

The effects of psychotropic drugs in different populations

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Although psychotropic drugs are known to be effective in all populations, the known differences in terms of health and disease in different parts of the world have not been related to the effectiveness of such drugs. Nutritional/metabolic, genetic, cultural, and ecological/climatic factors that could be important in this respect are discussed. The benefits that could accrue from a knowledge of proper drug dosage, namely, fewer side effects and reduction in cost, particularly for developing countries, are highlighted.

The introduction in the early 1950s of the phenothiazines for the management of severe mental disorders, particularly schizophrenic psychoses, significantly improved the prognosis of these disorders all over the world. This discovery was particularly momentous for psychotic patients at mental hospitals in the less technologically developed countries because these poor countries could not afford the treatment procedures, notably insulin-coma, that were then in vogue. As is now well known, research into the pharmacology of promethazine soon led not only to the discovery of a wide range of substituted phenothiazines (trifluoperazine, thioridazine, promazine, etc.) but also contributed to the discovery of different kinds of antipsychotic agents such as the butyrophenones and thioxanthenes. Antineurotic and antidepressant agents also enjoyed a similar popularity. Thus, it cannot be denied that science, through research, has provided man over the last 25 years with a considerable number of psychoactive agents to help him cope with his problems.

Just as it is true that the effectiveness of psychoactive agents in general has been demonstrated in all populations, so it is true that the effectiveness and adverse effects of the medicaments may not have received adequate attention in all parts of the world. The customary areas of interest have been, *inter alia*, the range of dosage presenting danger to the respiratory and cardiac centres of experimental animals and teratogenic effects on the offspring of laboratory animals. The therapeutic effectiveness of any drug is known to be related to the body weight of the patient, the rate of absorption of the drug into the system, and the rate of breakdown, transport, and ultimate disposal of the drug from the body. These factors are also known to contribute to the emergence of unwanted side effects. In other words, factors such as body weight and physical health assume greater importance in relation to effective dosage and undesirable side effects when it is realized that these factors are different from population to population. Some of these factors, which are hereditary, sociocultural, nutritional, and climatic, are discussed in greater detail below.

HEREDITARY FACTORS AND PSYCHOTROPIC DRUG EFFECTIVENESS

It is known that there are different but distinct characteristics relating to body weight for different populations. Some are heavily built or constitutionally tall and others are not

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so naturally endowed. While it could be argued that nutrition may be a factor, there is no doubt that heredity also contributes to the different average weights noted for different populations of the world. What is the importance of this for drug effectiveness? For example, it has been stated that for an Indonesian patient, 25 mg of chlorpromazine three times a day could be expected to produce as good a result as 100 mg of chlorpromazine three times a day in some other cultures. By implication, therefore, if side effects develop in the Indonesian patient, they would probably be more severe if the patient were given the dose conventional in some other cultures. Even if the patient tolerated the side effects, it could be argued that such a level of medication would amount to a waste of expensive drugs, especially if other drugs had to be used to counter the side effects. In terms of the scarce national resources of most developing countries, this point ceases to be of mere academic interest.

NUTRITIONAL STATUS AND PSYCHOTROPIC DRUG EFFECTIVENESS

The nutritional status of an individual is often the result of many interrelated factors. It is influenced by the adequacy of food intake both in terms of quantity and quality, and also by the physical health of the individual. This is largely because the rate and completeness of digestion and absorption are dependent on the state of health of the gastrointestinal tract. In many parts of Africa, Asia, and Latin America there is a prevalence of endemic parasitic and intestinal diseases that bring about poor nutritional status in a very large percentage of the population. This is in addition to a poor diet brought about by ignorance of what is actually beneficial to the body; nutritionally important items of food are forbidden to some religious sects and the harsh climate and the method of preparation often reduce the nutritional value of the food. The likely effects of the nutritional status of a patient on the potency of psychotropic drugs are further emphasized when implications for the absorption, transport, storage, and excretion of drugs are more closely examined.

