The Interface of Multiculturalism and Psychopharmacology

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The impact of culture and ethnicity on psychopharmacological drug response continues to be a topic of interest and research. Diagnostic issues among patients of different races and cultures and also the influence of race and culture of the treating clinician are factors to consider before pharmacotherapy is even prescribed, although it also appears to affect the type of pharmacotherapy prescribed as well. Culture and ethnicity may also influence the response rates to treatment with pharmacotherapy along with affecting the reporting of adverse effects, compliance with the treatment regimen, and perception of need for such treatments compared to alternative health beliefs. African Americans may be diagnosed with a more severe disorder compared to Caucasians, and African Americans may also receive comparatively different, and higher, doses for the same level of symptoms compared to white patients. Asian patients may require different doses of psychotropics compared to Caucasian patients. Some of these dosing differences may be explained by pharmacogenetic differences, whereas some may be explained by cultural perceptions of illness among the different patient populations. This interface between biology, ethnicity, and cultural issues poses a challenge for the practitioner to pay attention to the multiple factors that may influence an individual's response to pharmacotherapy.

KEY WORDS: Ethnicity, psychotropic, pharmacokinetics, pharmacogenetics, multicultural, multiculturalism, psychopharmacology.

TO ADDRESS THE ISSUE, or interface, of multiculturalism and the response of different ethnic groups or races to various psychopharmacological agents, certain questions can be asked. Is there a difference in response rates among racial or ethnic groups to antidepressants, antipsychotics, anxiolytics, and mood stabilizers? If there are differences, can the response rates be accounted for by cultural perceptions of mental health and its treatment by pharmacotherapy versus alternative and more culturally accepted treatment modalities, or can the differences be solely due to genetic differences affecting pharmacodynamic and pharmacokinetic aspects of drug therapy, such as receptor expression or metabolism? Also, are there diagnostic or access to health care differences among the ethnic groups and would this possible difference be accounted for by other factors, such as the socioeconomic status of the patient or the racial prejudices that may be inherent between cultures and groups? This overview will address some of these questions in a topical fashion, but not in specific detail except to provide examples. However, there is the likelihood that this overview will raise other questions that may not be fully answerable at this time. Education and training to develop cultural competence should be a priority of the practitioner treating patients in the mental health arena.

PERCEPTIONS AND INJUSTICES IN MENTAL HEALTH

Given the common misperceptions and prejudices of the not-so-recent past regarding racial differences in the United States and elsewhere, it should be noted that these prejudices may have affected diagnostic issues and expected treatments. Recall the common diagnosis 150 years ago of *drapetomania* for

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slaves wishing to escape.[1] This was an accepted diagnosis with obvious and significant cultural and racial misperceptions regarding mental illness. It is a reminder of a practice that some good instructors have engaged in with medical residents in psychiatry. After a new resident or student cavalierly prescribed a potent psychotropic for a new patient with minimal clinical evaluation performed and a relative indifference to the patient, the instructor would sometimes say to the new medical resident, "Don't just quickly hand out a medication like Haldol until you have taken a dose yourself." Some instructors actually requested the medical resident take a single dose of some different psychotropic agents to gain a different perspective and respect for what they may be doing to their patients. That usually prompted a medication change for the patient being treated by the resident. Perhaps physicians of the 19th century should have sampled the common treatment of "whipping" for drapetomania before it was so readily prescribed for treatment. It could be said that in the early years of psychiatric practice in this country, and according to certain perceptions and guidelines and criteria for psychiatric diagnosis, psychiatrists in the United States tended to diagnose schizophrenia often. The diagnosis of schizophrenia occurred at an even greater rate in the African American population compared to the Caucasian population.[2-4] Unfortunately, the issue of the possible misdiagnosis of African American patients as having schizophrenia appears to still be occurring, even though they may present with symptoms consistent with mania or depression. These diagnostic and prescription biases are reported in a series of studies consistently demonstrating that African American patients not only are far more likely to be assigned a more severe diagnosis such as schizophrenia but also are far more likely to be treated with neuroleptics irrespective of diagnosis.[5] The treatment doses of antipsychotics also tend to be higher for African Americans than whites.[6] The disturbing realization to this writer is that these possibly prejudice-based diagnoses toward schizophrenia spectrum disorders still occur today. A more recent paper by Strakowski et al reports that when ethnically blinded evaluators reviewed the medical records, and recorded transcripts of 195 African American and white patients with at least one psychotic symptom at admission, it was found that African American men with an expert-consensus-derived affective disorder were significantly ($P < .03$) more likely than other patients to be diagnosed with a schizophrenia spectrum disorder by an unblinded clinical assessment and interview.[7] In another study assessing the use of antipsychotics as maintenance therapy for patients diagnosed with bipolar disorder, the African American group compared to the white group received antipsychotics for a significantly greater percentage of time ($P < .007$), were more likely to receive antipsychotics during periods without psychotic symptoms, and were more likely to receive older, conventional antipsychotics compared to the newer atypical antipsychotics currently approved for bipolar disorder.[8]

