CHAPTER

4

Psychopharmacology in Cross Cultural Psychiatry

Keh-Ming Lin, Michael W. Smith and Ricardo P. Mendoza
Department of Psychiatry, Harbor-UCLA Medical Center, Torrance, CA, USA

INTRODUCTION

Findings of substantial and clinically significant cross ethnic differences in psychotropic responses have been repeatedly reported since the early 1960s [1–5]. However, despite this body of literature, most clinicians and researchers have remained unaware of such a possibility and often suggestions of ethnic differences in drug responses were regarded as either unlikely or unimportant. Reflecting this general attitude, very few well-designed research efforts have been made to examine the validity and clinical relevance of these observations, as well as the mechanisms responsible for them. This is ironic and regrettable, especially in light of the potency of modern psychopharmacology, with its promise of miraculous cure, as well as the danger of substantive harmful effects when administered inappropriately. Since the 1950s, these modern psychotropics have revolutionized psychiatric care world wide; their widespread use attests to their efficacy and utility. At the same time, however, it is disconcerting to realize that, despite the remarkable success in the practice of psychopharmacology across cultural and ethnic lines, so little is currently known regarding the potential contribution of cultural and ethnic factors in determining whether a particular patient would benefit from a particular treatment regimen, or if he or she is at a particular risk for certain potentially dangerous or devastating adverse effects.

THE NEGLECT OF ETHNICITY AND CULTURE IN PSYCHOPHARMACOLOGICAL RESEARCH

Many factors possibly contributed towards such neglect. First of all, contrary to clear evidence indicating otherwise [5], there is a pervasive belief in psychiatry that equates biology with universality, and attributes cross cultural/cross ethnic diversity

Cross Cultural Psychiatry. Edited by John M. Herrera, William B. Lawson and John J. Sramek.
© 1999 John Wiley & Sons Ltd.

51. **Lin KM**, Smith MW & Mendoza RP: Psychopharmacology in Cross Cultural Psychiatry In Herrera JM, Lawson WB, & Sramek JJ (Eds). Cross Cultural Psychiatry. John Wiley Sons, New York, pp 45-52, 1999

only to psychosocial factors [6]. Such a belief leads to the neglect of remarkable biological diversities that exist in all living organisms, including the human species, both within and between ethnic groups, and has been at least partially responsible for the slow progress of cross cultural research on biologically related issues.

Similarly, because of the long history of the racist misinterpretation and distortion of scientific data [7], researchers and clinicians are often uncomfortable with the idea that people with divergent ethnic and ancestral backgrounds might differ significantly in their biological endowments, including pharmacological responses. This 'color-blind' approach, 'politically correct' and innocuous in appearance, probably results in the neglect of issues that may be of pressing importance for ethnic minority populations. Further, because of past incidents of the flagrant abuse of minority patients in biomedical research [7], there is a pervasive sense of distrust in many minority communities towards the 'mainstream' biomedical establishment in general and research endeavors in particular. These forces, as well as other more general factors related to the accessibility of healthcare, combined to make it difficult for patients and volunteers of ethnic minority to participate in biomedical research in general, and research in psychopharmacology in particular. As a result, until most recently, most studies drew their conclusions from subjects that were almost exclusively 'white males.' Ironically, once published, such findings are typically applied to the populations that have been largely excluded from research. Further, the absence of data indicating ethnic variation in responses is then taken to mean that ethnicity and culture do not represent significant factors in determining treatment effects. This leads to a vicious cycle, preventing the serious consideration of issues that may be of central relevance to the majority of our patients, who are increasingly culturally and ethnically diversified.

THE EMERGENCE OF PHARMACOGENETICS

The need to include ethnically diverse populations in psychiatric research, including psychopharmacological research, takes on a renewed sense of significance and urgency along with the emergence and rapid progress of molecular biology. As the field enfolds, it becomes increasingly clear that gene polymorphism exists widely in most, if not all, human genes, including those involved in the mediation of drug metabolism and/or responses. At the same time, for almost all of the genes demonstrating polymorphism, ethnic variation is the rule rather than the exception. For example, the activity of most extensively studied cytochrome P-450 (CYP) enzymes, such as the CYP2D6 and CYP2C19, is significantly influenced by a number of distinctive mutations, some of which are to a large extent ethnically specific. Receptor polymorphisms that have been identified thus far, such as those involving D_2 and D_4, also show remarkable ethnic variations in their mutation patterns [8–10]. Although the meaning and clinical relevance of these variations remain to be further examined, there is every reason to believe that such differences are far from trivial, both for clinical and for research purposes (for example, the

controversy regarding the association between D_2 polymorphism and alcoholism was partially generated by the neglect of ethnic difference in the former [11]). With the expectation that new developments in phenotyping (the measurement of enzyme activities) and genotyping (the detection of mutations using molecular biology methods) procedures will soon lead to the establishment of pharmacogenetic probes that could be applied widely in clinical settings, it is even more important that the role of ethnicity is not neglected. Otherwise, there may be situations where the probes are developed based on norms of one ethnic group, yet applied on other ethnic groups where they would yield little clinically useful information.

