
Ethnic and cultural factors in psychopharmacology

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Barring a few exceptions (such as rauwolfia), most of the psychiatric medications have been developed in the West, especially the USA, the UK and Europe. Their safety trials have been conducted in the populations living in these parts of the world. Although these drugs are used all over the world there is a limited research to determine accurate pharmacodynamic and pharmacokinetic profiles across different ethnic groups. Hence, clinicians usually adopt a 'universalist style' (seeing every condition and treatment as similar) of managing psychiatric illnesses, but this appears to neglect the information from the emerging literature which advocates a relativist approach to pharmacotherapy (see Lin *et al* 1995 for review). Anthropologists have encountered 'phenomenological absolutism' in a general tendency of people from one culture to perceive and value other cultures in terms unconsciously based upon their own, but phenomenologically experienced as absolute and universally applicable (also known as ethnocentrism). In addition to ethno-biological determinants of drug response, there are significant cultural factors: the concurrent use of pluralistic health systems, alternative therapies and folk remedies which might support, hinder or complicate pharmacotherapy and treatment adherence. In this paper we highlight some key factors of which clinicians need to be aware. These include pharmacodynamic and pharmacokinetic principles, and application of these principles in pharmacological management of psychiatric conditions. Ethnic differences in pharmacodynamics are most clearly demonstrated in the greater sensitivity to a variety of drugs in Caucasians than in Asians or in African-Caribbeans.

The therapeutic effect of pharmacologically active drugs is determined by pharmacokinetic and

pharmacodynamic processes. A recently recognised key factor in the study of pharmacokinetics has been pharmacogenetics; a pharmacogenetic variation according to ethnic group can lead to significant genetically determined modifications of metabolising enzymes (i.e. the pharmacokinetic handling of the drug by the body). This, in turn, leads to differing therapeutic levels and half-lives and, therefore, variable profiles of therapeutic and adverse effects.

Ethnicity

General issues

Definitions of ethnicity and ethnic group classifications provoke considerable discussion and debate. Ethnicity is a social construction and is often invested with greater stability, permanence and biological importance than is justified (see Box 1). Ethnicity has been defined as colour of skin (e.g. White), nationality (e.g. Indian) and a mixture of the two in the Office of Population, Censuses and Surveys (1992) criteria. Definitions of ethnicity can be based at a social level, at an individual identity level or, as is usual in medical practice and research, at a level which recognises a combination of social, cultural and phenotypic similarities rather than genotypic differences. It is the association of phenotypic similarity with pharmacogenetic variations in drug metabolism that render ethno-pharmacogenetic variations of clinical importance. The association of phenotypic appearance with culturally distinct health beliefs further emphasises the importance of a bio-psychosocial approach. At the identity level, individuals see themselves as

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Box 1. Definitions of race, ethnicity and culture

Ethnicity – Self or social ascription of belonging to a group with common geographical origins, race, language, religion, etc., which transcends kinship and neighbourhood. Ethnic categories retain a strong racial component. These are ascriptively mobilised by individuals. An ethnic group is a social group characterised by distinctive tradition, common history and maintained within the group across generations.

Race – Largely perceived by appearance and attributed to biological and genetic traits. Racial differences get perpetuated in society because they have cultural significance.

Culture – Shared system of concepts or mental representations established by convention and reproduced by traditional transmission. People live culturally rather than in cultures.

belonging to a group with common geographical origins, migratory status, race, language, religion or faith and ties which transcend kinship, neighbourhood and community boundaries. Ethnicity is also linked closely with shared traditions, values, symbols, folk music and folk memories. Settlements, food preferences and employment patterns all shape the definition and revision of ethnic identity boundaries. Such a range of features in the definition and understanding of ethnicity reflects a dynamic interaction between biological and social-cultural factors. It is this bio-psychosocial interaction that forms the context in which the doctor-patient relationship is located and in which medication is prescribed and taken.

Personality factors

Within a single ethnic group, various social and culturally distinct behaviours, beliefs and social

settings are important. Personality is moulded by social and cultural factors. Lin (1996) argues that little is known regarding the potential contribution of cultural and ethnic factors in determining whether particular patients will benefit from a particular treatment regimen.

