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ESSENTIAL DRUGS IN PSYCHIATRY

SUPPORT

DIVISION OF MENTAL HEALTH

WORLD HEALTH ORGANIZATION

GENEVA

ON THE INITIATIVE

WHO's **Initiative of Support to People Disabled by Mental Illness** is part of WHO's work on the prevention and treatment of mental disorders. It is an attempt to speed up the dissemination of information to governments and professionals about good community services for those with chronic mental illness and about new developments in this field.

The Initiative aims to help in reducing the disabling effects of chronic mental illness and to highlight social and environmental barriers which hinder treatment and rehabilitation efforts and which add to the stigma of chronic mental illness. It also stimulates consumer empowerment and involvement with planning, delivery and evaluation of mental health services.

The following sites have so far officially joined the Initiative and have participated in its various activities:

* The Queensland Northern Peninsula and Mackay Region Mental Health Service (centred in Townsville, Australia).

* British Columbia Ministry of Health - Mental Health Services (Vancouver, Canada).

* Centro Studi e Ricerche Salute Mentale - Regione Autonoma Friuli Venezia-Giulia (Trieste, Italy).

* Highland Health Board - Mental Health Unit and Highland Regional Council (Inverness, Scotland, UK).

* Stichting Overlegorgaan Geestelijke Gezondheidszorg (SOGG), (Rotterdam, the Netherlands)

The Dowakai Chiba Hospital (Funabashi, Japan) also takes part in some of the Initiative activities; other centres are at different levels of discussion concerning their joining the Initiative.

Further information on this Initiative can be requested from:

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ESSENTIAL DRUGS IN PSYCHIATRY

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This document describes the use of essential drugs for the treatment of people with mental disorders, following the WHO List of Essential Drugs.

It is the second in a series of four issues. The first one introduced the concept of essential treatments; the following two issues will deal with psychological and social essential interventions, respectively.

This document is part of WHO's Initiative of Support to People Disabled by Mental Illness.

Key-words: mental disorders, essential drugs, psychiatry, psychopharmacology, psychiatric treatment.

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FOREWORD

Although the impact of the introduction of chlorpromazine in psychiatric practice in the 1950s may have not been the same as that of the introduction of penicillin a decade earlier, it has nevertheless been heralded by some as a revolution in the history of psychiatry. Besides the remarkable quietening of some up to then ceaselessly agitated patients, it reinforced the notion that some mental disorders could indeed have a biological, biochemical nature, and hence be rendered manageable through biochemical means.

This notion, however, was not immediately and easily accepted, and at least some sceptical critics of it exist even today. The resistance or refusal to accept the benefits brought about by the introduction of modern pharmacological treatments in psychiatric practice, stemmed not only from ideological viewpoints about the etiology and nature of mental disorders, but also from the sometimes severe adverse consequences these new medicaments produce. Added to this, there was also the soon-discovered potential for abuse, either by individual users themselves or by those in power who indulged in the unacceptable, unethical chemical control of human mind and behaviour. In the long run, however, benefits supplanted risks and pharmacological treatment of mental disorders became not only acceptable but also mandatory in many cases.

One of the consequences of the utilizations of medicaments for mental disorders was the development of a sector in industry mobilizing huge amounts of money with proportional profits, with concerns in some quarters that less consideration might be given to patient's well-being. Further the constantly increasing number of pharmaceutical products available on the market inevitably created confusion about their best use among many practitioners. Advertisements suggesting the superiority of a particular product tended to mislead the significant number of medical practitioners who had had less than adequate instruction in medical schools concerning the identification of mental disorders and the use of pharmacotherapy. However, although some problems remain, increasing dialogue between the pharmaceutical companies and professional bodies, together sometimes with the intervention of governments, has led to the development of more responsible and helpful promotional strategies.

Several authoritative textbooks on psychopharmacology and on pharmacological treatment of mental disorders exist. They are usually addressed to psychiatrists and other mental health professionals. To the average general practitioner, however, this field remains wrapped in an aura of obscurity which they refrain from entering, greatly to the disadvantage of those suffering from mental disorders. Yet, several independent studies have now confirmed that the majority of people with mental disorders, many with severe forms, are seen at the primary health care level, by general physicians; indeed, some of these patients never come to the notice of mental health professionals.

Hence the paradoxical situation in which trained mental health professionals see a minority of patients - who certainly benefit from their knowledge and skills - and yet the majority of patients are seen by health professionals untrained to care effectively with these problems, thus missing the excellent occasion of receiving a more thorough benefit.

That paradox is exactly the point of departure of this book. It aims at providing general doctors with simple, adequate and updated information on the use of medicaments in the management of mental disorders, useful at the primary health care level. In this sense, it naturally stems from the strategy of Health For All, and more specifically from the work of WHO concerned with the use of essential drugs and the introduction of a mental health component into primary health care. As a consequence, it heavily relies on WHO experience and previous publications[1]

The precursor of this document is WHO's experience with the Essential Drugs List (EDL) (*1*), from which several criteria were adopted and adapted to the field of mental disorders. Starting in 1975 from the experience gained in some countries, WHO produced a list of selected drugs essential for the treatment of the majority of diseases of public health importance. This EDL

represented a considerable reduction of an almost endless and unmanageable list of all existing medicines. From the very beginning medicines essential for the treatment of most mental disorders were included in the EDL.

