Chapter 1

Psychopharmacotherapy in the Context of Culture and Ethnicity

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The advent of the modern era of psychopharmacology in the early 1950s represented one of the most significant and dramatic milestones in the history of psychiatry and mental health. In the last half century, this relatively young field has not only provided a myriad of increasingly safe and efficacious intervention methods but also invigorated research in neuroscience and substantially enriched our understanding of the function of the brain, both in normal and abnormal conditions (Bloom et al. 1995). In addition, by enabling a large number of severely disturbed patients to move from confined settings to community living, psychopharmacological advances contributed toward the development of effective psychosocial rehabilitative programs and thereby played a pivotal role in the reshaping of the mental health care delivery system.

The power of these modern-day wonder drugs is persuasively demonstrated by the fact that within a few years of their discovery, they were introduced into practically all geographic areas of the world and quickly became the mainstay for the care of mentally ill persons in all societies (Lin et al. 1993). This is in sharp contrast with other psychiatric traditions that originated in Western countries (e.g., dynamic psychiatry), whose penetration into most non-Western societies has been slow and limited. The effectiveness and specificity of different classes of psychotropics often seem to tran-

Supported in part by National Institute of Mental Health Research Center on the Psychobiology of Ethnicity Grant no. MH47193.

Lin KM & Smith MW: Psychopharmacotherapy in Context of Culture and Ethnicity. In Ruiz P (Ed) Ethnicity and Psychopharmacology (Review of Psychiatry Series, Vol.19, No.4; Oldham JO & Riba MB, series eds.). Washington DC, American Psychiatric Press, pp. 1-36, 2000.

Cultural Context of Psychopharmacotherapy

Perhaps one of the biggest problems in contemporary medical healing practice is its tendency to focus—often exclusively—on technological, biomedical interventions (Kleinman 1988). This tendency frequently obscures the fact that treatment almost always takes place in the context of interactions among individuals. In these interactions, all participants bring into play their own knowledge, predispositions, values, priorities, modes of thinking, and belief systems. Further, perhaps reflecting the bias of Western culture, these interactions are traditionally discussed in terms of the relationship between the clinician and the patient (Marsella et al. 1985). However, in reality, neither the patient nor the clinician acts in isolation. No matter how isolated, patients almost always make decisions within the context of real or imagined input from people around them. Clinicians, too, as members of professional groups, are profoundly influenced by the opinions of their peers and prevailing ideologies in the field. As medical care in most societies becomes increasingly organized, institutional control over and influences on the practice of physicians and other health care professionals become progressively more prominent. In addition, the pharmaceutical industry has a powerful influence on clinicians' prescription behaviors as well as researchers' foci and priorities. Thus, although most pharmacotherapeutic decisions may appear technically based and straightforward, on closer look they are always found to be affected by sociocultural factors that both the patient and the clinician have brought into the transaction (Smith et al. 1993).

Despite their apparent significance, these contextual issues have rarely received adequate attention from clinicians and researchers. Often they are regarded as "noise" or even a nuisance. Consequently, there has been a dearth of information regarding the nature and determinants of related issues, such as adherence (compliance) and the "expectation effect" (including the placebo effect). Even less is known about how sociocultural factors affect these processes. Although much awaits further clarification, the extant literature in aggregate does support the suggestion that social and cultural forces play a major role in determining the

expectations and behaviors of both clinicians and patients. These in turn affect the process and outcome of treatments.

