that many African American female patients will report significant adverse effects when given the generally recommended dose of paroxetine (20 mg) and fluoxetine hydrochloride (20 mg) and will better tolerate the medication and have an adequate therapeutic response when prescribed less than the recommended adult doses. Controlled studies clearly are needed. For now, we recommend close monitoring of the patient in the first few weeks, especially for fluoxetine because of its lengthy half-life (24-96 hours),[39] while watching for clinical signs suggestive of poor metabolism (ie, greater adverse effects and faster onset of clinical benefits).

ANTIANXIETY COMPOUNDS

A review of the existing research suggests slowed clearance and greater adverse cognitive effects and discloses more anxiety reduction from benzodiazepines in African Americans than Euro-Americans.[40] Several epidemiologic studies suggest that African Americans receive benzodiazepines less often than Euro-Americans whether the data are from a national database,[41] a southern community,[42] or a university hospital database of medical and surgical patients.[43]

In a study of the pharmacokinetics of adinazolam mesylate (J. C. Fleishaker, PhD, and J. P. Phillips, PhD, oral communication, April 1991), a triazolobenzodiazepine currently being investigated as an antidepressant and anxiolytic, 8 African American and 8 Euro-American normal volunteers were included in the study. The results showed that African Americans had increased clearance of adinazolam. Concurrently, however, the C_{max} (concentration of free [unbound] level of drug) and area under the curve of *N*-dimethyladinazolam, the metabo-

lite of adinazolam, were notably higher in African Americans. With these pharmacokinetic findings, African Americans also manifested notably larger drug effects on psychomotor performance. *N*-dimethyladinazolam has been shown to mediate exclusively the benzodiazepinelike adverse effects, including effects on psychomotor performance, after adinazolam administration. This may be responsible for the larger drug effects on African Americans despite their higher metabolic capacity for adinazolam.

SUMMARY AND CONCLUSIONS

Increased interest and scientific advances in psychopharmacology have facilitated some interesting and provocative ethnobiologic comparisons of pharmacogenetic, pharmacokinetic, and pharmacodynamic differences.Although some methodologic and other research design concerns make more definitive impressions premature, there is nevertheless an emerging body of data that identify important differential patterns of genetic, kinetic, and dynamic responsivity to various psychotropics among African American populations. These clinically significant group differences can contribute to a more culturally and ethnically sensitive and effective assessment, diagnosis, and treatment of the African American patients and their specific needs. This focus on the individual rather than his or her ethnic status is critical, because few Euro-Americans and African Americans are poor metabolizers. Physicians should attend to potentially greater efficacy, higher rates of adverse effects, and more resistance to comply with treatment for African Americans at a given dose when compared with Euro-Americans, while being careful not to assume that they are the "case" for a given patient. Lower starting doses may be in order as are closely monitored rising or tapering doses and plasma drug levels. A patient's past response to a drug in the same class of psychotropics often is instructive.

In general, the psychopharmacology literature on African Americans discloses important trends along several important pharmacogenetic, pharmacokinetic, and pharmacodynamic variables. Much work remains to delineate these important ethnobiological differences. Until this work is done, clinicians can be guided by findings of direct and indirect evidence for poor metabolism of antidepressants and anxiolytics, and by careful and frequent determination of adverse effects. Future psychopharmacology studies should control for patient nutritional status, diet, and alcohol and other drug use. Also, due to problems with accurate diagnosis of mood disturbance in African Americans, further efforts to improve assessment in this area should be undertaken. Although there is significant indirect evidence for cause and effect, the issue of medication compliance and metabolic status (ie, slow metabolizers) should be jointly studied. Finally, we noted few studies of benzodiazepine pharmacokinetics in this population despite their widespread use. Research relevant to kinetic and dynamic responses to anxiolytics in African American Americans is much needed.

Accepted for publication June 17, 1996.

Supported in part by grant MH47193 from the National Institutes of Health (Drs Strickland and Lin), grant RO1 DA08393 from the National Institute on Drug Abuse (Dr Strickland), and grants AG10123 and 85-76263 from the National Institute on Aging (Dr Strickland), Bethesda, Md.

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Practice Commentary

Although it is true that ethnicity should play a role in the management of most medical problems, it rarely is clear just how important that role should be. Researchers recently have begun to consider pharmacogenetic, pharmacokinetic, and pharmacodynamic differences based on race. The ethnic-related factors that could be considered in the pharmacotherapy of anxiety and mood disorders in African Americans, as pointed out in this article, must also include sociocultural influences. And while it is important to know that as many as 33% of African Americans may have a genetic predisposition that results in slower metabolism of some drugs, it is just as important to observe that African Americans are at greater risk for being given more severe psychiatric diagnoses despite lack of greater prevalence of these disorders when standardized diagnostic systems are used. The clear message for me is that physicians should look at the issue of psychotropic drug use with a broad, open mind and be objective, paying special attention to patients and their response and to the side effects of any medication, regardless of the patient's ethnic background.

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