This work, therefore, aims to:

i) present the **rationale for the identification of essential medicines** for the care of people with mental disorders;

ii) **identify biological interventions** essential for the care of people with mental disorders;

iii) briefly **describe those interventions**.

At any rate, medicaments are but one of the components of proper treatment of mental disorders. They should not be seen - and certainly not employed as such - as the only form of treament for those conditions. Essential treatments for most mental disorders include biological, psychological and psychosocial interventions; together, these three modalities of treatment represent the best and recommended approach for the management of mental disorders. Most mental disorders cannot be managed with medicines only: psychological and social interventions are essential for their management.

The document ESSENTIAL TREATMENTS IN PSYCHIATRY (4) discusses this approach in greater detail; readers are strongly recommended to become acquainted with its content. This one is the second in a series of four documents. Two other issues will follow, each one concentrating on particular aspects of psychological and social components, respectively, of this comprehensive approach. Specific elements of and information on each component should be sought in the forthcoming issues.

This document does not aim to represent a norm. It is rather an example of guidelines for the selection of essential treatments for mental disorders. The transformation of guidelines into norms with the necessary modifications can only be done at the local level, taking into consideration several socio-economic, epidemiological, cultural, historical and developmental factors, in addition to scientific background information. It was conceived to be used in a variety of countries with distinct socio-cultural and economic characteristics. In some its utilization will be straightforward, whilst in others it will have to face particular difficulties, e.g. deep rooted beliefs and practices opposing the use of medicaments, or problems in the procurement and sustainability of supplies, or lack of properly trained personnel, thus making its utilization more difficult. Any comments in this respect are welcome and should be forwarded to the address below.

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PART I

GENERAL INTRODUCTION

1. ESSENTIAL TREATMENTS AND ESSENTIAL DRUGS IN PSYCHIATRY

Since the introduction of chlorpromazine in psychiatric clinical practice in 1957, drug treatment has gradually become a very common treatment modality in psychiatry across cultures, health and mental health care systems and different psychiatric schools. It would undoubtedly be very hard to conceive of a clinical psychiatric practice without any psychoactive drug nowadays. Thanks to psychoactive drugs, significant progress has been achieved in the prevention and management of several severe and disabling mental disorders. This progress has also not only contributed to a significant reduction in the hospitalization needs for many patients and to a much greater emphasis being placed on community care, but has also had a significant impact in terms of real reduction in human suffering.

However, in a number of countries, mental health services are totally lacking and large segments of the population do not even have ready access to health facilities, which tend to be based in hospitals and oriented predominantly towards urban conditions. In an attempt to strengthen the health care system and achieve low-cost but effective and efficient health services, attention is being increasingly focused on the development of a primary health care strategy. Moreover, it has been repeatedly shown that much of psychiatric morbidity is seen at the primary care level. For these reasons the role of primary health care doctors becomes crucial for the delivery of effective and widespread mental health care. Unfortunately the training of general doctors in the rational prescribing of psychotropic drugs is not satisfactory everywhere, and it is sometimes clearly deficient. In addition, the practising doctor not only has to keep abreast with the development of new drugs and treatments, but is also exposed to a variety of sometimes conflicting influences - continuing education is therefore essential.

This manual is addressed primarily to general doctors and is intended to be a basic tool for their continuing education. It should be read in the framework of the context of essential treatments, subject of a previous WHO publication (4). In brief, this approach considers that medicines are **not the only form** of the proper treatment of mental disorders; they are but one component, besides psychological and social interventions.

> Essential treatments in psychiatry are those interventions both *necessary* and *sufficient* for the care of people with specific mental disorders.

During recent years WHO has devoted a great deal of effort to disseminating balanced information on both the benefits that can be derived from the use of psychotropic drugs and the dangers associated with their use. Efforts have been made to improve the training of physicians and other mental health workers in prescribing psychotropic drugs for patients in need of them. Projects aimed at improving prescribing practices and at suggesting methods for evaluating the effectiveness of treatment methods, including drug treatment, have been carried out (2), among others. It was nevertheless felt that there was a need to produce a clear, comprehensive manual which would first discuss general issues of prescribing and would then provide specific guidelines for the use of selected psychoactive drugs: a manual to specifically help the practitioner in prescribing drugs for the management of mental disorders.

In this document, terms like "psychoactive", "psychotropic", and "psycho-therapeutic" will be used synonymously to designate drugs, which, when compared with others, have the power to affect aspects of mind and behaviour, including thought patterns, mood, anxiety, cognitive performance and well-being.

The need for such a manual also has to be seen in the framework of the WHO policy on essential drugs, which, following resolution WHA28.66, has been carried out

by the Organization in an attempt to advise Member States on the selection and procurement, at reasonable cost, of essential drugs of an established quality corresponding to their national health needs.

Essential drugs have therefore been identified to mean that "they are of the utmost importance and are basic, indispensable and necessary for the health needs of the population" (*1*).

In the WHO Essential Drugs List (EDL), the following have been selected for the treatment and control of mental disorders:

amitriptyline
chlorpromazine
diazepam
fluphenazine
haloperidol
lithium carbonate

It should be noted that in the WHO EDL with the exception of lithium carbonate, all others are indicated as

> "an *example of a therapeutic group* and that various drugs could serve as alternatives. It is imperative that this is understood when drugs are selected at national level, since choice is then influenced by the comparative cost and availability of equivalent products."

