Basic elements of ethnopsychopharmacology

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Elementos básicos de etnopsicofarmacología

Summary

Ethnopsychopharmacology is the pharmacology area that studies the effect of psychoactive drugs on patients having different ethnic characteristics. Some important factors in the management of these patients are the differences in enzymatic characteristics, cultural practices in relation with medicine and food, and the biases of medical professionals in their relationship with patients from different ethnic group (which is called «cross-cultural transference»). At present, when immigration has become an important issue in our country, some basic knowledge on this subject seems compulsory.

Key words: *Ethnicity. Culture. Psychopharmacology. Immigration.*

Resumen

Ethnopsychopharmacology is the section of pharmacology that studies the effect of psychiatric drugs on patients from different ethnic characteristics. Some important factors in the management of these patients are the differences in enzimatic characteristics, cultural practices in relation with medicine and food, and the biases of medical professionals in their relationship with patients from different ethnic group (which is called «cross-cultural transference»). At present, when immigration has become an important issue in our country, some basic knowledge on this subject seems compulsory.

Palabras clave: *Etnicidad. Cultura. Psicofarmacología. Inmigración.*

INTRODUCTION

Traditionally, most pharmacological studies have been carried out in white, male, middle aged populations who live in the United States and Europe. It was assumed that the data obtained in this way could be extrapolated to the female gender, to the elderly and to the pediatric population, and to other ethnic groups other than white[1]. However, the present studies verify that this extrapolation was not so obvious, and that specific pharmacological trials are necessary not only in children and elderly, but also in women[2] and in different ethnic groups[3].

Thus, it is important to know the meaning of the concepts «race» and «ethnic group». Traditionally, «race» has been used to identify genetic and biological properties and characteristics[4,5], however, the distinction between racial groups no longer exists and the use of this term leads to confusion. Thus, at present, the use of the term «ethnic group» is recommended to describe belonging to a group that shares a common national or regional origin[4]. This is also a difficult concept to define. It serves to describe the sense of belonging to a region or country of a group of persons who frequently share a language, religion and customs[5]. It is considered that there are five ethnic groups in the United States of America: Afro-Americans, Hispanics, Asiatics, native Americans and Eskimos and Europeans[4].

Ethnopsychopharmacology would include two principal characteristics: *a*) ethnopharmacogeneticsn, and *b*) the sociocultural influences in pharmacotherapy.

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ETHNOPHARMACOGENETICS

As any other active ingredient, the effect of psychoactive drugs is determined by two parallel processes: pharmocokinetics (that determines what percentage of the pharmacological agent reached the target organ) and pharmacodynamics (that defines how the body responds to the drug). Of the four processes related with the pharmacokinetics (absorption, distribution, metabolization and excretion), metabolization presents the greatest interindividual and interethnic variations. The cytochrome P-450 enzymes are the principal determinants of the metabolism of the psychoactive drugs[6]. Of the more than 50 enzymes identified in this cytochrome, the four described in table 1 are those that metabolize most of the psychodrugs[7]. The activity of these enzymes is determined by genetic polymorphisms that vary widely in

TABLE 1. Principal enzymes of cytochrome P-450 and psychoactive drugs on which it acts

CYP1A2	
	Antidepressants
	Amitriptyline, clomipramine, imipramine, fluvoxamine
	Neuroleptics
	Haloperidol, phenothiazines, olanzapine, clozapine
CYP2C19	
	Benzodiazepines
	Diazepam
	Antidepressants
	Amitriptyline, clomipramine, imipramine, citalopram
CYP2D6	
	Antidepressant
	Amitriptyline, clomipramine, imipramine, nortriptyline, desipramine, fluoxetine, sertraline, paroxetine, venlafaxine
	Neuroleptics
	Chlorpromazine, thioridazine, perphenazine, haloperidol, risperidone, sertindole, clozapine
CYP3A4	
	Benzodiazepines and hypnotics
	Alprazolam, clonacepam, diazepam, midazolam, triazolam, zolpidem
	Antidepressants
	Mirtazapine, nefazodone, sertraline
	Neuroleptics
	Thioridazine, haloperidol, clozapine, risperidone, sertindole, quetiapine, ziprasidone
	Mood stablizers
	Carbamazepine, gabapentin, lamotrigin

the different ethnic groups. CYP2D6 is the most widely studied enzyme.