At the cellular level, malnutrition alters the biochemistry of the malnourished individual and important body constituents such as electrolyte ions become deficient. Another important and often striking result of malnutrition is vitamin deficiency. In this regard, vitamins of the B group are crucial because of their role as coenzymes in several biochemical reactions including the absorption, transport, and excretion of various substances such as drugs.^a Thus, apart from the well known diseases precipitated by deficiencies of vitamin B₁ (thiamine), vitamin B₂ (riboflavin), nicotinic acid, vitamin B₆ (pyridoxine), and vitamin B₁₂ (cyanocobalamin and hydroxocobalamin), such deficiencies have important implications not only for the effectiveness of psychotropic drugs but also for the incidence of side effects when these drugs are prescribed for malnourished patients.

One other sign of poor nutritional status is protein/energy imbalance. Serum proteins are important not only in the transport systems of the body but also for immune response. Edozien^b showed that serum proteins, particularly the albumin fraction, are altered in malnourished subjects in developing countries.

One other consequence of malnutrition is disturbed folic acid turnover. Carney & Sheffield^c have suggested that psychotropic drugs, especially phenothiazines and tricyclic antidepressants, may also contribute to serum folate deficiency, thus further compromising

^a BENNETT, T. P. & FRIEDEN, E. *Modern topics in biochemistry*. New York, Macmillan, 1967, pp. 43-56.

^b EDOZIEN, J. C. *Journal of clinical pathology*, **10**: 276-279 (1957).

^c CARNEY, M. W. P. & SHEFFIELD, B. F. *Journal of nervous and mental disease*, **150**: 404-412 (1970).

the nutritional status of malnourished patients. A recent review ^a of oral contraceptives (widely recommended in family planning programmes, often in malnourished populations) and vitamins showed that there appeared to be a clear link between disturbances in some pyridoxine-dependent enzyme systems and symptoms of mental depression. Low availability of pyridoxine induces deficiency of pyridoxine phosphate, which is a constituent of several coenzymes active in the tryptophan–nicotinic acid cycle. As some of the tricyclic antidepressant drugs have similar biochemical pathways, the influence of malnutrition on the effectiveness of these drugs becomes important. Carney & Sheffield also showed that the plasma concentration of vitamin B₁₂ and/or folic acid may be reduced during the ingestion of estrogen-containing oral contraceptives. All these points serve to highlight the importance of vitamins and the general state of nutrition on the effectiveness and side effects of psychotropic drugs.

The importance of nutrition in relation to psychotropic drugs is not limited to the role of vitamins as coenzymes in the body. Malnutrition combined with inclement weather, particularly a hot climate, can also affect serum ion levels. Kelly et al. ^b have reported deaths from ventricular tachycardia and fibrillation due to hypokalaemia, which may be precipitated not only by gastrointestinal diseases known to be common in developing countries but also by an inadequate diet. Finally, the pH of the urine is known to have pronounced effects on the excretion of partially ionized drugs.^c Hadzija ^d has suggested that the pH of the urine of malnourished Africans may be different from that of Europeans and that this may alter the ratio of metabolites to parent drugs in the bodies of Africans. He warned that it may be unwise to use the effects and side effects observed in clinical trials in developed countries to predict the effect of the same drugs in communities with different dietary customs.

In summary, psychotropic drug effectiveness and poor nutritional status can be related in a number of ways. First, the mechanism of the sensitivity of patients to particular drugs is not fully known; what are the implications of this in terms of the immune potential of malnourished patients? Second, the presence of a concurrent disease may alter the therapeutic action of a drug to produce unexpected results. For example, agranulocytosis is thought to be partly the result of a direct toxic effect on the myeloid elements of bone marrow by chlorpromazine as well as other phenothiazines and tricyclic antidepressants. Although these adverse effects are rare, what are the implications of such side effects in patients with impaired natural defences?

The issues raised above are important and should encourage drug houses, clinicians, health planners, and administrators in both developed and developing countries to take into account the different effects of psychotropic drugs in different populations. Apart from the importance of ensuring the reduction (through research) of the unwanted side effects of drugs, the cost–benefit ratio of the huge investment on drugs *vis-à-vis* other national priorities in developing countries in particular ought to be kept under constant surveillance. This is why the present World Health Organization Project on the Effects of Psychotropic Drugs in Different Populations is particularly timely. It is hoped that at the end of the study WHO will be in a position to advise Member States on the effectiveness and limitations of the psychotropic drugs most commonly prescribed.

^a LARSSON-COHN, U. *American journal of obstetrics and gynecology*, **121**: 84-90 (1975).