Thus, in the EDL

amitriptyline represents tricyclic anti-depressants;
chlorpromazine, phenothiazines;
diazepam, benzodiazepines;
fluphenazine, injectable long-acting neuroleptics; and
haloperidol, butyrophenones.

Although this list is basically valid at a global level, on the whole there is a wide variation between countries in the quality and capabilities of primary health care doctors, in drug policies and in disease prevalence. It was therefore felt, according to opinions of experts from the WHO Expert Advisory Panel and collaborating centres that other drugs of significant importance for daily clinical practice should be added to the original EDL. Following this, a wider list of psychoactive drugs was prepared and for each of these drugs a detailed explanation and suggestions for a rational use were provided.

Clearly, the description of an appropriate medicine is only the first step in using it: issues such as education about the medicine, about compliance, about unwanted side effects, about failure to respond, given adequate dosage for a sufficient length of time, and further education about early signs of relapse once recovered, are all vital in determining the effectiveness of any drug treatment. Yet these issues are seldom subjected to scrutiny and controlled research. Moreover, an effective psychiatric treatment can best be the result of an adequate and balanced combination of pharmacological, psychological and psychosocial treatment methods. Didactic and practical reasons nevertheless point to the need for issuing separate manuals instead of a single textbook on psychiatric treatments.

CARE FOR PEOPLE
instead of just
TREATING DISEASES

In Section I of this manual several basic aspects relevant to the pharmacological treatment of mental disorders -- such as influencing factors, prescribing practices and ethical issues, the role of pharmacotherapy at different levels of the health system, and evaluation of pharmacotherapy in psychiatry are reviewed and discussed. Section II presents some basic principles for rational prescribing, and of pharmacokinetics relevant to a more efficient utilization of medicine.

In Section III, all the categories in the F chapter of ICD-10 are briefly described, followed by an indication of the most efficient treatment available - whether pharmacological or not - based on the most updated scientific evidence. Specific strategies for the acute phase as well as for the maintenance treatment are described; wherever pertinent, a section on special problems is also present.

In many countries prescribing is a prerogative of doctors and, as indicated earlier, they constitute the target audience of this manual. It is our belief, however, that

non-prescribing members of the health care team will benefit from its reading. It will not only help them better understand the field of pharmacotherapy of mental disorders in itself, but will also give them a more comprehensive view of mental health care as a whole, adding to their own professional or functional perspective.

2. PSYCHIATRIC MEDICINES IN PRIMARY HEALTH CARE

Not all countries can afford to have all patients treated by a medical doctor. In many of the developing countries over 80 % of outpatient consultations are done by medical assistants, clinical officers, nurses and village health workers operating from district hospitals, health centres, dispensaries, and dressing stations right down to the village level. In many other countries, all consultations are done by doctors, and the health centre or hospital outpatient clinic may be the first level of care, rather than a referral level.

The criteria for selection of drugs to be used at the primary health care level are: efficacy, optimal benefit/risk ratio, satisfactory therapeutic margin and low cost. For several diseases for which long term treatment is needed, such continued treatment can be given and its effect monitored at a lower level than that at which the diagnosis was made and treatment initiated. Such "down-referral" has important implications in countries with scarce resources.

Harding and Chrusciel (3) have outlined the following five essential steps to facilitate the rational use of psychiatric medicines in primary health care. The steps listed imply a series of interdependent actions, designed to increase the rational and effective use of psychotropic drugs. It is not implied that such steps be carried out in any particular sequence.

Focus on a limited number of conditions. Effective training will not be possible if the target conditions are poorly defined or too numerous. Health workers at most levels should not be expected to master the complex psychiatric classifications used by psychiatrists; nor can they be expected (in view of the limited time available) to cope with the whole range of mental disorders, even if they are clearly defined. In the preliminary phase, therefore, it is necessary to focus on a very limited range of conditions, i.e. those:

i) that are known to be *prevalent;*
ii) that have *marked harmful consequences;* and
iii) for which drug therapy is of *clear benefit.*

The selection of priority conditions must be carried out in each country and should reflect, in addition to prevalence, the expressed needs of the people, and the general level of socio-economic development. These conditions will have to be defined clearly with an agreed terminology that is precise and easily understood.

This requires close collaboration between those responsible for training and those concerned with services. In general, the list of priority conditions is likely to include psychiatric emergencies and acute psychoses, chronic psychoses, severe depression, severe anxiety disorders and certain problems related to drug and alcohol abuse; local conditions may require that this list be modified or added to.

Availability of a limited range of drugs for defined situations. The definition of a limited range of psychotropic drugs for use in a particular country facilitates bulk purchase or local manufacture and helps to ensure a relatively cheap and constant supply, adequate quality control and a lesser risk of drug abuse. It also allows a more rational and efficient approach to training, since trainers can ensure that information is relevant to subsequent practice. Unnecessary duplication, different dosage regimes, and confusing nomenclature should be avoided. Psychiatrists and physicians may resist "restriction of freedom to prescribe". In countries with a large private health sector, there will be problems of implementation. There would inevitably be disagreements concerning which drugs should be included in the limited range, and this could lead to a situation in which drug suppliers might use pressure of various kinds to influence decisions. Nevertheless, the potential advantages of a defined, limited range of drugs are such that it is essential to overcome these problems with the help of professional organizations and health authorities.