Given the same diagnosis, African American men are more likely to be placed on depot (long-acting injectable antipsychotics) rather than oral medications, presumably reflecting the clinicians' heightened concern with problems of compliance.[9,10] This issue seems to continue today. In a study by Arnold et al evaluating ethnicity and antipsychotic medication use in patients with psychosis, the investigators found that African American men received more depot antipsychotics than African American women or white patients. Also if the African American patients were diagnosed with psychotic mood disorders, they were discharged on higher doses of antipsychotics than matched white patients.[11] If a possibly more appropriate diagnosis of depression had been made in these discussed studies or in usual clinical practice settings, then African American patients would have likely been spared the significant side-effect burden of the older neuroleptics and would have received potentially less toxic but more effective and diagnosis-specific antidepressants. The significant side effects of neuroleptics, including irreversible tardive dyskinesia and other movement disorders, would likely have a significant impact and contribute to the observed high rates of medication noncompliance in the African American schizophrenic population.[2,3] Dosing discrepancies among Asians treated with antipsychotics have also been observed. One study noted that Asian patients required only half (1000 mg chlorpromazine equivalents daily) of the mean treatment doses compared with matched whites (over 2000 mg chlorpromazine equivalents) for similar levels of symptoms, but in a nearby usual clinical practice setting, the white patients received less than half (355 mg chlorpromazine equivalents) of the usual Asian doses.[12]

Interestingly, regarding treatment response in earlier large-scale drug trials involving multiple ethnic groups or cross-national comparisons, there is some evidence suggesting that non-Caucasians may be more responsive to placebo treatment than Caucasians.[13,14]

This may reflect alternative views and cultural perceptions of mental illness and its management in other ethnic groups, or it may reflect the significant impact of the family structure in minority groups compared to Caucasians. However, this difference in response to placebo may reflect significant biological differences among these various groups, though this is unlikely. Studies also have elegantly demonstrated that the perception and reporting of side effects are intimately influenced by the patients' culturally determined beliefs and expectations.[10,15] Sporadic reports also have shown that medication compliance or adherence might be a particularly serious problem in cross-cultural clinical settings. In a study assessing adherence differences between white and African American patients with bipolar disorder, the African American participants endorsed a fear of becoming addicted to medications and feeling that medications were symbols of mental illness as the principle factors leading to medication nonadherence.[16] In a report by Ayalon et al that assessed adherence in elderly black and Latino populations, intentional nonadherence to antidepressants on the part of both ethnic groups was associated with perceived risk of adverse effects, the stigma associated with taking psychotropics, and interestingly, the attribution of a lesser importance of antidepressants compared with other, nonpsychotropic medications that the patient may have been taking.[17] In addition, level of stress, quality and quantity of social support, and personality styles all have been reported to significantly influence psychotropic response. Cultural forces impinge upon all of these factors, although systematic research has not been adequately performed in these interesting and important areas.[10] When interacting with health care providers, the clinician may not recognize a certain culture's social rules and may misinterpret the patient's behavior as a symptom. For example, the Asian or Eastern Indian patient may not make contact with the clinician and be relatively quiet during the interview period. This may just be a sign of respect, rather than symptoms of depression. This may also be due to deference to doctors or a reluctance to share deeply personal information. In the Hispanic and Asian cultures, other family members may be making decisions about a patient's treatment, and thus if the clinician does not involve the family in the care of the patient, then a potentially therapeutic opportunity can be missed. Again, failure to recognize the multiple nonbiological factors in our patients' treatment of mental illness with psychopharmacological agents will likely inhibit our ability to achieve a full therapeutic response.

BIOLOGICAL AND GENETIC MECHANISMS AFFECTING DRUG RESPONSES

Biologically speaking, psychotropic medication responses are generally determined by pharmacokinetic and pharmacodynamic factors. Of these, the biotransformation process (metabolism) shows considerable interindividual as well as cross-ethnic variation, and has been an active and productive area of research.[18,19] Distribution of a medication is often affected by protein-binding interactions, and differences have been reported between Chinese and Caucasian groups in this area of study.[20] The rate of biotransformation is determined by both genetic and environmental factors such as diet and smoking. Evidence suggests that ethnicity and culture exert substantial influences on drug response through both mechanisms.