Clinician Attitudes

A large body of literature indicates that patients' cultural or ethnic backgrounds significantly determine the way clinicians conceptualize and label their problems, which in turn dictates the choices for therapeutic intervention (Mezzich et al. 1995). Using case vignettes that were identical except for ethnic group identification, investigators in a number of studies demonstrated that significantly more severe diagnoses were made in cases identical in every other aspect if the patients were identified as belonging to ethnic minority groups (Gaw 1993; Lopez 1989). Paralleling such a tendency, African American psychiatric patients have been significantly more likely than their Caucasian counterparts to have their conditions diagnosed as schizophrenia (Littlewood 1992; Lopez 1989). Interestingly, in studies in which patients were reassessed with the use of structured interviews, such differences largely disappeared, further supporting the thesis that this differential diagnostic pattern is largely determined by variables related to clinician bias rather than to patients' clinical conditions (Adebimpe 1981; Marquez et al. 1985; Mukherjee et al. 1983; Roukema et al. 1984). It is likely that similar biases led to the pervasive use of higher doses of neuroleptics in treating African American patients, irrespective of diagnosis. Studies have also shown that African American patients were more likely than their Caucasian counterparts to be treated with depot neuroleptics, presumably because of a general perception that African Americans have problems with compliance (Price et al. 1985; Strickland et al. 1991).

The potential consequence of these diagnostic and treatment biases may be far from innocuous. Several large-scale studies have documented that the rate of tardive dyskinesia also is significantly higher in African Americans (Morgenstern and Glazer 1993; Sramek et al. 1991; Swartz et al. 1997). Although other reasons for this heightened risk of tardive dyskinesia among African Americans have not been ruled out, it is very likely that their increased exposure to neuroleptics accounts for at least part of this risk.

ramidal and anticholinergic side effects but also problems such as paradoxical agitation and weight gain—have been found to contribute significantly to noncompliance and treatment termination. Some of the most dramatic and disabling untoward effects of these therapeutic agents undoubtedly would be regarded with alarm by patients irrespective of their ethnic or cultural backgrounds (Glazer and Ereshefsky 1996). However, depending on patients' beliefs and expectations, many other drug effects could be interpreted as either negative or positive. For example, in a recent study of bipolar patients in Hong Kong who were treated with lithium, Lee et al. (1992) found that unlike Western patients, the Chinese rarely complained of "missing the highs" and "loss of creativity" and actually regarded polydipsia, polyuria, and weight gain as part of the therapeutic effect of the medicine. In contrast, lethargy, drowsiness, and poor memory were serious concerns for many of these patients and were prominent in their complaints, even though it was not likely that the conditions were due to the medication, given that they occurred at similar rates among matched control subjects. Such findings highlight the importance of culturally based beliefs and expectations in determining how physical and psychological experiences associated with drug treatment and recovery are attributed.

The explanatory model approach, as originally proposed by Kleinman (1988), may be a particularly effective way to assess such beliefs and expectations systematically. Methodically eliciting patients' perspectives on the symptoms that are most salient and worrisome to them (patterns of distress), their attributions (perceived causes), their help-seeking experiences and preferences, and their perceptions of stigma permits the discrepancy between patients' and professionals' explanatory models to be systematically identified and bridged (Weiss 1997). Currently being studied are the effectiveness and utility of such an approach with regard to enhancing treatment compliance, especially in terms of the use of psychotherapeutic agents, in various cultural settings. Elements of the explanatory model are also found in Appendix I of DSM-IV (American Psychiatric Association 1994), which includes an outline for cultural formulation. It is likely that the routine use of tools such as this will enable clinicians to improve adherence.

Expectation (Placebo) Effects

Although placebo control is an essential ingredient of modern clinical trials, the nature and determinants of the so-called placebo effect remain largely elusive and unexplored (Kleinman 1988; White et al. 1985). What is generally recognized, at least by researchers and administrators of regulatory agencies, is that such effects are typically substantial and often account for a larger proportion of the improvement than that attributable to the specific effect of the therapeutic agent being tested (Shepherd 1993; Swartzman and Burkell 1988). Despite the potency of the placebo, it has rarely been the primary focus of researchers' attention. Consequently, much ambiguity currently exists concerning this important phenomenon, and there is not even a consensus regarding which term to use when referring to such effects. The most commonly used term, *placebo*, carries a negative connotation and is easily misunderstood to imply deception as well as ineffectiveness. The term *nonspecific effect* could be similarly misleading, because many of the therapeutic effects elicited by "inert" agents might well be mediated through specific biological mechanisms (Weiner and Weiner 1996).