Simplification of the division of tasks in the use of medicines. The division of tasks in the use of medicines is usually rather rigid. A physician makes a decision concerning the choice of medicine and its dose, route of administration, and duration. This decision is translated into a written "prescription",

often supplemented by direct verbal information and explanation to the patient. The prescription is interpreted by a pharmacist or a nurse who supplies the medicine to the patient. Further decisions concerning change of dose, cessation of treatment, use of other medicines, etc, are taken by the physician on the basis of clinical observation and information given by the patient. In some cases this may be supplemented by information from nurses and/or relatives of the patient. The limiting factor in such a system is the physician, since he/she must be available for all decision-making. In view of the great shortage of physicians, particularly those with adequate training in the use of psychiatric medicines, the effective use of these drugs is severely limited.

Coordinated training programmes. The successful introduction of the approach described above would depend primarily on the institution of appropriate and effective training (and retraining) of all health workers involved. This would require an integrated approach so that training of each category of health worker matched the subsequent work requirements.

Sensible training programmes must also take into account problems posed by side effects, by abuse potential, by failure to take drugs as prescribed, by the risks of overdose, and by the fact that for some psychiatric conditions effective drug treatments are not yet available.

There is often too little continuity between the training of health workers and their subsequent work. Physicians and nurses are usually trained in hospitals where teaching on psychotropic drugs may be based on selected populations and may reflect the particular views and practices of one or more hospital-based psychiatrists. In actual practice the physician or nurse may have to deal with a different range of conditions in a different environment. Drugs used in the training hospital may not be available or may have a different name. Lack of coordination may lead to drugs being supplied for which health personnel have not received training.

The setting up of a central policy body. None of the steps above can be instituted without the full agreement and cooperation of practising psychiatrists, nurses, and those responsible for training, administration and health planning. There may problems of legal responsibility and professional rivalry. There need to be safeguards and regulations to limit the abuse of drugs. This could be achieved by a central planning body for mental health within the health ministry with access to the various professionals groups, training schools and institutions involved.

2.1 Secondary and tertiary levels of health care

The secondary level of health care is generally represented by district hospitals or by large health centres serving between 50,000 and 500,000 people. In some systems smaller health centres occupy an intermediate position between these and community clinics. Depending on their size, district hospitals will probably have a number of specialists and at least one *general clinician*. These centres should have a *qualified psychiatrist*, or a *psychiatric assistant* or a *senior nurse with specialized psychiatric training*. In many situations these general health care centres will serve as the main resources for the delivery of mental health care to more complex cases; moreover, in some countries where there is a shortage of psychiatric hospital units, there is now extensive experience with patients with psychiatric disorders in need of hospitalization and being admitted to general medical wards. Examples are patients with severe depression, mania, schizophrenia. In these situations, pharmacological treatment becomes one of the most important treatment options and needs to be adequately administered by medical personnel working in these units supervised by a psychiatrist.

In mental health care, the tertiary, or second-referral level is represented by *qualified psychiatric personnel* working in specialized mental health facilities, which may be independent or may be part of large general hospitals. Such specialized facilities may also be teaching institutions. At this level, mental health specialists will deal with complex problems of diagnosis and treatment referred from secondary and primary levels; in terms of drug treatment, the most complex treatments will be administered, at least during the initial phase, at this level, as well as treatment still at an experimental stage.

3. ETHICAL ISSUES

In "ESSENTIAL TREATMENTS IN PSYCHIATRY" (4) this issue has been dealt with in some detail. Interested readers might wish to consult it. Some of the key topic areas discussed in that publication include:

i) right and access to treatment;

ii) right to information;

iii) consent to/refusal of treatment; and

iv) clinical responsibility.

While variations in dominant lay opinion between cultures impose differences in what may be perceived to be proper medical behaviour, these differences may relate more to divergence between what is habitual than to real ethical disparities.

All persons have the right to the best available mental health care, which should be part of the health and social care system.

Principle 1
UN Resolution 46/119

4. RATIONAL PRESCRIBING

4.1 Principles of rational prescribing

According to a report of the Council on Medical Services of the American Medical Association (*5*) care of high quality is the one that:

a) produces the optimal improvement in the patient's physiological status, physical function, emotional and intellectual performance and comfort at the earliest time possible consistent with the best interests of the patient and relatives;

b) emphasizes the promotion of health, the prevention of disease or disability, and the early detection and treatment of such conditions;

c) is provided in a timely manner, without either undue delay in the initiation of care, inappropriate curtailment or discontinuity, or unnecessary prolongation of such care;

d) seeks to achieve the informed cooperation and participation of the patient in the care process and in decisions concerning that process;

e) is based on accepted principles of medical science and the proficient use of appropriate technological and professional resources;

f) is provided with sensitivity to both the stress and anxiety that illness can generate among the relatives and with concern for the patient's overall welfare;

g) makes efficient use of the technology and other health system resources needed to achieve the desired treatment goal; and

h) is sufficiently documented in the patient's medical record to enable continuity of care and peer evaluation.

> Treatment should have the shortest possible duration

The above elements are certainly helpful for the establishment of principles for good treatment and rational prescribing as well. More specifically, the following, adapted from Ghodse & Khan (*6*), are indicated as additional principles for the rational prescribing of psychoactive medication:

1. There should be a clear target symptom or symptoms that the medicine is known to affect, e.g., depressive mood, thought disorder, anxiety, restlessness, insomnia or the like.