Culturally determined personality traits, like dependence or independence, orthodoxy or adventurousness or subjective response all play an important role in pharmacodynamics and pharmacokinetics and need to be studied along with ethnicity (Box 2).

The belief of researchers and clinicians alike in the universality of conditions and treatments, and that differences must be due to psychosocial factors only, often leads them to ignore significant and authentic individual variations. Ethnicity and culture might indirectly influence personality traits, which in turn might influence an individual's response to medication. Such a neglect of human biological diversity has been partially responsible

Box 2. Pharmacokinetics and pharmacodynamics – definitions

Pharmacokinetics – The study of how a biological organism affects the fate and distribution of a drug. This is determined by four processes – absorption, distribution, metabolism and excretion. The processes of metabolism exhibit substantial cross-ethnic, as well as individual, differences. Height, weight, differences in gastric acidity and percentage body fat are all affected by race and culture and can also affect the pharmacokinetics of drugs.

Pharmacodynamics – The study of the effects of a drug on the person. It refers to the neurotransmitter, neurophysiological, behavioural, psychological and social effects of psychotropic drugs and their mechanisms of action. An interesting and fairly common variation highlighted by Westermeyer (1989) is the flushing response to alcohol which has a variable distribution across races due to differences in enzymes acting on alcohol metabolism. Although the mechanics of alcohol flushing have been well described, the relationships between differences in blood levels, therapeutic responses and dosage are not so well understood, and are a function of more than variable pharmacokinetics.

for the slow progress of cross-cultural research on biological diversity and factors which affect metabolism of drugs. Such a 'colour-blind' approach confirms the view that people with divergent ethnic backgrounds might not differ in their biological responses or perceptions of drug treatment. This makes patients who complain of 'adverse effects' and request 'dosage variations' sound as if they are 'non-compliant' rather than accurately reporting their response to medication. The use of clinical practice guidelines is escalating, but these originate from the existing evidence base, most of which has not included ethnic minority patients. Norms and guidelines, based on research on White populations, may have little relevance to the effective treatment of psychiatric disorders among other ethnic and cultural groups. Individual personality factors play an important role in help-seeking, in the chosen models of care, and as an influence on treatment adherence.

Environmental factors

Some environmental factors, such as housing and employment, will differ across ethnic groups even within the same country (see Box 3).

Environmental factors can affect pharmacogenetics and associated pharmacokinetics of psychiatric drugs. If certain cultural and ethnic groups are exposed to specific environmental factors over a long period of time, it can lead to adaptations of metabolism, leading to a differential response which is associated with ethnicity (Smith & Mendoza, 1996).

Westermeyer (1989) has argued that additional factors affecting pharmacokinetics may include the use of tobacco, caffeine (in cola, tea and coffee), food additives, over-the-counter medications and herbal remedies, as well as levels of air pollution. Social and family support at a macro level, and personal factors such as response to stressors can affect the prognosis and outcome of psychiatric treatment. People exposed to greater stressors, while having lower levels of tolerance and low levels of social support, are more likely to develop mental illness, and also to have a poor social and clinical outcome. Lin *et al* (1995) argue that alterations in the levels of stress and social support may also change the effective therapeutic dosages of different psychotropic drugs. For example, the role of high expressed emotion (characterised by frequent criticism, hostility and emotional overinvolvement) is well known in affecting prognosis and causing relapse even with standard dosages of neuroleptics.

Various physical diseases can be caused by dietary factors which, in turn, will affect the

pharmacodynamics of prescribed drugs. Also, religious rituals and taboos may affect timings of drug-taking and absorption.