The concept of expectation effect, commonly used in psychotherapy research, may represent a broader and less controversial notion for such a phenomenon (Kirsch 1990; Tinsley et al. 1988). The term reflects the importance and power of expectation and beliefs concerning treatment effects in determining patient response to any therapy, whether psychosocial or pharmacological. Expectations regarding the safety and effectiveness of any therapeutic intervention, in turn, are shaped by patients' sociocultural backgrounds as well as individual experiences (e.g., past experiences of side effects). Given that patients' beliefs concerning medical treatments are often shaped by their cultural backgrounds, such cultural beliefs should potently determine patients' expectations regarding therapeutic effects of offered treatments.

Despite rapid modernization, traditional medical theories and practices remain deeply rooted and influential with regard to individuals' health beliefs and behaviors in many societies (Okpaku 1998; Rappaport 1977; Wig 1989; Wolffers 1989). For example, em-

and typically fail to inform their physicians of use of herbs unless specifically asked, toxicities or treatment failures due to herb-drug interactions are likely widespread, of significant clinical consequence, but frequently unsuspected.

As will be elaborated later in this chapter and elsewhere in this volume, a limited number of enzymes are involved in the biotransformation of all drugs, including psychotropics. Although the activity of these enzymes is crucial for determining the pharmacokinetics and hence the fate and disposition of modern drugs, their primary targets are not the medications prescribed by physicians but xenobiotics (natural substances) existing in the organisms' environments that are potentially toxic (Gonzalez and Nebert 1990). Many herbs are thus natural substrates for these drug-metabolizing enzymes. Further, through inhibition and/or induction, xenobiotics, including a large number of herbs (Liu 1991), exert powerful influences on the expression of these enzymes, which then determines the rate of metabolism of the medications prescribed. Thus, herbal medicines may modulate the effect of modern therapeutic agents, including psychotropics, not only at the pharmacodynamic level (the effect of the drugs on the organism) but also at the pharmacokinetic level.

Biological Diversity and Psychotropic Responses

The central importance of biodiversity in maintaining and ensuring the survival of any species and promoting its adaptation to the local environment is a fundamental principle that often has not been adequately appreciated (Hughes et al. 1997; Marwick 1995). Possibly because of the underappreciation of the extent and significance of biological diversity in the past, recent findings of the widespread existence of genetic polymorphisms have appeared surprising to many researchers. However, emerging data now convincingly demonstrate that for the majority of the genes, polymorphism is the rule rather than the exception. Furthermore, the frequency and distribution of alleles responsible for such polymorphisms often vary substantially across ethnic groups, and

Table 1–1. Genetically variable enzymes of drug metabolism

N-Acetyltransferase[a]	Dihydropyrimidine dehydrogenase
Alcohol dehydrogenase[a]	Dopamine β-hydroxylase
Aldehyde dehydrogenase[a]	Glucuronyl transferase[a]
Butyryl cholinesterase	Glutathione *S*-transferase (class μ)[a]
Catalase	Monoamine oxidase
Catechol *O*-methyltransferase[a]	Phenol sulfotransferase[a]
CYP1A2[a]	Serum paroxanase/arylesterase[a]
CYP2A6[a]	Superoxide dismutase
CYP2C19[a]	Thiol methyltransferase[a]
CYP2D6[a]	Thiopurine methyltransferase[a]
CYP2E1[a]	
CYP3A4[a]	

[a]Polymorphic variation.
Source. Adapted from Kalow 1992 and Lin and Poland 1995.

therefore ethnicity should always be considered in genetic studies (National Institute of Mental Health 1999). These phenomena have long been recognized in blood and human lymphocyte antigen typing (Polednak 1989). In recent years, it has become increasingly clear that equally extensive polymorphisms exist in genes governing key aspects of how drugs are metabolized (see Table 1–1) as well as how they affect the target organs. These processes, commonly called *pharmacokinetics* and *pharmacodynamics*, are depicted in Figure 1–2 (Greenblatt 1993). Together, these genetic factors may explain to a large extent the often extensive interindividual cross-ethnic variations in drug responses (Kalow 1992; Lin et al. 1993). In the following sections, some of the relevant findings in these regards are highlighted.