2. The dosage should be adjusted according to risk/benefit principles, taking into account the target symptom and its severity; patient's characteristics such as sex, age, weight, ethnic background, nutritional status and eventual special states such as pregnancy or lactation; other concomitant medical conditions and treatments; environmental factors such as temperature; and availability and access to emergency care, if needed.

3. As little amount of the drug as possible should be supplied, based on an assessment both of how much of it is required to affect the target symptom and of the patient's social, psychological and geographical situation, e.g., a patient from a rural area who must make an arduous journey to obtain treatment will require a larger supply than one with easier access to a pharmacy.

4. The physician should be aware of all the drugs, both medical and non-medical, being taken by the patient and the possible interactions, e.g., between alcohol and drugs with sedative properties. Synergism, the multiplicative effect of drugs when taken together, is a possibility for which the clinician must be constantly on guard. Many drugs taken for a variety of conditions, such as hypertension, interact with psychoactive drugs either to enhance sedation or to cause hypotension. Reading package inserts as a routine is a good practice in this regard. Other reference works also carry information on interactions. Investigation of history of substance abuse, including alcohol and illicit drugs, should also be included.

5. The expected duration of the treatment should be made clear to the patient: in some cases it may be for a limited period of time. This period may be related to the pharmacological properties of the drug employed, e.g., it takes 2-3 weeks for dependence on barbiturates to develop; or, in a patient who has not previously abused alcohol or used central nervous system depressants, it may be 20 weeks or so until dependence on long-acting benzodiazepines, in therapeutic dose ranges, begins. This is a natural pharmacological window and illustrates the kinds of factors that determine the length of the period. Another example is the rapid appearance of tolerance to many sedative hypnotics. In other instances it may have a much longer duration or be eventually for life, e.g. in some cases of chronic, severe schizophrenia, or for the prevention of rapid-onset and severe relapses of mania with lithium salts.

6. The patient should be informed of possible side-effects, e.g., morning dullness after taking sedative hypnotics; effects on driving performance after taking tranquillizers or sedative hypnotics; effects on the fetus if pregnancy occurs while patients are taking psychoactive drugs; hypotension caused by phenothiazines, etc. The occurrence of side-effects and the measures taken to respond to them, e.g. reassurance that they are temporary or perhaps a reduction in the dose, should also be entered in the patient's records.

7. The patient should be monitored for general progress, for compliance and misuse and specifically to assess the effects of the drug on the target symptom. The response should be measured and entered in the patient's records.

8. If at all possible, family members should be involved as part both of the management plan and of the monitoring. They usually play an important part in adequate prescribing and monitoring.

9. Suicide is more frequent in patients with some mental disorder, such as depressive disorders. Rapidly escalating life stress frequently triggers suicidal thoughts and behaviour. A history of previous suicidal thoughts or attempts and a family history of suicide are important indications of possible suicidal behaviour. Such patients should be specifically asked about suicide and, if it is possible, the clinician must limit the amount of psychoactive drug prescribed and should also construct a regimen in which there is frequent clinical monitoring and also, if at all possible, monitoring by family and friends. Talk of suicide should always be taken seriously. The physician should be alert to respond by hospitalization if the clinical situation of a patient with suicidal potential deteriorates. If there is severe physical or psychiatric disorder and, in particular, a history of substance abuse, the risk of suicide is high.

10. The physician should always take a history of substance abuse. A past history of alcoholism, for example, is often present in patients liable to misuse drugs. However, a history of alcoholism or drug abuse does not preclude the use of psychoactive drugs for diagnosed psychiatric disorders, but the level of control and monitoring must be greater and such monitoring more frequent than would otherwise be necessary.

11. The drug or drugs with the least potential for abuse should be used for any given indications.

More often than not, non-pharmacological means, such as counselling, will be both applicable and effective, and without risk of drug misuse or drug dependence. The decision to treat with drugs should be based on a clinical determination that the patient's psychological and social resources have been, or are in danger of being, overwhelmed; for example, a sustained period of inability to sleep following the death of a loved one represents a typical case in which pharmacological treatment of insomnia may be considered. The clinical question is, can this patient, within the limits of the available resources, regain equilibrium without drug therapy? If the answer is yes, and particularly if the answer is yes with relatively bearable suffering or

with relatively little discomfort, then non-drug approaches are indicated. Counselling or participation with others undergoing life stress in self-help groups, or still other approaches discussed elsewhere in this publication may be tried before drug therapy is attempted. If the answer is no, then the next clinical question is, what are the dangers to this patient from drug treatment? If the risks and benefits are carefully assessed, the decision to treat or not to treat with psychoactive drugs will emerge from the assessment.

Some disorders, such as phobic states, panic disorders, and the like, may require long-term therapy with drugs which have a definite dependence liability, such as the benzodiazepines. The clinician needs to monitor such cases carefully and to discuss with the patient and the family the possible development of dependence. With most such patients, dependence is not a problem if the dose is tapered off when the drug is no longer needed or a drug "holiday" is being taken.