The progress of pharmacogenetics and molecular biology also makes it increasingly clear that the expression of genes is typically remarkably responsive to environmental, and thus cultural, influences. This is very clearly seen in the case of pharmacogenetics: major CYP enzymes, such as CYP1A2, CYP3A4 and CYP1E2, have been demonstrated to be particularly sensitive to the influences of environmental factors [12–17]. A large number of natural substances, including constituents of tobacco, micronutrients, macronutrients, herbs, industrial toxins and even environmental pollution, could either induce or inhibit the expression of these enzymes in a significant manner [12–17]. For example, the activity of CYP3A4 is significantly lower in Mexican Americans and Asian Indians than in other groups [18]. Although the reason for such a difference is not completely clear, it is assumed that it is most probably caused by ethnic differences in dietary practices, especially the intake of certain vegetables that may inhibit the enzyme. Similar explanations may be applicable to earlier observations of lower clearance rates in Asian Indians and Sudanese people for substances such as antipyrine [19–20] and clomipramine [21] than seen in their British White counterparts. This hypothesis was further strengthened by the fact that those who switched from their traditional (mostly vegetarian) diet to a British diet (which included meat) developed a metabolic pattern similar to that of the Whites. Other factors might also be responsible for changes in the metabolic profiles in migrants who moved from rural to urban settings. As an example, a recent study reported the rate of metabolism of CYP1A2 to be higher in a group of Koreans living in urban areas than in their compatriots residing in rural Korea [22]. Since both groups were non-smokers and had similar dietary intake, the authors suggested that exposure to a higher level of air pollution might be responsible for the induction of the drug-metabolizing enzyme in the urban group.

While the Western world is going through a resurgence or revival for the medicinal use of herbs [23], such practices have always been extremely common among ethnic minorities in the USA, and among non-Westerners around the world [24]. Herbs as well as other natural substances are the natural substrates for the 'drug-metabolizing' [1], and are thus likely to modify the activity of these enzymes through induction or inhibition [25]. Because many of these herbs are taken concurrently with psychotropic medications, drug–herb interactions are most likely to occur, but have rarely been reported because such a possibility is rarely considered.

Thus, for a number of important reasons, advances in pharmacogenetics have contributed greatly to our understanding of the mechanisms underlying cross ethnic as well as interindividual variations in drug responses. The incorporation of these research tools and concepts in future studies is crucial, not only for the further clarification of the extent, of and mechanisms responsible for, such variations but also for the establishment of guidelines for rational psychopharmacotherapy that are ethnically and culturally appropriate and useful.

DANGER OF STEREOTYPING AND OVERGENERALIZATION

As amply demonstrated throughout this volume, cross ethnic differences in pharmacological responses are often substantial and of clinical significance. However, unless these findings are understood in the context of interindividual variability in drug responses that exist in any given ethnic group, they are likely to be interpreted stereotypically and simplistically. Such a misunderstanding might lead to the indiscriminate treatment of all patients from a particular group with a set dose range, thereby neglecting the need for individual tailoring of any treatment regimen in the clinical settings. Figure 4.1 shows that in one of our earlier studies of the metabolism of haloperidol, cross ethnic and interindividual variations are both substantial, and superimposed [26].

Largely for political reasons, populations in the USA are customarily divided into several major ethnic groups, including African Americans, Asians, Caucasians, Hispanics and Native Americans. Included in each of these major groupings are a large number of distinct cultural or 'nationality' groups. Although these 'subgroups' often share important historical and cultural roots, as well as biological traits, each is unique in many aspects, rendering indiscriminate generalization a precarious business. For example, although the CYP2D6*4 (B mutation) may be regarded as a Caucasian-specific mutation because it is extremely rare in Asians and African Blacks but is commonly seen in all Caucasian groups ranging from Latvian to Spanish, studies conducted in Spain have consistently shown a lower rate relative to the other Caucasian groups (but still substantially higher than any non-Caucasian groups studied thus far) [27]. Another prominent example is the enzymes involved in the metabolism of alcohol and acetaldehyde (alcohol dehydrogenase and aldehyde dehydrogenase, respectively) [28]. Although high rates of specific mutations involving these enzymes render close to half of any given East Asian populations (e.g. Chinese, Japanese and Koreans) extremely sensitive to the effect of alcohol [29–30], this is not the case with Asians with Malay origin, such as Filipinos, Filipino Americans and Taiwanese aborigines [31].