More than 50 mutant alleles have been identified for this enzyme, so that the individuals can be classified into four groups: poor, intermediate, extensive and ultrafast metabolizers[8]. Each one presents different clinical significance, so that the poor and intermediate metabolizers can hardly metabolize these substrates and present important undesired effects when normal doses are used with them. On the contrary, the ultrafast metabolizers require significantly higher doses than normal[9]. As an interesting datum, the ultrafast metabolizing population of this enzyme is maximum in Arabic countries (20%), intermediate in Spain (5%) and practically null (1%) in the rest of the European countries. It is hypothesized that the gene arose in the Middle East and expanded to Spain during the Muslim invasion of the peninsula[8,9]. However, the clinical correlate of this genetic finding, that would mean that an important percentage of Arabs would not adequately metabolize the substrates of this enzyme, has not been sufficiently proven[6]. It is also known that 20% of the Far West Asiatics (compared to only 5% of the Europeans) would present poor metabolization of the enzyme CYP2C19, which would mean that they are very sensitive to medications such as diazepam, imipramine or citalopram[7].

Together with genetic influences, the activity of P-450 enzymes may be modified by other external factors (such as food and alternative medicines) or internal ones (hormones and other endogenous substances). The most affected enzymes are:

1. *CYP1A2.* Its activity may be induced by raw vegetables (cabbage, soybean), carbohydrates generated during the preparation of foods (roast meat) and tobacco consumption. It is known that the patients who initiate smoking during pharmacotherapy present greater rates of relapse because tobacco reduces blood concentration of many antidepressants and neuroleptics by more than 50%[10]. Diet is also important: those who present elevated percentages of proteins (typically western population) induce their activity while carbohydrate rich diets (predominant in underdeveloped countries) present the contrary effect[11]. In fact, when Africans and Asiatics emigrate to the West and modify their native diet for the Western one, increased induction of this enzyme is verified[11].
2. *CYP3A4.* It can be induced by multiple substances, among them new wine[12] or mugwort[13]. This fact is especially important, given the extensive use of alternative medicines in Western countries[14], because the patients are not aware of their effects and when they take them together with psychoactive drugs, the herbs can be the cause of the undesired effect and not the psychoactive drug.

SOCIOCULTURAL INFLUENCES IN PHARMACOTHERAPY

The patient is not a passive subject who takes psychoactive drugs automatically and with maximum compliance. Pharmacotherapy principally makes up a process of social transaction and its effects are determined by contextual factors that determine the physician-patient relationship. Generally, the medical professionals only know the biological characteristics of pharmacotherapy when it is considered that they are less important than the contextual ones[17]. On the other hand, when the contextual factors are analyzed, focus is placed exclusively on the patient, as if the physician was not influenced, consciously or unconsciously, by the cultural setting.

These contextual characteristics influence, for example, the degree of compliance to treatment or in the placebo effect that we will analyze later. They are also related with the use of traditional or indigenous medicines, frequently used concomitantly without telling the physician, which can produce important drug interactions. Other aspects, such as the way treatment is administe-

red, are also cultural: in most of the non-Western cultures, treatment is administered only once. The need to continue a treatment for several weeks before experiencing the therapeutic effects (as, for example, in the case of antidepressants) is incomprehensible in many cultures and radically decreases compliance[15]. Furthermore, the amount of the drugs prescribed can be interpreted differently: many Western patients are afraid of drug interaction and reject treatments with multiple drugs. On the contrary, there are patients from some cultures who do not adhere to the treatment if they are only administered a single drug because they doubt the competence of the clinician[16].

