Biological Differences in Depression and Anxiety Across Races and Ethnic Groups

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A growing number of studies clearly indicate the importance of race and ethnicity in the psychopharmacologic management of depression and anxiety disorders. The data highlight important pharmacokinetic, pharmacodynamic, and pharmacogenetic ethnic differences that may have profound implications for the efficacy and safety of psychotropic therapies. General treatment considerations based on these differences include greater attention to adverse event profiles, the possibility of improved clinical response at any given dose, and the potential need for lower starting doses and slower increases in dosage. Continued research in this area is clinically important as patients with increasingly divergent ethnic and cultural backgrounds seek treatment for a range of depressive and anxiety disorders. *(J Clin Psychiatry 2001;62[suppl 13]:13–19)*

For many years, when people have considered ethnic or cultural differences in disease profiles and treatment response, they have focused on the cultural diversity of the groups. However, there is now evidence to suggest that significant biological diversity may exist, and there is a need for further research to assess the impact of this on the treatment of psychiatric disorders in patients from different ethnic backgrounds. In addition to research comparing pharmacologic responses across ethnic groups, my colleagues and I, as well as others, have been researching differences in sleep architecture and neuroendocrinologic parameters in depressed individuals from various ethnic and cultural backgrounds. Some of the major findings derived from these recent studies will be briefly reviewed below.

NEUROBIOLOGICAL CORRELATES

Studies investigating the effect of ethnicity on the neurobiological correlates or biological markers of depression and anxiety disorders have focused on electroencephalographic (EEG) sleep patterns and also on neuroendocrine changes, more specifically hypothalamic-pituitary-adrenal (HPA) axis activity and cortisol secretion.

Sleep EEG Patterns

It is well established that alterations in sleep patterns and sleep disturbances are very common presenting complaints in psychiatric disorders. The total sleep time (how much time is spent actually asleep during the total sleep period [period of time from sleep onset to final awakening]), sleep efficiency, and rapid eye movement (REM) latency are all reduced in depression.[1] In contrast, REM sleep as a percentage of total sleep time is increased in depression.[2] Insomnia is also a common feature of this condition[2] and is highlighted as one of the most consistent symptoms of depression across samples from various countries.[3]

Although much is known about the changes in sleep patterns associated with psychiatric disorders, there is little information regarding the relationship between ethnicity and these changes. The data that are available suggest that there may be ethnic differences in the architecture of sleep stages. A World Health Organization (WHO) collaborative study[4] assessed the reliability and consistency of EEG sleep abnormalities in major depression. Compared with controls, depressed patients showed sleep-continuity disturbances such as increased sleep-onset latency and decrease in total sleep time and in sleep efficiency. This was in agreement with the findings of other studies.[1,2] This study[4] also reported that sleep stages 2 and 3, as percentages of total sleep time, were reduced in depressed patients, REM latency was shortened, and REM density was increased. However, the REM latency was consistently shorter in depressed patients from Tokyo and Mexico City than in depressed patients from other centers. A more recent study[5] evaluated the effect of race, specifically the

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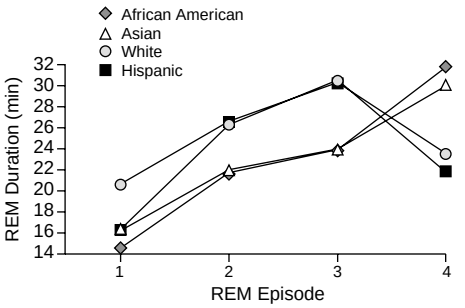
African American race, on EEG sleep and the clinical symptom profile in unipolar major depression. African American patients with depression had less total sleep, less slow-wave sleep, more stage 2 sleep, longer REM sleep latency, less REM sleep, and lower REM density than white patients. There were no differences in the clinical symptom profiles of the 2 groups.