A general principle is that psychoactive drugs should be used on a short- or long-term basis depending on the chronicity of the disorder. Fear of development of dependence, or of abuse or possible resale of the drugs prescribed, should not prevent the physician from providing the indicated therapy. Fear of these possibilities should rather be the motive for careful monitoring, not only of the progress of the drug regimen but also of the person to whom the drugs are prescribed. It is also important for the physician to keep up with the literature. For instance, many psychoactive drugs, e.g. the benzodiazepines, are metabolized much more slowly by the elderly than they are by younger patients. This has only been widely realized in the last decade or so. The difference in age and in metabolism is clinically meaningful and requires dose reduction and more frequent monitoring in the elderly than with younger patients. For insomnia in the elderly, the use of sedatives or drugs with sedative properties, e.g. phenothiazines or antidepressants, 2-3 times per week instead of on a daily basis may be a way to avoid the possibility of dependence while still providing relief for what is frequently a trying clinical problem. The same strategy is, of course, applicable in any clinical situation in which the aim is to avoid dependence or perhaps just not to provide too large a drug supply.

Numerous drug interactions, as noted above, dictate that drugs should be prescribed only after the data from the history, physical examination and laboratory results have been reviewed and a diagnosis established, and the costs and benefits of a particular therapy assessed. The attitude that addiction is to be avoided at all costs, cannot be justified. When such an attitude does determine clinical decisions, it frequently causes much unnecessary suffering.

Prescribe
as few different drugs
as possible in
as few doses per day
as possible

Finally, it should be stressed that several studies have shown that the dosage of psychotropic drugs sufficient to obtain therapeutic effects may be lower among specified ethnic groups, e.g. Asians. Therefore the dosages indicated in this document should be considered with caution and possibly adapted to the needs of special ethnic groups, in particular people of Asian origin, including Native Americans.

4.2 Topics relevant to rational prescribing

4.2.1 History taking

Interviewing is probably the oldest and most frequently used of the assessment procedures. As it usually takes place during the first meeting between patient and health care worker, the interview has a significant influence on the patient's expectations and on the outcome of subsequent interventions. The interview may vary from being highly structured, in which the topics discussed follow a questionnaire or prearranged format, to being flexible or unstructured, in which the interviewer follows cues given by the patient and does not restrict questioning to specific topics. Often both techniques are used, background information about age, previous medical history, etc. being elicited in the structured interview, while flexible questioning elicits additional information.

Before any treatment strategies can be initiated, patient and therapist must discuss and agree on the behavioural changes to be effected and the approach to be used. Such discussions are repeated periodically so that treatment effectiveness can be assessed and new goals for behavioural change may emerge. One aspect of a behavioural assessment based on a typical diagnostic interview is that not only are problem behaviours targeted but behavioural strengths are identified; this is important, since they are useful in the treatment approach.

Apart from its value in assessment, the interview may be therapeutic in its own right, because helping the patient to identify the underlying problem can be very useful, as can the relationship between patient and health care worker, initiated at the interview.

Other assessment procedures may also be used, including questionnaires, self-monitoring, behavioural observation and psychophysiological measurement. The importance of thorough assessment cannot be overemphasized, because behavioural intervention is not like using a recipe book - there cannot be a single recipe for every symptom. Rather, the process is tailored to the individual's unique problems in their particular context, and these problems must be clearly defined. The purpose of all the different assessment procedures, therefore, is to specify and select target behaviours, identify antecedent and consequent variables relating to the target behaviour, and collect data about the target behaviour and the variables affecting it.

4.2.2 Diagnostic assessment

A careful diagnosis is the first, essential step for a rational prescribing and ensures that the treatment is being delivered for the disorder likely to be responsive to that treatment. Up until a few years ago, psychiatric practice had been hampered by the existence of variable, different diagnostic criteria; in the field of treatment, this has led to marked differences in the choice of the target symptoms for treatment, in the selection of patients to be admitted to certain treatments and in the assessment of treatment response. The recent introduction of the ICD-10 will undoubtedly foster the adoption of uniformed, specified diagnostic criteria in different countries of the world and will facilitate the achievement of more homogeneous, adequate standards of drug treatment.

4.2.3 Doctor-patient relationship

The establishment of an effective doctor-patient relationship represents an essential step in any drug treatment; indeed, it is the core of the practice of medicine. A good relationship, even more than a cure, is expected by the patient; it is typical of patients to be tolerant of the therapeutic limitations of medicine. It has been often stressed that there are no diseases; there are only sick people. Therefore failure of the doctor to establish good rapport accounts for much of the ineffectiveness in the care of patients.

Drugs can play an important role in the doctor-patient relationship. The doctor should make an effort to enlist, recruit and involve the patient in a collaboration with him/her related to the prescribed medication: Gutheil (7) has called this "the pharmacotherapeutic alliance", characterized by "participant prescribing". In this way, by making the patient a partner in treatment, the doctor emphasizes and reinforces the patient's strengths as a person instead of his weaknesses in a dependent, sick, role thus, opening the door for more flexible, appropriate, responsive, and responsible drug therapy.

Given the many and often disturbing side effects associated with drug treatment, it is important that a systematic, routine inquiry be made into the patient's eating, eliminating, sleeping, and sexual functions. An open discussion about these aspects of the patient's life and the changes induced by the medication will reassure the patient and will prevent both a breakdown in the relationship and non-compliance with treatment.