Similar danger exists in the indiscriminate lumping together of different Hispanic groups. Although Puerto Ricans and Mexican Americans share important biological and cultural roots, there are also distinct differences in the history of

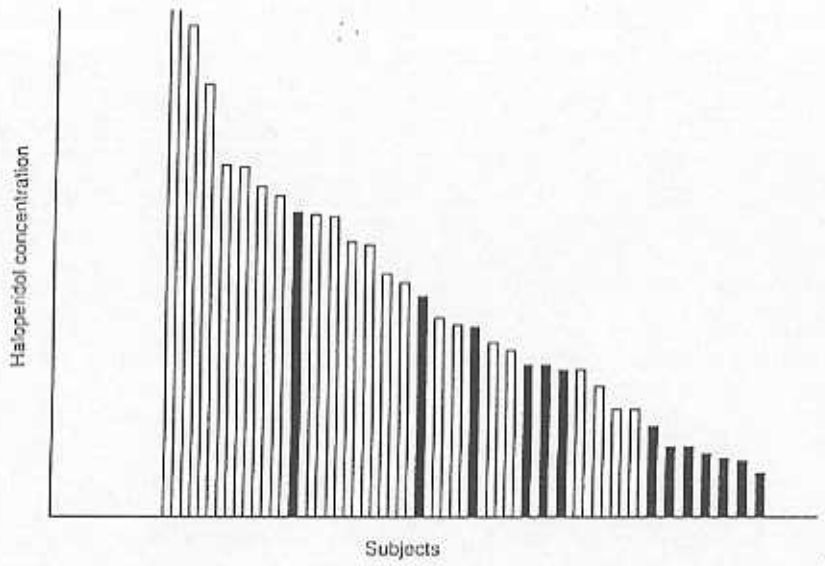

FIGURE 4.1 Variability of haloperidol concentrations in normal Asian (□) and Caucasian (■) volunteers after the administration of haloperidol (1.0 mg, orally). The graph shows: (1) substantial interindividual variability within each of the ethnic groups; (2) dramatic differences in the pharmacokinetics of haloperidol between the two ethnic groups; and (3) overlap of the pharmacokinetics between the two groups

migration and the intermixture of various racial groups leading to significant variations in behavioral patterns and possibly pharmacological responses. This may be a reason for the discrepancy previously observed in Hispanics' responses to tricyclic antidepressants: while a clinical study conducted in New York showed that Puerto Ricans were extremely sensitive to the medication [32], research conducted by Gaviria *et al.* [33] and by our group showed little difference between Mexican Americans and their Caucasian counterparts in the metabolism of these medications [33].

THE IMPORTANCE OF 'NON-PHARMACOLOGICAL' FACTORS

Lastly, it should be emphasized that, irrespective of specificity and potency of any given pharmacological intervention, treatment effects are invariably even more powerfully determined by factors that are primarily 'non-biological' in nature [34]. These include issues related to expectations, adherence (compliance), placebo

response and clinician–patient relationships [32]. As these responses are all largely mediated through processes that are symbolic and interactive in nature, there is little question that culture should play an extremely important role in shaping them, and in turn powerfully determine whether any given patient will respond to a particular treatment regimen.

As important as these issues are, unfortunately they have thus far rarely been the focus of systematic research attention, and the literature covering this important area is meager or next to non-existent. However, data derived from a large variety of sources, including clinical reports, anthropological observations and utilization studies, converge to support the hypothesis that cultural factors are indeed extremely important in influencing patients' attitudes, adherence and ultimately responses to pharmacological treatment [34–38]. As an example, among Asians and Asian Americans there is a widespread belief in the danger of the long-term use of 'Western' medications, which may contribute significantly to problems of non-compliance [34]. However, without systematic research data the extent to which this may be the case remains unclear.

The therapeutic relationship is a two-way process, and the outcome of the therapeutic interaction is influenced not only by the patient but also by the clinician. In the cross cultural situation, the clinician's ability to accurately assess a patient's symptoms as well as his or her responses to treatment may be hampered by lack of an adequate understanding of the patient's cultural norms [34], as well as misperceptions. This is probably the reason for higher doses of neuroleptics being prescribed for African American patients than to their Caucasian counterparts [39]. In several studies, African Americans have also been shown to suffer from a higher rate of tardive dyskinesia [40–42], which is probably related to their exposure to higher doses of neuroleptics over time. This is thus not an innocuous condition and deserves more careful and systematic exploration.