The influence of ethnicity on the manifestation of EEG sleep changes has been investigated in patients with unipolar major depression from 4 ethnic groups. The sleep patterns of these patients were compared with those of age- and gender-matched normal volunteers from the same ethnic groups.[6,7] Sleep continuity, sleep architecture, and REM sleep were generally comparable among the 4 ethnic groups. For the normal volunteers, the results were similar to those reported by other studies. The African American subjects showed evidence of more stages 1 and 2 sleep but had diminished stage 4 sleep, and the Hispanic subjects had higher REM density than the white and Asian groups. Among depressed patients, the African American and Asian subjects had less total REM sleep and shorter REM duration during the first 3 REM episodes but longer REM duration during the fourth REM episode, compared with white and Hispanic subjects (Figure 1).

These findings suggest that although sleep patterns are remarkably similar across cultures, there are important cross-ethnic differences, particularly in the depth of sleep and in phasic REM measures. However, the pathologic implications of these differences remain to be explored in careful prospective studies of depressed patients from different ethnic backgrounds and in well-characterized, racially matched control comparisons.

Figure 1. Rapid Eye Movement (REM) Duration Profiles During the Night in African American, Asian, White, and Hispanic Patients With Major Depression[a]



[a]Adapted, with permission, from Poland et al.[7]

HPA Axis Activity

Activation of the HPA axis is an important component of the normal stress response. Prolonged HPA overactivity occurs at all levels of this axis in depressed patients. A commonly used marker for HPA axis function is the dexamethasone suppression test (DST), which measures suppression of cortisol, and a nonsuppression rate of approximately 50% has been reported for depressed patients.[8]

DST results from several studies suggest that depressed nonwhite patients have different patterns of HPA axis activity compared with depressed white patients. One such study[9] showed that depressed African American patients had a relatively low rate of DST nonsuppression compared with depressed white patients (25% and 58% nonsuppression, respectively). Of the 8 Hispanic depressed patients included in this study, none were found to have nonsuppression. Comparable results were reported by another group who observed DST nonsuppression in 43% of depressed white patients but in none of the depressed African American patients.[10] Other studies[11–13] had similar findings and consistently suggest that DST nonsuppression is lower in depressed nonwhite patients.

My colleagues and I have examined the HPA axis function of depressed patients and normal volunteers from 4 ethnic groups. Two groups of patients with chronic fatigue were also recruited; these included white and Chinese subjects. Selection criteria for the white subjects were based on the Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome, whereas for the Chinese subjects they were based on the ICD-10 criteria for neurasthenia. Overall, depressed patients tended to show higher HPA axis activity than normal volunteers, whereas the chronic fatigue patients tended to show lower HPA axis activity than the normal volunteers.

The results of a comparison of free cortisol and urinary cortisol levels in these same groups suggest that there may be ethnic differences on these measures, although the results did not reach significance. Both groups of African American subjects (normal volunteers and depressed patients) tended to have higher baseline urinary cortisol levels but lower free cortisol levels than individuals from the 3 other ethnic groups. The Chinese and white patients with prominent fatigue showed lower postdexamethasone cortisol levels than the other 2 groups (K.M.L., R. E. Poland, Ph.D., unpublished data, September 2000).

Overall, there appear to be similarities in the patterns of EEG sleep and neuroendocrine changes in depressed patients. Among the ethnic groups, statistically significant differences are consistently seen, although the interpretation of why they exist is unclear. One possible explanation is that the biological markers proposed for one group may not necessarily work well in other groups. For example, in the DST, dexamethasone is known to be metabolized at different rates in different patients, and this may also be the case across ethnic groups, with the result that ethnic variations in metabolic rate affect the results of these studies. In addition, relatively few studies examining ethnicity and biological markers have included nonwhite subjects, and these studies have involved a small sample size. This is in contrast to the vast number of studies that have been conducted in the Western population. In order for a fair comparison to be

made, additional studies in nonwhite groups are needed. The results of these will provide a clearer picture of which aspect of the chronobiological and neuroendocrinologic changes in depression may vary between ethnic groups.