4.2.4 Problems of treatment compliance

Making sure that patients take the medicines prescribed to them by doctors has always been a problem. The problem varies from the patients who forget the occasional tablet, to those who never even bother to get their prescriptions dispensed. Among medical patients non-compliance range between 31 to 59% of patients in long-term drug treatment, as shown in a number of studies (*8*). Non-compliance can therefore

represent a serious obstacle to the achievement of therapeutic objectives. It also can indicate a breakdown of confidence and mutual respect between the patient and his doctor.

> Compliance increases if **less than three medicines** are prescribed at the same time

In psychiatry non-compliance is made more problematic by the reduced insight accompanying many mental disorders. The lack of adequate insight, especially in psychotic disorders, can act as an important obstacle for the patient in understanding the need for a regular, careful compliance with the drug treatment administered.

Among factors affecting compliance, an important one is the complexity of the drug regime. Several studies have found that, if three or more medicines are being prescribed concurrently, compliance falls significantly. This fact stresses the need for a simplification of the drug treatment schedule and the need to avoid prescribing more than one medicine at the same time, which is also known as *polytherapy*, in addition to the other reasons which induce refraining from such a practice.

Other important reasons to explain non-compliance, frequently given by patients who abandoned treatment, include the occurrence of side-effects and the absence of any noticeable subjective feeling of improvement, or worsening of the condition. In psychiatry, where side effects, sometimes severe, are quite common during many pharmacological treatments, this is an especially important reason of non-compliance. Greater awareness by the doctor about this problem can therefore minimize the risk of occurrence of side-effects, through a more careful selection of the needed drug and the therapeutic regime, and can prevent many unnecessary cases of adverse effects. An improved communication between the doctor and the patient, with availability of the former to give the patient all the information he/she may require about the drug treatment administered, and its possible or likely adverse effects, can significantly reduce the non-compliance phenomenon and create the best climate for a shared inquiry about the treatment, the establishment of mutual goals and a mutual participation in both experiencing and observing the process.

4.2.5 Therapeutic failures

The failure of a specific drug trial should prompt the clinician to consider a number of possibilities.

First: was the original diagnosis correct? This reconsideration should include the possibility of an undiagnosed organic mental disorder.

Second: are the observed remaining symptoms actually the medicine's adverse effects and not related to the original disease? Antipsychotic drugs, for example, can produce both akinesia, which resembles psychotic withdrawal, or akathisia and neuroleptic malignant syndrome, which resemble increased psychotic agitation.

Third: was the medicine administered in sufficient dosage for an appropriate period of time? Patients can have different drug absorption and metabolic rates for the same drug, and plasma drug levels should be obtained to assess this variable, although the high costs associated with plasma drug levels measurements make it hardly affordable by the large majority of psychiatric institutions in the world.

Fourth: was there a pharmacokinetic or pharmacodynamic interaction with another drug the patient was taking that reduced the efficacy of the psychotherapeutic drug?

Fifth: did the patient actually take the medicine as prescribed? As mentioned above, drug non-compliance is a very common clinical problem.

4.2.6 Choice of medicine

The first two steps in selecting a drug treatment, the diagnosis and identification of target symptoms, should be carried out, whenever possible, when the patient has been in a drug-free state for 1 to 2 weeks. The drug-free state should include the absence of medications for sleep (e.g. hypnotics), as the quality of sleep can be both an important diagnostic guide and a target symptom. Psychiatrists often evaluate symptomatic patients who are already on one or more psychoactive medications, and

so it is usually necessary to wean the patient from current medications and then to make an assessment. An exception to this practice occurs when patients present themselves to the psychiatrist on a sub-optimal regimen of an otherwise appropriate drug. In such cases, the psychiatrist may decide to continue the drug at a higher dose in order to complete a full therapeutic trial. From among the drugs appropriate to a particular diagnosis, the specific drug should be selected according to the patient's past history of drug response (compliance, therapeutic response, and adverse effects), the patient's family history of drug response, the profile of adverse effects for that drug with regard to a particular patient and the psychiatrist's usual practice. If a drug has previously been effective in treating a patient or a family member, it should be used again unless there is some specific reason not to use the drug. A past history of adverse effects from a specific drug is a strong indicator that the patient would not be compliant with that drug regimen.

It is unfortunate that patients and their families are often quite ignorant of what drugs have been used before, in what doses, and for how long. This finding may reflect the tendency of psychiatrists not to explain drug trials to their patients, and should encourage psychiatrists to give their patients written records of drug trials for their personal medical records. A caveat to obtaining a past history of drug response from patients is that, because of their mental disorder, they may inaccurately report the effects of a previous drug trial. If possible, therefore, the patients' medical records should be obtained to confirm their reports. Most psychotherapeutic drugs of a single class have been demonstrated to be equally efficacious; however, these drugs do differ in their adverse effects on individuals. Thus the drug selected should minimally exacerbate any pre-existing medical problems that a patient may have.

4.2.7 Therapeutic trials

A drug's therapeutic trial should last for a previously determined length of time. Because behavioural symptoms are more difficult to assess than other physiologic symptoms (e.g. hypertension), it is particularly important for specific target symptoms to be identified at the initiation of a drug trial. The doctor and the patient can then assess these target symptoms over the course of the drug trial to help determine whether the drug has been effective. There are a number of objective rating scales available to assess a patient's progress over the course of a drug trial. If a drug has not been effective in reducing target symptoms within the specified length of time and if other reasons for the lack of response can be excluded, use of the drug should be tapered off and stopped. Another common clinical mistake is the routine addition of medications without the discontinuation of a prior drug. Although this practice is indicated in specific circumstances (e.g. lithium potentiation of an unsuccessful trial of antidepressants), it often results in increased adverse effects, unwanted pharmacokinetic interactions and non-compliance, as well as the clinician's not knowing whether it was the second drug alone or the combination of drugs that resulted in a therapeutic success.