Biological factors

Lin *et al* (1995) point out that drugs and other foreign substances (xenobiotics) are metabolised by a number of enzymes whose activities vary substantially across individuals and ethnic groups both for genetic and environmental reasons. Although individual and inter-ethnic differences are substantial, the mechanisms responsible for such variations are less well understood (Lin *et al*, 1993). In addition to classical examples of drug responses across ethnic groups, the genetic control of a large number of drug-metabolising enzymes has been established. For example, the cytochrome P-450 enzyme system has been linked with the oxidation of several chemotherapeutic agents. More than 20 P-450 iso-enzymes exist and each is encoded by a specific gene. Both the phenotypes and genotypes of this enzyme system show clear individual and cross-ethnic variations which have been linked to differential adaptation to divergent environmental exposure,

Box 3. Social and environmental factors affecting ethnic differences

Demographic factors

Ethnicity
Age
Gender

Pharmacogenetic factors

Enzymic differences

Pharmacokinetic factors

Enzymic differences
Dietary habits
Smoking
Concurrent drugs

Dietary factors

Dietary taboos
Special foods
Body fat and weight

Environmental factors

Alternative models
Alternative drugs
Health care systems
Prescribing habits

especially diet. Clear diversity is seen with some P-450 iso-enzymes leading to poor or good metabolism. Lin *et al* (1993) report that the ethnic variations in these enzymes occur from 1% in east Asian people to 8.1% in Black American people. Other enzymes show a similar range of variation. Beta-blockers, for example, have been shown to be relatively ineffective in treating hypertension in African-American patients but are more effective in Asians, with Caucasians falling in between (Dimsdale *et al*, 1988). Similarly, clozapine-induced agranulocytosis has been more commonly observed in Ashkenazi Jews, especially in those with a cluster of HLA types (Lieberman *et al*, 1990). Ethnic differences in therapeutic effects, dosages and side-effects are discussed below.

Established ethnic differences in therapeutic effects

Most of the data available on ethnicity and psychopharmacology come from the USA and of all the psychotropic drugs, neuroleptics are most likely to be discussed. Across various ethnic groups additional factors like smoking, dietary taboos and dietary habits are seen to play a role but are not discussed very often.

Neuroleptics

Cross-racial differences in doses of neuroleptics which produce side-effects have been studied extensively in Asian-Americans (Japanese, Korean and Chinese Americans). Binder & Levy (1981) reported that 95% of Asian people in their sample had developed extrapyramidal side-effects whereas only 60% of Black patients and 67% of White patients did so within two weeks of commencing treatment. Although the numbers of patients in each group are small, these are significant differences. Jann *et al* (1989) reported that Chinese people had higher levels of extrapyramidal side-effects with haloperidol and their blood levels were comparably high on equivalent dosages. Chang *et al* (1991) reported that reduced haloperidol plasma levels and steady-state haloperidol ratios were generally lower in Chinese patients when compared with non-Chinese patients, suggesting that different metabolic factors may be acting here, thus confirming their earlier findings (Chang *et al*, 1987).

Asian-Americans reportedly had significantly higher serum levels of haloperidol and also had a more pronounced prolactin response when compared with the White group. The lower ratios of reduced haloperidol : haloperidol in Asian-Americans are said to be due to slower rates of

reduction and metabolism (Chang *et al*, 1987; Jann *et al*, 1989, 1993). It has been hypothesised that the enzyme CYP2D6 plays a crucial role in pathway of such a metabolism. Lin *et al* (1988) demonstrated higher serum haloperidol levels in healthy Americans of Far Eastern ancestry compared with White volunteers, and were able to show in a later study that Asian-Americans with schizophrenia responded optimally to significantly lower serum haloperidol concentrations (Lin *et al*, 1989). This has not been confirmed in other ethnic groups, but if it were the case, then clinicians would need to review their prescribing habits.