PSYCHOPHARMACOLOGIC RESPONSE

It is well known that racial and ethnic differences exist in terms of response to various nonpsychotropic therapies.[11,14] However, for psychotropic medication, data confirming clinical impressions and elucidating the underlying mechanisms have emerged more gradually, culminating in an accumulation of data over the last decade that clearly demonstrate that ethnic differences do exist in terms of response to psychotropic therapy.[11,15] Early studies[16–18] examined dosage and adverse event profiles and found that Asian patients experience adverse events at lower dosages of psychotropic medication than white patients. These results may have been influenced by physicians' preferred dose and may also be subjective in terms of whether patients report side effects. However, one study[19] reported that the dosages of most drugs marketed in non-Western countries tend to evolve from a unit dose that is much lower than that commonly marketed in the United States and Europe. This means that patients in non-Western countries receive a lower dosage, probably one quarter or one third of that prescribed in Western countries.

Some data demonstrate clear ethnic differences in the pharmacokinetics and pharmacodynamics of psychotropic drugs. There is a move toward using pharmacogenetics to determine whether pharmacokinetic and pharmacodynamic differences can be predicted and whether these in turn can explain differences in clinical response and adverse event profile.

Pharmacokinetics

One of the early studies investigating pharmacokinetic differences between various ethnic groups examined serum haloperidol levels in normal male volunteers.[20] Serum haloperidol concentration was measured in whites, American-born Asians, and foreign-born Asians over a 7-hour period following haloperidol administration (0.5 mg given intramuscularly or 1.0 mg given orally). The results were similar between the 2 Asian groups but significantly different between white and Asian subjects. After controlling for body surface area, whites still had lower serum haloperidol concentrations than both Asian groups.

A number of studies have investigated ethnic differences in the pharmacokinetic profiles of tricyclic antidepressants. One such study[21] compared the kinetics of a single dose of nortriptyline in Japanese and white Americans. Following a single dose of 100 mg of nortriptyline, the area under the curve (AUC) for the white American subjects was 730 ng/mL/h. The Japanese subjects received a lower dose of 50 mg, since there were concerns about possible side effects. However, they still achieved higher blood levels of drug (AUC of 1150 ng/mL/h) than the whites.

A study[22] in the United Kingdom compared the pharmacokinetic profile of clomipramine in South Asian, Indian, and Pakistani immigrants with that in British whites.[21] Following a single dose of 25 mg or 50 mg of clomipramine, the South Asian, Indian, and Pakistani subjects all had higher blood levels of drug than the white subjects. The study was repeated with just those South Asian subjects who had changed to a more Western diet. The previously observed difference in blood levels of drug in the immigrant subjects compared with the white subjects disappeared. Clomipramine is mainly metabolized by CYP3A4, and so the results of this study suggest that any ethnic differences in the pharmacokinetics of this drug may be secondary to the effect of dietary practices.

Pharmacodynamics

There are few data that provide clear evidence of ethnic differences in the pharmacodynamics of drug therapy. However, there are suggestions in the literature that differences may exist. In one of the studies described previously,[20] prolactin response differences in normal male white and Asian volunteers were measured in addition to serum haloperidol concentrations. Following low doses of haloperidol, the prolactin response was generally increased. In this study the white subjects had less prominent prolactin responses than the Asian subjects, and the difference between the groups was more pronounced following intramuscular administration of haloperidol. This variation in response could not be explained by differences in serum haloperidol concentrations between the 2 groups.

Similarly, it appears that a lower therapeutic lithium concentration is used for Asian patients compared with whites. In the United States and Europe, the therapeutic level is between 0.8 mg and 1.2 mg, but in Asian patients the therapeutic level is between 0.4 mg and 0.8 mg.[16,23–25] The use of a lower therapeutic level appears to be consistent across a number of Asian countries. However, this difference may be largely due to physicians' practice patterns. In Europe there has been a move toward using lower therapeutic levels of lithium, but higher levels are still used in the United States.

These results suggest that both pharmacokinetic factors, including absorption and hepatic first-pass metabolism, and pharmacodynamic factors (dopamine receptor-mediated responses) contribute to ethnic differences in response to the administration of psychotropic drugs.