GENERAL PHARMACOLOGICAL ASPECTS FROM THE TRANSCULTURAL PERSPECTIVE

Treatment adherence

The problem of non-compliance is valued at 20-90% of the patients who follow psychiatric treatments[17], values similar to those found in other non-psychiatric chronic diseases[18]. A series of dependent variables of both patient and physician has been described[19]. Adherence is a serious problem from the transcultural perspective as has been verified in different studies[20]. An important aspect is that called "transcultural contratransference," that is, how ethnicity itself influences the treatment of the patients[21,22]. Thus, it is necessary to examine our values and ethnocentric ideas (based on our culture) and be critical of them to be able to approach positions of cultural relativism (assume that are values are not superior to those of other cultures). Many of these thoughts and feelings are not conscious while others, being conscious, are not «acceptable» by the clinician (due to their clear dose of racism), but they contribute to promoting inappropriate behaviors towards certain patients. For example, it is known that white psychiatrists underdiagnose psychiatric disease in black patients although they erroneously overevaluate isolated aspects such as verbal skill or adequacy for psychology therapy. In the same way, black psychiatrists overdiagnose psychiatric disease in white race patients[23].

It is not easy to separate the impact of culture regarding the influence of other aspects such as low cultural level, lack of knowledge of diseases or functioning of drugs, factors that are also generally present in non-Caucasian ethnic group patients[24]. Thus, the use of an explanatory model, originally proposed by Kleinman[25], has been recommended. This would be effective to assess systematically the beliefs and expectations of the patients (table 2).

Using this model, it is possible to decrease the differences between the explanatory models of disease that are defended by the patient and clinician[26]. In fact, it has been demonstrated that the development of special programs to establish cultural bridges between patients and clinicians improves adherence to the drugs and, thus, the disease prognosis[27].

TABLE 2. Kleinman's explanatory model [25]

It would consist in questioning the patient systematically on the following aspects:

- *Malaise patterns.* The perspective of the patients on the symptoms that are more important for him/her, those which produce the greatest concern. They can be different from the most serious or important symptoms from the perspective of Western medicine
- *Attribution.* Cause of the disease perceived by the patient. It includes magic or religious aspects
- *Preferences and previous experience* in the search for medical help. It includes the relationship with traditional or shamanic medicines
- *Perception of stigma* associated to the disease in his/her cultural setting

Placebo effect and expectation

The so-called placebo effect, one of the most important elements that determine the effectivity of the drugs[28] is still practically unexplored from the cultural perspective[25]. Expectations of the patients in relationship with the drugs are determined by cultural factors. For example, in controlled studies, it is verified that while the white population considers that the black capsules are stimulants and the white ones are analgesics, the black population considers exactly the opposite[29].

This effect would also include expectations regarding interpretation of the undesired effects. For example, the side effects of lithium in the treatment of bipolar disorders are similar in the Chinese and in Europeans. However, while the Europeans poorly tolerate symptoms such as polydipsia and polyuria, the Chinese do not complain because they interpret that both symptoms indicate that the body is being purified of toxic elements. However, the Asiatics support fatigue worse than the Europeans because it prevents them from working[30].

RECOMMENDATIONS ON THE MANAGEMENT OF PSYCHOACTIVE DRUGS IN DIFFERENT ETHNIC GROUPS

There is no perfect ethnic-response relationship. In fact, the present studies better correlate the response of the drugs to genetic-enzymatic aspects than to simple racial or ethnic models[7]. However, the weight of tradition and the simplification permitted by this model make it necessary to continue to use it as a pattern. The recommendations that we offer do not aim to be exhaustive but rather an extensive summary of the principal data that are presently known, without losing the perspective of the frequent contradictory characteristic of the findings that occur in this field.

Psychoactive drugs in the black race

Anxiolitics

Anxiety disorders in the black race are frequently overdiagnosed as psychosis. Specifically, patients with anxiety disorder and agoraphobia, the most frequent disease in this ethnic minority[31], present hallucinations or delusional fears with certain frequency and they are interpreted as psychosis[32]. Obsessions, a little diagnosed disease in the black race, can also be interpreted as delusions or thought disorders and be diagnosed as psychosis when they are egodystonic[32]. However, the disorder in which diagnostic errors are the most frequent is that of post-traumatic stress, since the individuals of this latter race more frequently present psychotic and paranoid ideation symptoms than other groups[33]. From this ethnopsychopharmacological point of view, there are no compared data that recommend departing from the pattern that is generally used with anxiolytics in this ethic group.