Genetic Polymorphism of Genes Encoding Drug-Metabolizing Enzymes

As shown in Figure 1–2, of the four factors (absorption, distribution, metabolism, and excretion) that together determine the fate and disposition of most drugs, variability in metabolism is most substantial and usually is the reason for interindividual and cross-ethnic variations in drug responses (Lin and Poland 1995). Most drugs are metabolized in two phases. Phase 1, commonly mediated by one or more of the cytochrome P450 (CYP) enzymes, leads

Table 1–2. Major human cytochrome P450 enzymes and their psychotropic substrates *(continued)*

Enzyme[a]	Substrates	Genetic polymorphisms
CYP3A4	*Antidepressants:* mirtazapine, nefazodone, sertraline *Neuroleptics:* thioridazine, haloperidol, clozapine, quetiapine, risperidone, sertindole, ziprasidone *Mood stabilizers:* carbamazepine, gabapentin, lamotrigine *Benzodiazepines:* alprazolam, clonazepam, diazepam, midazolam, triazolam, zolpidem *Calcium channel blockers:* diltiazem, nifedipine, nimodipine, verapamil *Steroids:* androgens, estrogens, cortisol *Others:* erythromycin, terfenadine, cyclosporine, dapsone, ketoconazole, lovastatin, lidocaine, alfentanil, amiodarone, astemizole, codeine, sildenafil	No clear evidence of polymorphism; recent reports of functional significance of variant with mutation in regulatory region (**1B*) disputed; prevalence of **18* is 10% in Caucasians and unknown in other ethnic groups; preliminary reports of two other promising alleles (**2* and **3*), but details of these mutations not yet available

[a]Other important human cytochrome P450 enzymes include CYP2A6, CYP2B6, CYP2C8, CYP2C9, and CYP2E1. CYP2A6 is involved in the metabolism of nicotine and cotinine; CYP2C9 is responsible for the biotransformation of drugs, including phenytoin and warfarin; and CYP2E1 metabolizes acetaminophen and theophylline, as well as alcohol, and is associated with the production of free radicals.

Functionally significant genetic polymorphisms exist in most of the CYPs (Lin and Poland 1995), leading to extremely large variations in the activity of these enzymes in any given population. CYP2D6 is the most dramatic example, with more than 20 mutations that inactivate, impair, or accelerate its function (Daly et al. 1996). Significantly, most of these mutant alleles are, to a large extent, ethnically specific. For example, *CYP2D6*4 (CYP2D6B)*, which leads to the production of defective proteins, is found in approximately 25% of Caucasians but is rarely identified in other ethnic groups. This mutation is mainly responsible for the high percentage of poor metabolizers (PMs) among Caucasians (5%–9%), who are extremely sensitive to drugs metabolized by CYP2D6 (see Figure 1–3). Instead of *CYP2D6*4*, extremely high frequencies of *CYP2D6*17* (Leathart et al. 1998; Masimirembwa and Hasler 1997) and *CYP2D6*10* (Dahl et al. 1995; Roh et al. 1996; Wang et al. 1993) were found among those of African and Asian origins, respectively. Both of these alleles are associated with lower enzyme activities and slower metabolism of CYP2D6 substrates (Figure 1–3) and may be responsible in part for previous findings of slower pharmacokinetic profiles and lower dose ranges observed in Asians, with regard to both classes of psychotropics, and in African Americans, with regard to TCAs (Lin and Poland 1995). Our recent study showed that Mexican Americans had very low rates of any of these "impairing" mutations. Correspondingly, they also showed evidence of significantly faster overall CYP2D6 activity (Mendoza et al., submitted).