Pharmacogenetics

The focus of pharmacogenetic studies has largely been on those genes that encode enzymes responsible for the metabolism of medications. However, there is an emerging belief that genes controlling the function and response of therapeutic targets may also be involved in ethnic dif-

Table 1. Psychotropic Drugs Metabolized by CYP2D6

Antidepressants
Amitriptyline, clomipramine, imipramine, desipramine
Nortriptyline, trimipramine, *N*-desmethylclomipramine
Fluoxetine, norfluoxetine, paroxetine, venlafaxine
Sertraline
Neuroleptics
Chlorpromazine, thioridazine, perphenazine, haloperidol
Reduced haloperidol
Risperidone, clozapine, sertindole
Others
Codeine, opiate, propranolol, dextromethorphan, etc.

Table 2. Drugs Metabolized by CYP3A4

Typical antipsychotics
Thioridazine, haloperidol
Atypical antipsychotics
Clozapine, quetiapine, risperidone, sertindole, ziprasidone
Antidepressants
Nefazodone, sertraline, mirtazapine, tricyclic antidepressants
Mood stabilizers
Carbamazepine, gabapentin, lamotrigine
Benzodiazepines
Alprazolam, clonazepam, diazepam, midazolam, triazolam, zolpidem
Calcium channel blockers
Diltiazem, nifedipine, nimodipine, verapamil
Others
Androgens, estrogens, erythromycins, terfenadine, cyclosporine, dapsone, ketoconazole, lovastatin, lidocaine, alfentanil, amiodarone, astemizole, codeine, sildenafil

ferences. A classic example of the differences that exist between different ethnic groups is the metabolism of alcohol. One of the enzymes responsible for the metabolism of alcohol is aldehyde dehydrogenase (ALDH), and 40% to 50% of Asian subjects have a mutation that renders this enzyme inactive. The result of this is that if subjects drink even a very small amount of alcohol they have a "flushing" response, which makes them feel very uncomfortable.[26,27] There is some controversy over whether this is also true for American Indians, as some studies suggest that it is, since others have found no evidence to support the hypothesis. However, it is now known that mutation in a single nucleotide is responsible for the production of the inactive form of ALDH, and so the hypothesis can be tested.[28,29]

Psychotropic drugs are mainly metabolized by the cytochrome P450 enzymes. There are approximately 20 of these enzymes, and they are often responsible for the rate-limiting step of drug metabolism. Of these, the 3 that are most commonly involved in psychotropic drug metabolism are CYP2D6, CYP3A4, and CYP2C19.

CYP2D6 is involved in the metabolism of almost all of the psychotropic drugs (Table 1) and has some very complicated mutation patterns. The number of functional genes varies from 0 to 13 copies. The functional risk of mutations encoding this enzyme is important. For example, nortriptyline is metabolized very slowly in patients who lack a functional gene. However, in individuals who have multiple copies of functional genes, the drug is rapidly metabolized.[30] A similar effect is also seen with venlafaxine, with metabolism being slower in those individuals lacking a functional gene.[31,32] CYP2D6 is also involved in many drug-interaction problems.[33,34] The reason for such interaction is that CYP2D6 is inhibited by substrates such as quinidine, and if the enzyme is inhibited, the individual becomes a slow metabolizer, regardless of how many copies of the functional gene are present. Ethnic differences exist in terms of the activity of CYP2D6. Some groups rapidly metabolize psychotropic medication and so need a higher dose compared with "poor metabolizer" groups who are very sensitive to medication. For example, Saudi Arabian and Ethiopian populations are able to metabolize drugs much more rapidly than Northern European populations.[35,36]

CYP2C19 is another of the cytochrome P450 enzymes that is involved in the metabolism of a number of psychotropic drugs. Major ethnic differences exist in the activity of this enzyme. Across various groups the percentage of poor metabolizers ranges from 3% to 20%. The reduction in activity of this enzyme is caused by 2 specific mutations, one of which is specific to Asian individuals and is not found outside of Asian populations. The percentage of poor metabolizers has been reported to be 20% in Asians, approximately 5% in Hispanics, and approximately 3% in whites.[37,38] The rate in African American populations is unclear, with incidences of between 4% and 19% being reported.[36]

CYP3A4 is involved in the metabolism of 80% to 90% of all currently available drugs (Table 2). It has attracted attention from both physicians and pharmaceutical companies, since there have been incidences of fatal drug interactions that have resulted in the withdrawal of some drugs from the market. An example of ethnic differences in the activity of this enzyme comes from a study examining the metabolism of the calcium channel blocker nifedipine.[39,40] Asian Indians were found to metabolize nifedipine at a slower rate than British whites, as determined by AUC values. Another study[41] reported similar differences between white and Asian volunteers in the rate of metabolism of alprazolam. In this study, Asian subjects had higher plasma levels of alprazolam than the white subjects following intravenous and oral administration of the same dose.