Antidepressants and mood stabilizers

Affective disorders that occur in black patients are diagnosed erroneously as schizophrenia in more than 50 % of the cases by the psychiatrists, so that they are prescribed antipsychotic agents[34] and they are admitted more to psychiatric hospitals and frequently involuntarily[35]. Clearly, this is a cultural bias with racist connotations[36] because the prevalence studies between the white race and the black one do not show any differences in this sense[37]. However, there would be some clinical traits in these patients that could partially explain this diagnostic bias: the subtype of rapid cyclers and episodes with psychotic symptoms, principally hallucinations, all these pictures with resistance to lithium, are more frequently presented in the bipolar patients of the black race than in the white ones[38]. Furthermore, paranoid traits and existence of suspiciousness in these patients are more frequent in depression[39].

Regarding the effect of the antidepressants, it seems that the black race responds faster than the white one to tricyclics[40]. In the same way, it has also been demonstrated that the tricyclics are more toxic in them[41]. For example, it has been demonstrated that delirium is a toxic effect of the tricyclics that is more frequent in this race than in the white one[42]. It is considered that a high percentage of the black race, between 45 and 70 %, would be slow metabolizers, which would explain this process[43]. In general, it is considered that the antidepressants, SSRI, would be the one of choice in this ethnic group due to its lower effect in the hepatic P450 system, which would reduce toxicity. It also appears that they require lower doses of SSRI than the white race[41].

On the other hand, lithium seems to be metabolized in a different way by these patients, so that there would be a greater frequency of side effects from this drug[23]. It is not clear that they require lower doses, but it is clear that lithium must be used with care in them. The use of new mood stabilizers is recommended in the black race due to their lower side effects and because, in addition, some of them are more effective in atypical clinical forms, such as those that predominate in these patients. Furthermore, the excess of use of neuroleptics in blacks could partially explain their lower tolerance to lithium, since its association is frequent.

Neuroleptics

Black race patients are more frequently diagnosed of schizophrenia[44], they are administered higher doses of neuroleptics[45] and they are injected the depot form more frequently because it is considered that they are not going to follow the treatment adequately[45]. In general, they are seen as more violent and dangerous patients[46]. It is not clear what the cause of this intense racial bias is, although anthropological reasons have been suggested in relationship to the fear that the white population has developed towards the black race, who is associated with delinquency[47]. In fact, different attitudes towards these patients according to the ethnicity of the psychiatrists are observed. Thus, white clinicians shorten the hospital stay of these patients[48] while black psychiatrists, surely due to identification, recommend significantly longer stays[49]. There are no studies that verify this negative bias towards other non-white races in the United States[49]. However, the existence of this bias towards the black race has been verified (with the consequence of overdiagnosis of schizophrenia and excessive use of neuroleptics) in other countries such as Great Britain[50], Holland[51] and Denmark[52]. Another interesting aspect regarding the treatment is that the blacks are administered atypical neuroleptics less frequently than the Caucasian patients[45].

Due to the effect of the neuroleptics, it seems that blacks would respond faster and more intensely than whites to neuroleptics. The most important differential effect that has been described is greater frequency of tardive dyskinesia in these patients[53,54], who reach rates of 47% compared to 26% in whites[55]. It is not clear if the individuals of the black race present a congenital or enzymatic defect or, which is more likely, this side effect is a consequence of the excessive administration of neuroleptics that is performed in them as we have already described. In any case, classic neuroleptics would be less recommendable in these patients due to the high risk of tardive dyskinesia[53-55]. An interesting alternative could be clozapine. However, besides the difficulty of its use and the high cost imposed by the need to make repeated blood tests to control agranulocytosis, there is a factor that limits its use in the black population. In this race, the normal levels of leukocytes are significantly lower than the levels considered normal, an effect called «benign leukopenia»[56]. The fact, without clinical importance, makes the use of clozapine difficult because it is difficult to assess the leukopenic effect of this drug, thus its use is restricted in this ethnic group[57]. For all these reasons, the use of the new neuroleptics such as olanzapine or risperidone would be recommended in these patients.