SUMMARY AND CONCLUSION

In this short chapter we focused on some of the conceptual issues that may be of particular relevance for research and practice of psychopharmacotherapy in the cross cultural setting. Although observations suggesting the existence of ethnic differences in psychotropic responses appeared soon after the introduction of these powerful therapeutic drugs in the 1950s, objective data documenting such differences started to emerge only in the last two decades. Progress of the field in recent years has accelerated. Together with the phenomenal growth of pharmacogenetics and the maturation of research methodology in other relevant areas, it is expected that our knowledge in the application of psychopharmacology in cross cultural psychiatric practices will continue to expand, such that the use of these powerful agents will become increasingly targeted, rational and effective irrespective of a patient's ethnic and cultural backgrounds.

ACKNOWLEDGMENTS

This study was undertaken by the Research Center on the Psychobiology of Ethnicity and the Department of Psychiatry, Harbor-UCLA Medical Center. It was supported in part by NIMH Research Center on the Psychobiology of Ethnicity MH47193.

REFERENCES

1. Kalow, W. ed. 1992. *Pharmacogenetics of Drug Metabolism.* New York: Pergamon Press.
2. Nebert DW, Weber WW. 1989. Pharmacogenetics. In: *Pharmacogenetics. Principles of Drug Action,* 3rd ed. Churchill Livingstone, pp. 469–531.
3. Mendoza R, Smith M, Poland R, Lin K, Strickland, T. 1991. Ethnic psychopharmacology: the Hispanic and Native American perspective. *Psychopharmacol Bull* 27: 449–61.
4. Goedde HW, Agarwal DP, eds. 1986. *Ethnic Differences in Reactions to Drugs and Xenobiotics.* New York: Liss.
5. Lin KM, Poland RE, Nakasaki G. 1993. *Psychopharmacology and Psychobiology of Ethnicity.* Washington, DC: American Psychiatric Press.
6. Kleinman A. 1988. *Rethinking Psychiatry.* New York: Free Press.
7. Lawson W. 1986. Racial and ethnic factors in psychiatric research. *Hosp Community Psychiatry* 37: 50–4.
8. Lee MS, Lee KJ, Kwak DI. 1997. No association between the dopamine D2 receptor gene and Korean alcoholism. *Psychiatr Genet* 7: 93–5.
9. Blum K, Noble EP, Sheridan PJ, Finley O, Montgomery A, Ritchie T *et al.* 1991. Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. *Alcohol* 8: 409–16.
10. Dobashi I, Inada T, Hadano K. 1997. Alcoholism and gene polymorphisms related to central dopaminergic transmission in the Japanese population. *Psychiatr Genet* 7: 87–91.
11. Chen CH, Chien SH, Hwu HG. 1996. Lack of association between TaqI A1 allele of dopamine D2 receptor gene and alcohol-use disorders in atayal natives of Taiwan. *Am J Med Genet* 67: 488–90.
12. Dollery C, Fraser H, Mucklow J. 1979. Contribution of environmental factors to variability in human drug metabolism. *Drug Metab Rev* 9: 207–20.
13. Shils ME, Young VR, eds. 1988. Diet, nutrition and drug reactions. In: *Modern Nutrition in Health and Disease,* 7th ed. Philadelphia: Lea & Febiger.
14. Conney AH, Pantuck EJ, Hsiao KC, Kuntzman R, Alvares AP, Kappas A. 1977. Regulation of drug metabolism in man by environmental chemicals and diet. *Fed Proc* 36(5): 1647–52.
15. Ereshefsky L. 1996. Pharmacokinetics and drug interactions: update for new antipsychotics. *J Clin Psychiatry* 57 (Suppl 11): 12–25.
16. Murray M, Reidy G. 1990. Selectivity in the inhibition of mammalian cytochromes P-450 by chemical agents. *Pharmacol Rev* 42: 2–101.
17. Anderson KE, Conney AH, Kappas A. 1986. Nutrition as an environmental influence on chemical metabolism in man. Ethnic differences in reactions to drugs and xenobiotics. *Progr Clin Biol Res* 214: 39–54.
18. Ahsan C, Renwick A, Waller D, Challenor V, George C, Amanullah M. 1993. The influences of dose and ethnic origins on the pharmacokinetics of nifedipine. *Clin Pharmacol Ther* 54: 329–38.
19. Desai NK, Sheth UK, Mucklow JC. 1980. Antipyrine clearance in Indian villagers. *Br J Clin Pharmacol* 9: 387–94.