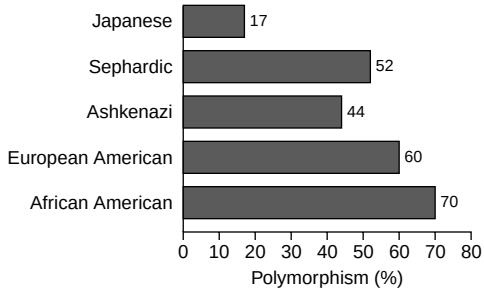
The reasons for these differences in metabolism are uncertain. There is a likelihood that environmental factors and dietary practices are both involved. What is certain is that there are combinations of genetic differences that are quite specific across ethnic groups, and these differences can be tested and investigated alongside possible environmental and dietary factors that may cause differential expression of these genes.

Polymorphism in those genes encoding drug-metabolizing enzymes and genes controlling the function

Table 3. Genes Possibly Associated With Increased Susceptibility for Psychiatric Disorders

Genes encoding the biosynthesis and catabolism of neurotransmitters
Tryptophan hydroxylase (TPH)
Tyrosine hydroxylase (TH)
Catechol-*O*-methyltransferase (COMT)
Monoamine oxidase (MAO)
Receptor genes
e.g., 5-HT_{2A}, 5-HT_{1A}, DRD2
Transporter genes
Serotonin transporter (5-HTT)
Norepinephrine transporter (NET)
Dopamine transporter (DAT)

Figure 2. Percentage of Serotonin Transporter Gene (SLC6A4) Polymorphism Among Different Populations[a]



[a]Data from Gelernter et al.[42]

of therapeutic targets (e.g., transporters, receptors) is thought to be related to the pathogenesis of many psychiatric disorders as well as temperament, personality disorders, and personality traits (Table 3). Variations in the rate of genetic polymorphism have been observed across the ethnic groups. For example, the rate of polymorphism in the serotonin transporter gene (SLC6A4) ranges from approximately 20% in Eastern Asian, Japanese, and Chinese subjects to approximately 70% in African American subjects (Figure 2).[42] This is a functional polymorphism and has been reported in some studies to be irrelevant in terms of risk factor for depression or suicide.[43,44] However, such findings pose serious questions regarding whether genetic polymorphisms might lead to differential vulnerability of ethnic differences in psychopathology across ethnic groups.

Whether the dopamine D_2 receptor gene (DRD2) A1 polymorphism is functional remains controversial.[45] Again, there is a large variation in the rate of polymorphism between the ethnic groups, ranging from 9% in Yemenite Jews to 79% in some American Indians.[46,47]

Catechol-*O*-methyltransferase (COMT) catalyzes the *O*-methylation of neurotransmitters, catechol hormones, and drugs such as levodopa and methyldopa. COMT activity is caused by a single mutation. This means that it is possible to have subjects who are homozygous for the low-activity allele, i.e., having the lowest enzyme activity, homozygous high-activity subjects, and also those who are heterozygous and have intermediate activity. Ethnic differences in COMT activity have been observed across several populations with major differences occurring between Asian and white populations in terms of the percentage incidence of low activity COMT (18% and 50%, respectively).[48,49] This is a functional polymorphism that may be clinically important in terms of the pathophysiology of disorders such as depression, the risk of psychopathology (schizophrenia or mood disorders), and the treatment of many neuropsychiatric disorders.[50–54]

A recent Italian study of 5-HTT promoter region polymorphism and response to fluvoxamine found that individuals with the short allele were less likely to respond to treatment than those with the long allele.[55] Such a relationship was recently confirmed by Pollock et al.[56] in a U.S. white sample treated with paroxetine. However, the opposite was found in a study conducted in Korea in which the short allele was predictive of significantly better response.[57] In the latter study, the promoter region polymorphism was in linkage disequilibrium with another polymorphism in intron 2, which might in part explain the discrepancy. Nevertheless, these observations do highlight the importance of ethnicity in studying genetic and other biological variables in relation to psychotropic responses as well as the vulnerability of psychiatric conditions. Since ethnic differences are known to exist in the rate of the long allele, this may explain some of the ethnic differences in treatment response. However, further studies are needed to investigate whether an individual's likelihood of responding can be predicted.