Antidepressants

Some key differences across different ethnic groups have been reported in antidepressants as well. Allen *et al* (1977), Lewis *et al* (1980) and Rudorfer *et al* (1984) have reported that Caucasians appear to have lower plasma levels of tricyclic antidepressants and attain plasma peaks later when compared with Asians (of Far Eastern ancestry as well as those from the Indian subcontinent). These differences have been attributed to a greater incidence of slow hydroxylation among Asians when compared with Caucasians (Kilow, 1982). When studying the kinetics of nortriptyline in non-depressed volunteers, Gaviria *et al* (1986) observed that purported hypersensitivity to the drug in their Hispanic volunteers was due to receptor hyper-sensitivity, as this group was reported to respond to lower doses and had more side-effects when taking tricyclic antidepressants. Lin *et al* (1995) confirmed this, although research evidence remains inconsistent. Kishimoto & Hollister (1984) and Rudorfer *et al* (1984) have suggested that Asians metabolise tricyclic antidepressants slowly, but others have not been able to confirm this (Pi *et al*, 1986, 1989; Silver *et al*, 1993).

Two studies from Asia (Yamashita & Asano, 1979; Hu *et al*, 1983) showed that severely depressed Asian patients responded to lower combined concentrations of imipramine and desipramine in comparison with dosages used for White groups. African-Americans have been reported to have higher levels of neurological side-effects due to antidepressants (Escobar & Tuason, 1980), but the mechanisms of such actions are not clear. The dosages of antidepressants should be carefully individualised over a prolonged period. Intra-group variation in tricyclic pharmacokinetics greatly exceeds the observed inter-group differences, and the slow peak performance in Whites may be due to a more rapid hydroxylation in this group.

The data on newer antidepressants, as well as atypical neuroleptics, are even scantier regarding dosage measurement and assessment of side-effects

across different ethnic groups. It is possible that newer antidepressants such as moclobemide will show greater variation in metabolism compared with other antidepressants because of variations in monoamine oxidase activity across ethnic groups.

Lithium

Racial differences in red blood cell sodium and lithium levels are well recognised (Westermeyer, 1989). Pharmacokinetic differences may exist, but their precise nature and clinical impact have not been identified. Lithium has proved effective at lower levels among Japanese patients. Taiwanese patients are maintained at higher levels than the Japanese but lower than the Americans (Chang *et al*, 1987). Taiwanese patients are maintained at lithium levels of 0.5–0.79 mEq/L, whereas Chinese patients respond to levels around 0.71–0.73 mEq/L, but in Chinese–Americans no pharmacokinetic differences were reported. Environmental factors such as weather, and personal factors such as diet become even more important in the prescription of lithium and the maintenance of individual patients on lithium.

Benzodiazepines

The evidence concerning response to benzodiazepines and their dosages across ethnic groups remains inconclusive. Although American–Asians clear diazepam more slowly and have higher serum levels, its use did not demonstrate any significant agonist effects in one study (Ghoneim *et al*, 1981) although other researchers have shown pharmacokinetic differences in two groups, that is, Asian–Americans and Caucasians (Kumana *et al*, 1987; Lin *et al*, 1988; Zhang *et al*, 1990). On investigating the effects of adinazolam, African–Americans had a notably increased clearance and significantly higher concentrations of its metabolites and greater drug effects on psychomotor performance. This has been attributed to hepatic oxidation and renal excretion, which may explain the greater drug effect on African–Americans despite their higher metabolic capacity for adinazolam.

Other physical treatments

Other drugs, such as analgesics, and other physical treatments may be used by individual patients and their carers irrespective of indication or need. Often, individuals from minority ethnic groups will use pluralistic approaches to help-seeking and, therefore, it is likely that other drugs, prescribed or non-prescribed, along with other environmental factors, will affect the pharmacokinetics of psychiatric prescriptions.

These variations may be due to genetic, pharmacokinetic variations, dietary or environmental factors or variations in the prescribing habits of clinicians (Frackiewicz *et al*, 1997). Dosage studies and the study of adverse effects are only the first steps in understanding the inter-ethnic variations of pharmacological agents.

Non-biological factors

As mentioned earlier, both biological and non-biological factors play a crucial role in response to medication. This interaction is less well studied in ethnic minority groups. Cultures differ in the way in which they train their members to be on guard against certain types of mental state and behaviours.

Stress

There is no doubt that culture defines sickness, sick role and stress along with protective factors which influence the individual response to stress. Any alterations in the levels of stress and availability of social support, and interpersonal relationship conflicts will affect response to treatment. The role of continuing stress in refugees and ethnic minority groups may mean that individuals could be taking other medication, from herbal or other medical systems (such as Ayurvedic or Unani), making interactions more likely.