20. Branch R, Salih S, Homeida M. 1978. Racial differences in drug metabolizing ability: a study with antipyrine in the Sudan. *Clin Pharmacol Ther* 24: 283–6.
21. Shimoda K, Minowada T, Noguchi T, Takahashi S. 1993. Interindividual variations of desmethylation and hydroxylation of clomipramine in an Oriental psychiatric population. *J Clin Psychopharmacol* 13(3): 181–8.
22. Chung WG, Kang JH, Lee KH, Roh HK, Cha YN. Differences of CYP1A2 activity between urban and rural people. *Clin Pharmacol Ther* 63: 216.
23. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. 1993. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med* 328(4): 246–52.
24. Lam CL, Cataivas MG, Munro C, Lauder IJ. 1994. Self-medication among Hong Kong Chinese. *Soc Sci Med* 39(12): 1641–7.
25. Liu G. 1991. Effects of some compounds isolated from Chinese medicinal herbs on hepatic microsomal cytochrome P-450 and their potential biological consequences. *Drug Metab Rev* 23: 439–65.
26. Lin KM, Finder E. 1983. Neuroleptic dosage in Asians. *Am J Psychiatry* 140: 490–1.
27. Agundez JAG, Martinez C, Ledesma MC, Ladona MG, Ladero JM, Benitez J. 1994. Genetic basis for differences in debrisoquin polymorphism between a Spanish and other white populations. *Clin Pharmacol Ther* 55: 412–17.
28. Agarwal D, Goedde H. 1990. *Alcohol Metabolism, Alcohol Intolerance and Alcoholism: Biochemical and Pharmacogenetic Approaches*. Berlin: Springer-Verlag.
29. Shibuya A, Yoshida A. 1988. Frequency of the atypical aldehyde dehydrogenase-2 gene (ALDH2/2) in Japanese and Caucasians. *Am J Hum Genet* 43: 744–8.
30. Yoshida A. 1983. *Differences in the Isozymes Involved in Alcohol Metabolism Between Caucasians and Orientals*. New York: Alan R. Liss.
31. Lubben JE, Chi I, Kitano HH. 1988. Exploring Filipino American drinking behavior. *J Stud Alcohol* 49: 26–9.
32. Marcos LR, Canero R. 1982. Pharmacotherapy of Hispanic depressed patients: clinical observations. *Am J Psychother* 36(4): 505–13.
33. Gaviria M, Gil AA, Javaid JI. 1986. Nortriptyline kinetics in Hispanic and Anglo subjects. *J Clin Psychopharmacol* 6: 227–31.
34. Smith M, Lin KM, Poland RE, Nuccio I, Zheng Y, McGeoy S, Lesser I. 1993. Ethnicity and imipramine response: I. Pharmacokinetic comparisons (submitted for publication).
35. Smith M, Lin K, Mendoza R. 1993. 'Non-Biological' issues affecting psychopharmacotherapy: Cultural considerations. In: Lin K, Poland R, Nakasaki G, eds. *Psychopharmacology and Psychobiology of Ethnicity*. Washington: American Psychiatric Press.
36. Smith M, Lin KM. 1996. Biological Implications for Ethnic Differences in Treatment. In: Kato PM, Mann T, eds. *Health Psychology of Special Populations: Issues of Age, Gender, and Ethnicity*. New York: Plenum.
37. Moerman D. 1979. Anthropology of symbolic healing. *Curr Anthropol* 20: 59–80.
38. Jenkins JH. 1988. Conceptions of schizophrenia as a problem of nerves: a cross-cultural comparison of Mexican-Americans and Anglo-Americans. *Soc Sci Med* 26: 1233–43.
39. Strickland T, Ranganath V, Lin K, Poland R, Mendoza R, Smith M. 1991. Psychopharmacologic considerations in the treatment of Black American populations. *Psychopharmacol Bull* 27: 441–8.
40. Jeste DV, Lindamer LA, Evans J, Lacro JP. 1996. Relationship of ethnicity and gender to schizophrenia and pharmacology of neuroleptics. *Psychopharmacol Bull* 32(2): 243–51.
41. Glazer WM, Morgenstern H, Doucette J. 1994. Race and tardive dyskinesia among outpatients at a CMHC. *Hosp Community Psychiatry* 45(1): 38–42.
42. Lawson WB. 1996. Clinical issues in the pharmacotherapy of African-Americans. *Psychopharmacol Bull* 32:2): 275–81.