^b KELLY, H. G. ET AL. *Canadian Medical Association journal*, **89**: 546-554 (1963).

^c BECKETT, A. H. & TUCKER, G. T. *Journal of pharmacy and pharmacology*, **18**: 72-75 (1966).

^d HADZIJA, B. W. *Journal of pharmacy and pharmacology*, **21**: 196-197 (1969).

RÉSUMÉ

Les effets des médicaments psychotropes dans différentes populations

Dans la lutte contre les troubles mentaux graves, l'application dès les années cinquante d'une chimiothérapie axée notamment sur l'administration de phénothiazines a constitué un grand progrès pour les pays en développement particulièrement démunis de ressources. Les recherches sur la prométhazine ont permis de découvrir, outre toute une variété de phénothiazines de remplacement (trifluopérazine, thioridazine, promazine, etc.), des agents antipsychotiques comme les butyrophénones et les thioxanthènes, auxquels se sont encore ajoutés depuis de nombreux neuroleptiques et antidépresseurs. Si l'efficacité de ces agents a été partout démontrée, on ne s'est pas suffisamment préoccupé des variations dans leur action et leurs effets secondaires qui peuvent être liées à l'état sanitaire des populations considéré au sens large, c'est-à-dire incluant l'état nutritionnel aussi bien que l'ensemble des facteurs psycho-sociaux et écologiques.

Parmi les risques le plus généralement étudiés chez des animaux de laboratoire figurent ceux qui menacent l'appareil respiratoire et l'appareil circulatoire, ainsi que les effets tératogènes possibles. On sait que la posologie doit tenir compte du poids du malade et de la biodisponibilité du médicament. Or les facteurs héréditaires influent notamment sur le poids, à tel point qu'on a pu dire que la dose de chlorpromazine efficace pour le traitement d'un malade indonésien était le quart de celle à administrer dans d'autres populations. Il convient de noter que les effets secondaires d'un médicament — et la dépense que celui-ci représente — varient eux aussi dans les mêmes proportions.

L'état nutritionnel est également important. Or il dépend naturellement des aliments absorbés et de leur préparation, mais aussi du bon fonctionnement de l'appareil digestif, qui peut lui-même être affecté par des maladies parasitaires et intestinales largement répandues. Sur le plan biochimique, certaines réactions importantes pour l'assimilation, le stockage et l'élimination des médicaments peuvent être compromises par une carence en vitamines B ou en ions électrolytiques. La malnutrition protéino-énergétique, en agissant sur l'albumine sérique, affecte les mécanismes d'assimilation et la défense immunitaire. Le sérum peut également présenter une carence en folates sous l'effet combiné des médicaments psychotropes et de la malnutrition. Lors d'études concernant l'effet des contraceptifs oraux sur la concentration plasmatique des vitamines B, on a constaté une carence en pyridoxal-phosphate — forme co-enzymatique importante dans le métabolisme de plusieurs acides aminés. Or certains des médicaments antidépresseurs agissent par les mêmes voies biochimiques. La malnutrition, combinée à des conditions climatiques défavorables, notamment la chaleur, peut aussi provoquer une grave hypokaliémie. Enfin, elle agit sur le pH de l'urine, lequel est déterminant dans l'élimination des médicaments partiellement ionisés.

L'importance du rôle joué par l'état nutritionnel dans l'action d'un médicament rend donc douteuse la valeur des essais cliniques effectués dans les pays développés pour préjuger son efficacité dans des populations aux habitudes alimentaires différentes. Il faut particulièrement veiller à ce que des malades dont les mécanismes de défense immunitaire sont altérés par un mauvais état nutritionnel ne soient pas exposés aux effets toxiques possibles de certains médicaments psychotropes (par exemple une agranulocytose provoquée par la chlorpromazine).

Le projet lancé par l'Organisation mondiale de la Santé pour étudier les effets des médicaments psychotropes dans différentes populations est donc venu à son heure. Il devrait permettre, grâce à de nouvelles recherches sur les plus couramment utilisés de ces médicaments, de réduire les effets secondaires de ceux-ci et d'établir de manière plus précise la relation coût/avantages à prendre en considération pour toute décision quant à l'opportunité de leur emploi dans des pays en développement.