CYP2D6 also is unique in that the gene often is duplicated or multiplied (up to 13 copies). Individuals possessing these duplicated or multiple genes have proportionally more enzymes and faster enzyme activity and are termed *superextensive metabolizers*. This phenomenon is found in 1% of Swedes, 5% of Spaniards (the percentage of white Americans who are superextensive metabolizers is between these two figures), 19% of Arabs, and 29% of Ethiopians. Superextensive metabolizers are likely to fail to respond to usual doses of medications biotransformed by CYP2D6; they typically require extremely high doses of these drugs to achieve therapeutic levels. There have been reports of superextensive metabolizers' being regarded as noncompliant because

The following are selected examples from recent years: 1) A number of the newer antidepressants—including fluoxetine and paroxetine, two of the most widely used selective serotonin reuptake inhibitors (SSRIs)—are potent inhibitors of CYP2D6, capable of converting an extensive metabolizer into a PM. Thus, when one of these drugs is prescribed to a patient who has already been taking a CYP2D6 substrate (e.g., a TCA or a neuroleptic), the concentration of the substrate could be pushed unexpectedly into the toxic range (Aranow et al. 1989; Bergstrom et al. 1992; Brosen 1995). 2) Smoking has long been known to reduce the serum concentration of psychotropics significantly, and it is likely that many patients relapse soon after discharge from the hospital because they resume smoking (Guengerich et al. 1994). This effect is now known to be due to the induction of CYP1A2 by constituents of tobacco (DeVane 1994). 3) Many drugs and natural substances significantly inhibit the activity of CYP3A4, altering its ability to metabolize drugs that are dependent on this enzyme for their biotransformation. A widely known example is grapefruit juice (Fuhr et al. 1993; Oesterheld and Kallepalli 1997), which is capable of increasing severalfold the blood level of antiviral drugs as well as psychotropics such as nefazodone and alprazolam, if the juice and one of these drugs are taken concurrently. In addition, reports of death caused by the combination of ketoconazole and terfenadine have led to the withdrawal of the latter from the market (Jurima-Romet et al. 1994). 4) A large body of literature indicates that high-protein and high-carbohydrate diets also significantly influence the activity of CYP enzymes. A high-protein diet accelerates the metabolism of drugs such as antipyrine and theophylline, and a high-carbohydrate diet appears to have the opposite effect (Anderson and Kappas 1991; Branch et al. 1978; Fraser et al. 1979).

These examples demonstrate that environmental factors substantially modify the activity of these drug-metabolizing enzymes. Patients from different ethnic or cultural backgrounds have divergent lifestyles and likely are exposed to unique substances that may have strong effects on the expression and activity of drug-metabolizing enzymes. Thus, what is currently known about environmental influences on drug metabolism may represent only the tip of the iceberg. This may be especially true in regard to ethnic minority and other non-Western populations. For example, studies have shown that Asian Indians and Africans were significantly slower in metabolizing substrates of CYP1A2, such as theophylline, antipyrine, and clomipramine. However, after they immigrated to Europe and adopted the new dietary habits, their metabolic profiles for these drugs became indistinguishable from native Westerners' (Allen et al. 1977).

As discussed earlier, herbal medicines are routinely and extensively used by people worldwide, and there are theoretical bases, supported by empirical data, for believing that many herbs significantly modify the expression of drug-metabolizing enzymes by either inhibition or induction (Liu 1991). Because patients typically are not aware of the potential of herb-drug interactions, they often combine the use of herbs with the use of Western medicines. When severe toxic effects subsequently occur, they usually blame them on drugs prescribed by clinicians, rather than on herbal preparations obtained over the counter or from practitioners of traditional or alternative medicine (Smith et al. 1993). Because thousands of herbs are in wide use, and the indication and popularity of these herbs vary a great deal across cultural traditions, the potential for interactions between herbs and modern pharmaceutical agents is endless and largely unexplored (Smith et al. 1993).