Psychoactive drugs in hispanics

Anxiolytics

There are no clear conclusions on these drugs in Hispanics, so that they should be used in the normal way.

Antidepressants and mood stabilizers

The Hispanics seem to show better response to tricyclics with practically half the dose of the whites, so that they also present side effects more frequently (78% in Hispanics compared to 33% in whites) and greater discontinuation of the treatment (17% compared to 4 %)[58]. However, other later studies do not show any differences between Hispanics and whites regarding the response to tricyclics[59]. It also seems that there are no differences between both races in relationship to effectivity and side effects with serotoninergics[60,61].

Neuroleptics

There are several studies that verify that the doses of typical neuroleptics that are administered to both Asiatics as well as to Hispanics are significantly lower than those used in whites and that, in general, low power neuroleptics are used more frequently in the latter patients[62,63]. The explanation used most is that haloperidol, the neuroleptic used most when the studies were performed, is metabolized by the enzymes CYP1A2 and CYP3A4, both sensitive to environmental influences such as diet and use of tobacco. In short, it is believed that these differences are not necessarily explained by enzymatic or genetic variations in the metabolization, but rather are due to environmental effects linked to culture such as diet, exposure to toxins or use of tobacco.

Similar data have been found with the atypical neuroleptic clozapine in Hispanics that require maintenance doses of 300 mg/day, values inferior to those used in the United Stated in the white race[64]. On the contrary, the risperidone dose required by the Hispanics, about 6 mg/day as maintenance, are similar to those used in the white population[64]. Regarding effectivity, it seems that olanzapine produces a greater effect in Hispanics than whites both in the target symptoms as well as in the reduction of extrapyramidal symptoms[65]. Greater fastness and effectivity in the antipsychotic response have also been confirmed with risperidone when compared to white patients[66].

Psychoactive drugs in asiatics

Anxiolytics

There are studies that show that Asiatics require lower doses of benzodiazepines than those used in the Western white population. Greater serum concentrations and lower clearance have been verified in some benzodiazepines, which could justify this fact[67].

Antidepressants and mood stabilizers

Although there are contradictory studies[68], it is accepted that these patients require lower doses of tricyclics and show therapeutic responses at lower blood levels[69]. In fact, it is said that in Japan, the optimal therapeutic range would be 0.4-0.8 mEq/l, certainly lower than the range of 0.8-1.2 mEq/l considered therapeutical in the West and of the new accepted therapeutical range of 0.7-1 mEq/l[23].

The antidepressants that are monoamino oxidase inhibitors (MAOI) tend to not be used in Asiatics because many of their traditional foods (soy sauce, etc.) have tyramine and they would produce the «cheese effect»[70]. When it is decided to use MAOI in the Asiatics, high doses of phenelzine should be used because most of the patients of this race are rapid acetylators. There are no comparative studies with serotoninergic antidepressants so that specific recommendations cannot be offered[72]. In relationship to mood stabilizers, they seem to respond with lower plasma doses, in the range of 0.3-0.9 mEq/l, in relationship to those used in non-asiatics[23].

Neuroleptics

It has already been described that Asiatics, as Hispanics, receive significantly lower doses of typical neuroleptics in the United States and that the cause seems to be interactions with their diet. However, in the specific case of the Asiatics, the well-controlled pharmacokinetic studies confirm the existence of higher levels of antipsychotics in plasma with the same dose per weight, which would explain the need for lower doses[73]. In addition, in the case of the atypical antipsychotic clozapine, it seems that the Asiatics require lower doses[74]. The Asiatics present greater risk of acute dystonias in prospective studies[75], however, there are no differences in regards to the risk of acathisia[75]. In relationship to the frequency of Parkinsonism, the data are contradictory and it is not possible to reach conclusions[75]. Finally, regarding tardive dyskinesia, it is accepted that the Asiatics present greater risk of suffering it[76], so that it would be necessary to use lower doses in them than in the Caucasian race[69].

CONCLUSIONS

Ethnopsychopharmacology is still found to be in its beginning and methodologically more conclusive studies are necessary to be able to establish exact clinical recommendations. The phenomenon of immigration, important in all the Western countries, is going to mean a decisive stimulus for investigation in this area.

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