Ethnicity and Pharmacogenetics

The development of the field of pharmacogenetics as an academic discipline has been closely intertwined with findings of dramatic ethnic differences in drug responses that were found to be genetically determined. The genetic control of a large number of drug-metabolizing enzymes has been established, and the activities of many of these enzymes also show substantial cross-ethnic differences. Some classic examples include the differential rates of "isoniazid toxicity" between Asians and Caucasians, which led to the finding of slow versus rapid acetylation across ethnic groups. This accounted for the toxic effects of this drug in certain individuals and, more recently, accounted for the identification of ethnospecific loci of point mutations responsible for slow acetylation.[21] The "Primaquine hemolysis" found among African American soldiers fighting in Southeast Asia during World War II led to the discovery of an inborn deficiency of glucose-6-phosphate dehydrogenase, a condition that could result in severe hemolytic anemia when the afflicted is exposed to a variety of substances, including primaquine, a common antimalarial agent.[22,23] Also, the "flushing response" in Asians exposed to alcohol was proven to be principally due to a genetically determined deficiency of aldehyde dehydrogenase, which is accentuated further in some individuals by an overactivity of alcohol dehydrogenase.[24]

The cytochrome P-450 enzyme system represents a major focus of contemporary research in pharmacogenetics. Together, isozymes belonging to this system are responsible for the metabolism and detoxification of the majority of modern chemotherapeutic agents,

including practically all psychotropics that require oxidation prior to conjugation and excretion.[25] Because of specific polymorphic mutations, a certain proportion of any given population can be classified as poor metabolizers in contrast to extensive metabolizers, who do not have such deficiencies in some of these enzymes.[18] Interestingly, substantial cross-ethnic differences in the frequency of the poor metabolizer phenotype exist with these enzymes.

The remarkable diversity of the genotypes of drug-metabolizing enzymes poses a challenging question for evolutionary biologists. The historical survival value of the inborn deficiency of glucose-6-phosphate dehydrogenase is easier to explain, because those possessing such a trait are more resistant to malarial infection.[10] However, the case for the cytochrome P-450 isozymes is more puzzling. These isozymes together represent one of the most important defense systems that evolved in our ancestors through the millennia to protect against potentially harmful xenobiotics to which they were routinely exposed in their habitat. It has been argued that, just as genetic variability in susceptibility to infectious diseases has been shown to be conducive to the survival of populations, so does pharmacogenetic variability help to ensure the survival of a population facing an onslaught of toxic chemicals in the environment.[26]

Ethnicity and Other Pharmacokinetic Factors

Factors affecting pharmacokinetic differences in drug response include the areas of drug metabolism, which include both oxidation and conjugation pathways.[26,27] Studies have reported significantly slower glucuronidation of codeine in Asians, potentially leading to heightened sensitivity to this analgesic in many Asians.[28,29] Also, parameters such as volume of distribution, protein binding of medications, red blood cell (RBC)/serum lithium ratio, and other pharmacokinetic factors may play significant roles in drug response, and be subject to ethnic and cultural influences.[30-32]

Ethnicity and Pharmacodynamics

Contrasting the remarkably rich literature on ethnic variations in the structure and function of various drug-metabolizing enzymes with the relative paucity of information on receptors, it is suggested that while diversity in the former is evolutionarily adaptive because the substrates of the enzymes are predominantly xenobiotics, organisms can ill afford substantive variability in receptors because their substrates are endogenous. Some information does suggest that ethnic variations in receptors and receptor-coupled responses exist, although their functional implications have not been fully clarified. Clozapine-induced agranulocytosis serves as a different type of example of ethnic differences in drug responses that are mediated through nonpharmacokinetic mechanisms. In earlier drug trials, it was observed that this potentially life-threatening condition was significantly more prevalent among Azkenazi Jews.[33] This phenomenon led to the finding that a special cluster of human lymphocyte antigen typings, which is present among Azkenazi Jews with a significantly higher frequency, is associated with a substantially increased risk of clozapine-induced agranulocytosis. Such an association has also been observed in an American Indian patient.[34] Asians also appear to have a greater risk for this and other adverse reactions to clozapine as well.[35,36]

Ethnicity and Psychotropic Response

Reports of ethnic differences in psychotropic response can be traced back to the 1950s when these potent therapeutic agents were developed and quickly introduced worldwide. Throughout the past 4 decades, there have been numerous publications that have been based mostly on clinical impressions and surveys.[37] However, it is only in the past decade that researchers started to tackle these issues of ethnic and racial differences with vigorous study designs and sophisticated methodologies. Although many controversies remain unresolved, the results of these studies, taken together, clearly demonstrate that ethnicity is an important issue that should be considered in clinical settings for most, if not all, classes of psychotropics.