Genetic Polymorphism of Genes Encoding Receptors, Transporters, or Other Therapeutic Targets

Monoamines, including dopamine, serotonin, and norepinephrine, have been the focus of intensive research during the past several decades. In addition to being implicated in the pathogenesis of psychiatric disorders, including schizophrenia and major depression, they have also been regarded as the putative targets of psychotropics (Barker and Blakely 1996). Confirming the importance of the serotonin system in affective and other psychiatric disorders is the fact that a number of SSRIs have been developed and are now in use for a wide range of clinical conditions. At the same time, although the far more diffuse receptor-binding profiles of the atypical neuroleptics call into question the primacy of

Reflecting this, a higher percentage of Asians have been found to be poor responders to levodopa (Rivera-Calimlim and Reilly 1984). It is at present unclear whether such interindividual and cross-ethnic variations in the polymorphism of these enzymes influence the pharmacodynamics of psychotropics used in clinical settings.

It is commonly agreed that the signal transduction cascade, which is much less understood, is also of tremendous importance in mediating the effect of psychotropics. Components of this cascade include G proteins, ion channels, second messengers, and protein kinases (Manji et al. 1995). Interindividual and cross-ethnic variations in the genes coding these proteins likely exist and may also be responsible for the individual variability in drug response observed clinically.

Summary and Future Research Directions

This brief survey serves to highlight the significance as well as the complexity of issues surrounding the influence of cultural and ethnic forces on psychotropic responses. Taken together, the literature reviewed here clearly demonstrates the importance of these factors in practicing psychopharmacotherapy. At the same time, it is equally important that any findings regarding ethnic variations in pharmacological responses not be interpreted stereotypically. In this regard, it is useful to keep in mind that almost all ethnic and cultural contrasts are superimposed on usually very substantial interindividual variations in all human groups. (For an example of this, see Figure 1–4.) This is true not only with regard to biological traits such as the ones just reviewed, but equally so (or even more so) with regard to cultural and psychosocial variables. Stereotypical interpretations of cultural and ethnic differences in either psychological or biological characteristics are not only misleading but also potentially divisive and dangerous.

Further, in interpreting biological diversity, both within and across populations, it is important to keep in mind that biological systems are dynamic rather than static and the expression of genetic predisposition is constantly modified by environmental exposure. This is most clearly demonstrated in the case of the

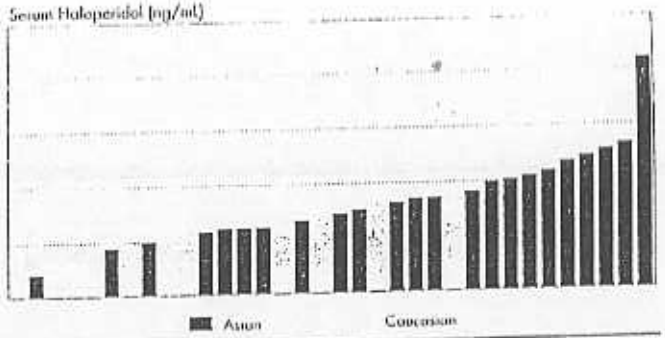

Figure 1–4. Variability of haloperidol concentrations in psychiatrically healthy volunteers after intramuscular injection of 0.5 mg haloperidol. The graph shows substantial interindividual variability within each ethnic group, dramatic differences in the pharmacokinetics of haloperidol between the two groups, and overlap of the pharmacokinetics between the two groups.

Source. Reprinted from Lin K-M, Poland RE, Lau JK, et al.: "Haloperidol and Prolactin Concentrations in Asians and Caucasians." *J Clin Psychopharmacol* 8:195–201, 1988. Used with permission.

induction and inhibition of the drug-metabolizing enzymes, which could radically alter an individual's metabolic profile, such that a genetic extensive metabolizer might appear to possess nonfunctioning gene(s). Although it is reasonable to believe that social and psychological events would similarly exert powerful influences on the functioning of relevant genes, such influences are likely to be far more subtle and complex and have remained largely unexplored.

In addition to culture and ethnicity, other key sociodemographic variables, such as age and sex, have also been known to influence significantly the pharmacokinetics and pharmacodynamics of psychotropics and other pharmaceutical agents (Jensvold et al. 1996). For example, the activity of most P450 enzymes declines substantially in older individuals (Kinirons and Crome 1997; Tanaka 1998), who are also likely to have progressive loss of neuron cells as well as receptors targeted by psychotropics (Salzman

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