DISCUSSION

Previously when ethnic differences have been discussed, the focus was on cultural rather than biological diversity. However, although it is important to investigate biological differences between populations, caution must be exercised to ensure that ethnic stereotyping does not occur. Although there are wide intergroup variations, there is also considerable intragroup variation. It is important for the psychiatrist to be mindful of the variations, but still to treat each patient as an individual. For example, in the haloperidol study,[20] white subjects had lower blood levels of haloperidol on average, but within the groups there was variation with some overlap: some of the white subjects had high blood haloperidol levels, whereas some Asian individuals had low levels. Therefore it cannot be generalized that Asian patients always need a lower dose of haloperidol than white patients.

Patients from different ethnic or environmental backgrounds may respond differently to psychotropic drugs. The underlying psychogenic, social, or biochemical cause of mental illness may vary between different cultures and

cause differences in the presenting symptomatology. The psychotropic effect of drugs may then differ or be interpreted differently. Also, the pharmacokinetics of drugs, particularly rates of metabolism, may differ on account of genetic and/or environmental factors. The relevance of such differences to general clinical treatment will depend on the type of drug. If the margin of safety of a particular compound is small, then variation due to ethnic origin may be an important factor. Clinical findings should not, therefore, be extrapolated from one culture to another without examination of the relevant ethnic groups.

Although striking ethnic differences in pharmacologic responses to various medications have been documented in the general medical literature, there is a paucity of such information in the psychopharmacologic literature. Recent work has provided a number of studies that illustrate interesting interethnic pharmacogenetic, pharmacokinetic, and pharmacodynamic differences.

Future studies should explore new assay methods and imaging techniques capable of measuring receptor-drug interactions, in addition to using existing research methodologies to scrutinize systematically the nature and extent of ethnic differences. They should be designed not only to ascertain differences in drug responses, but also to examine genetic and environmental factors (e.g., diet, exposure to enzyme inducers) that may contribute to these differences. Pharmacogenetic probes could be used in combination with studies examining pharmacokinetic and pharmacodynamic issues for such purposes.

Taken together, the literature clearly indicates that the disposition and effect of many psychotropic agents are influenced substantially by ethnicity and culture. Recent advances in the realm of pharmacokinetics, pharmacogenetics, and pharmacodynamics have led to a greater understanding of some of the mechanisms responsible for such differences. Racial and ethnic differences in response to psychotropic medication, such as higher blood levels of drug among some ethnic populations, affect dosage requirements and potential side effects. These findings highlight the importance of considering ethnic and racial factors in psychiatric research.

Drug names: alprazolam (Xanax and others), amiodarone (Cordarone and others), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), desipramine (Norpramin and others), dexamethasone (Decadron and others), diazepam (Valium and others), diltiazem (Cardizem and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol and others), ketoconazole (Nizoral and others), lamotrigine (Lamictal), levodopa (Sinemet and others), lovastatin (Mevacor), methyldopa (Aldomet and others), midazolam (Versed), mirtazapine (Remeron), nefazodone (Serzone), nifedipine (Adalat, Procardia), nimodipine (Nimotop), paroxetine (Paxil), perphenazine (Trilafon and others), propanolol (Inderal and others), quetiapine (Seroquel), quinidine (Quinidex and others), risperidone (Risperdal), sertraline (Zoloft), sildenafil (Viagra), triazolam (Halcion and others), trimipramine (Surmontil), venlafaxine (Effexor), verapamil (Calan and others), ziprasidone (Geodon), zolpidem (Ambien).

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