Regarding the antipsychotics, it has been demonstrated that Asians and Caucasians differ significantly in terms of haloperidol pharmacokinetics and pharmacodynamics.[38] Asian normal volunteers and schizophrenic patients had approximately 50% higher plasma haloperidol concentrations than their Caucasian counterparts when given comparable doses of medication. In general, antipsychotic dosing should probably be reduced, or at least dosed conservatively in Asian patients due to metabolic factors.[36] And though metabolism is not likely to be significantly different among African Americans and Caucasians, nevertheless, African Americans tend to be given larger doses of antipsychotics in the clinical practice setting and therefore the clinician should be mindful of possible

cultural or historical influences on their diagnoses and prescribing of antipsychotics and other psychotropics to African Americans, including utilization and access to newer atypical antipsychotics.[39-43]

The tricyclic antidepressant (TCA) studies of ethnic differences in pharmacokinetics have led to inconclusive results. Asians may metabolize TCAs significantly slower than Caucasians.[44] Data are inconsistent regarding differences in TCA response and metabolism. Hispanics may react to antidepressants differently due a combination of genetic and environmental or cultural influences.[45] Fewer data are available about a differential ethnic response to the newer antidepressants, although a recent article by Kim et al reports a difference in response rates to newer noradrenergic versus serotonergic antidepressants in a Korean inpatient and outpatient population.[46] Wagner et al reported a decreased response rate to fluoxetine by African Americans compared to whites.[47] Ethnicity has been shown to play a role in clinical presentation, diagnosis, antidepressant selection, and treatment outcomes.[48-50] Antidepressant response, given the multiple subtypes and presentations of depression, such as atypical or anxious depression, will continue to be a product of multiple factors related to ethnicity including biology, cultural traditions, belief systems, clinicians' cultural competence, and other environmental factors.

Cross-national comparison studies have replicated earlier reports from Japanese researchers regarding the need for lower doses of lithium as well as lower therapeutic lithium levels among Asians.[15] Thus, it appears that, compared to their Caucasian counterparts, Asian bipolar patients may require lower doses of lithium because of pharmacodynamic reasons. There may also be an ethnically related response to lithium in African Americans if the RBC/serum ratios are different between Caucasians and African Americans, and thus this group may be more susceptible to adverse effects and require altered dosing.[30] Other mood stabilizers such as carbamazepine and valproic acid have not been systematically studied to determine differential response rates between the ethnic groups.

Benzodiazepines have been a popular treatment for more than 40 years. There are limited data that suggest that African Americans may be more sensitive to certain benzodiazepines.[51] Agents such as diazepam and alprazolam demonstrate different pharmacokinetic profiles between Asians and Caucasians.[52] These reports of a slower metabolism of benzodiazepines in Asians have suggested that genetic factors are more important than environmental factors in the control of benzodiazepine metabolism. Therefore, dosing of benzodiazepines should be reduced, at least in the initial stages of treatment, and adjusted as needed. The common saying of "start low, and go slow" seems to apply well in the case of the Asian patient treated with benzodiazepines, though this philosophy should be applied in all areas of psychopharmacology and patient populations. In a study by Poland et al, there was no difference between Mexicans and European Americans with regard to midazolam pharmacokinetics.[53]

CONCLUSIONS

As discussed above, there are multiple factors including pharmacokinetics, pharmacodynamics, and various psychosocial or nonbiological factors that may be responsible for differences in psychotropic selection and response. Although progress has been made in identifying the mechanisms by which ethnicity and culture influence drug response, there is much that remains unknown. The available information clearly indicates that ethnicity and culture are important variables that should not be disregarded in the practice of psychopharmacology. Clinically, the importance of culture and ethnicity has been growing because of the rapid and accelerating population shifts occurring in the United States. Furthermore, because of the rapid pace of immigration throughout the country, most clinicians are no longer practicing in culturally or ethnically homogeneous settings. Today, patients seeking help enter the mental health care system with diverse beliefs, expectations, dietary practices, and social and genetic variables that are difficult for the untrained or unaware practitioner to stay informed of. All of these factors have the potential to significantly affect the outcome of prescribed psychopharmacotherapeutic treatments.

For pharmacokinetic and clinical trials to be conducted appropriately today, potential ethnic and cultural influences need to be identified and, if possible, quantified. Failure to do so might lead to the inappropriate application of study findings derived from one population to another, which may lead to potentially dangerous outcomes. Similar arguments could be made with regard to using safety and efficacy data derived from one particular group (in this country, most often the "young male white subjects") for approval of pharmaceutical agents, which are then used widely in other ethnic and culturally underrepresented populations.

In terms of research, it should be emphasized that throughout the history of the development of the field

of pharmacogenetics, as well as many other fields of medicine and psychology, ethnic diversity can serve as a major source of stimulus for new discoveries. Therefore, the practitioner needs to be mindful of the established differences and the as-of-yet undiscovered differences that various ethnic and cultural groups may have with regard to the perceptions and responses to psychopharmacological agents, and always apply caution and cultural sensitivity when treating all patients.

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