An additional feature related to stress is the gender of the individual, which affects the help-seeking and response in intervention (Dawkins, 1996). The gender role will determine expectations as well as social support. Gender roles will be affected by culture and ethnicity and may well produce their own stress, especially if in conflict with an individual's culture.

Prescription patterns

A wide variability in drug prescription and type of drugs across different cultures has been observed. Some of these factors rely on the availability of some drugs, and others on the local health care systems. In addition, beliefs and attitudes on the part of both patient and clinician will determine what drugs are prescribed and what drugs can be obtained over the counter. Another key factor in the pattern of prescription is the stereotype of patients that the physician may follow. For example, African–Caribbeans may be given higher doses of neuroleptics and given depot injections, suggesting not

only the clinical practice, but also the stereotype which suggests that these individuals may have problems with compliance.

Treatment adherence

Adherence with medication depends upon a number of factors such as dosage, side-effects experienced, models of illness and beliefs in health care. Many psychiatric patients require long-term treatment with either oral or depot medication. Although treatment packages have been developed for adherence therapy, their success in treating members of minority ethnic groups is not well demonstrated. Divergence in the beliefs between patients and clinicians and communication difficulties have been regarded as the major reasons for such ethnic differences in compliance (Lin *et al*, 1995). This has also been attributed to poor understanding of treatment protocols by some groups. It is possible that appropriate educational packages may well improve compliance provided these are culturally appropriate and targeted at appropriate levels.

Complementary medicine

Traditional herbal remedies, whether from the Ayurvedic or Unani medical systems, or simply from herbalists, have been used extensively across different ethnic groups. Many of these drugs are pharmacologically active and capable of significant interactions with prescribed drugs. The Unani medication itself may contain large quantities of heavy metals such as gold, silver, tin, copper, barium, lead, mercury, zinc, antimony and iron. In addition to herbal remedies or Unani medications, the Vaid or the Hakim may recommend dietary restrictions as well, which may affect the absorption of food and the prescribed medication. Other folklore remedies may be used. Several minority ethnic groups also use pluralistic approaches to health care and patients or their carers may not volunteer the information to the clinician. Health professionals must ask questions in a sensitive and careful manner (see Box 4).

Conclusions

Ethnic and cultural considerations are important in drug trials as well as prescriptions. Clinicians have to be aware of safety and efficacy effects of

pharmacological agents. In addition, these differences highlight the interaction between biological and cultural factors which may provide a clue to pharmacogenetic effects.

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Box 4. Planning pharmacological treatment for minority ethnic groups

Prior to prescribing

- Check diet
- Check religious taboos
- Check smoking, alcohol, drugs

While prescribing

- Start at lower dose
- Have low threshold for identifying side-effects/evidence-based
- Adjust dosages regularly if required
- Provide information

After prescribing

- Monitor side-effects
- Check compliance
- Check environmental/dietary factors

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Multiple choice questions

- Pharmacokinetics:
 - is the study of handling of the drug by the body
 - is not affected by ethnicity
 - is not affected by stress
 - has to be understood separately from pharmacodynamics.
- Antipsychotics:
 - may interact with some traditional remedies
 - produce higher levels of side-effects in some ethnic groups
 - produce the same effects with higher doses in some ethnic groups
 - are affected by CYP2D6 in metabolism.
- Tricyclic antidepressants:
 - produce lower plasma levels in Caucasians
 - have faster hydroxylation among Asians
 - show hypersensitivity in some ethnic groups
 - show higher levels of neurological side-effects in African-Americans.
- Lithium:
 - shows variable levels in relation to environmental factors
 - levels in some groups should be maintained at low levels
 - needs to be withdrawn carefully
 - has no interaction with salt intake.

MCQ answers

1	2	3	4
a T	a T	a T	a T
b F	b T	b F	b T
c F	c F	c T	c T
d T	d T	d T	d F