4.2.8 Adverse effects

Patients will generally have less trouble with adverse effects if they have previously been told to expect them. It is not unreasonable to explain the appearance of adverse effects as evidence that the drug is working. But clinicians should distinguish between probable or expected adverse effects and rare or unexpected adverse effects.

An extreme adverse effect of drug treatment is an attempt by a patient to kill himself by overdosing on a psychotherapeutic drug. Whatever the motivation, doctors should be aware of this risk and prescribe the safest possible drugs. It is good practice to write non-refillable prescriptions for small quantities of drugs when suicide is a possibility. In extreme cases, attempts should be made to verify that patients are actually taking the medication and not hoarding the pills for a later overdose attempt. It is a common clinical observation that patients may attempt suicide just as they are beginning to get better. Clinicians, therefore, should continue to be careful about prescribing large quantities of medication until the patient is almost completely recovered. Another consideration for psychiatrists is the possibility of accidental overdose, particularly by children in the household.

Patients should also be advised to keep psychotherapeutic medications in a safe place.

4.2.9 Patients' attitudes toward medicines

Some patients' ambivalent attitudes toward medicines often reflect the erroneous belief that taking a psychotherapeutic drug means that they are really sick or not in control of their lives or that they may become dependent on the medicine and have to take it forever. A simplified approach to these concerns is to describe the psychiatric disorder partially as any medical disease. Doctors should also explain the difference between drugs of abuse that affect the normal brain and psychiatric medicines that are used to treat emotional disorders. They should point out to patients that antipsychotic, antimanic and antidepressant medicines usually do not create dependence.

> Patients and families want to know what is going to happen to them

5. PRINCIPLES OF PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics is the quantitative study of the processes involved in the absorption, distribution, biotransformation and elimination of a drug in the human body. *Pharmacodynamics* describe the effects of a drug on the body. The knowledge of the kinetic profile of a drug and the characteristics linked to the patient can lead to a rational choice of the drug and/or an appropriate modification of the treatment schedule in order to achieve and keep adequate concentrations of the drug at the various action sites. Despite this, pharmacokinetics remains poorly known and outside daily clinical practice. Some basic concepts related to pharmacokinetics will be discussed here.

The principal steps studied by *pharmacokinetics* are:

- drug absorption,
- distribution,
- metabolism, and
- excretion.

Regarding *absorption*, a psychotropic drug can only reach the brain if it is carried by blood. *Orally* administered drugs must dissolve in the fluid of the gastrointestinal tract before the body can absorb them, the absorption depending on the drug's concentration and lipid solubility and the gastrointestinal tract local pH, motility and surface area. If the pharmacokinetic absorption factors are favourable, the drug may reach therapeutic blood concentrations more quickly if it is administered *intramuscularly* (i.m.). If a drug is coupled with an appropriate carrier molecule, intramuscular administration can sustain the drug's release over a long period of time, as in the case of the depot antipsychotic drugs. Finally, *intravenous (i.v.)* administration is the quickest route to achieve therapeutic blood levels, although it does not necessarily lead to faster steady-state concentrations; it also carries the highest risk of sudden and life-threatening adverse effects.

The *distribution* of a drug is dependent on the amount of drug freely dissolved in the blood plasma, bound to dissolved plasma proteins (primarily albumin) and dissolved within the blood cells. The distribution of a drug to the brain is determined by the blood-brain barrier, the brain's regional blood flow, and the drug's affinity with its receptors in the brain, and can vary accordingly.

Metabolism is somehow equivalent to 'biotransformation'. The four major metabolic routes for drugs are oxidation, reduction, hydrolysis, and conjugation. Although the usual result of metabolism is to produce inactive metabolites that are more readily excreted than is the parent compound, several psychaoctive substances have active metabolites. The liver is the main site of metabolism and bile, faeces and urine are the major routes of excretion. *First pass metabolism* refers to the liver metabolism of the drug which follows the oral administration and, to a much minor extent, the rectal administration. The first pass metabolism consists in the pre-systemic metabolism performed by the liver on the drug absorbed by the gastro-intestinal tract before it can enter into the systemic circulation. In this case a pre-systemic elimination of the drug will take place, reducing its bioavailability, but not its percentage of absorption. This mechanism regards only some selected psychotropic drugs (e.g., phenothiazines and haloperidol). It should be stressed that psychotropic drugs can have very different bioavailabilities: for instance, phenothiazine bioavailability can be up to 100 fold different between individuals. Similarly, a reported 30-40 fold variation exists with TCAs.

Two important concepts regarding metabolism and *excretion* are time of peak plasma level and half-life of a drug. The time between the administration of a drug and the appearance of peak concentrations of the drug in plasma (peak plasma level) varies primarily according to the route of administration and absorption. The half-life of a drug is defined as the amount of time it takes for one half of a drug's peak level to be metabolized and excreted from the body. A general guideline is that if a drug is administered in repeated doses, it will reach 97% of its steady state plasma concentrations in a time equal to five times its half-life.

The major *pharmacodynamic* considerations include:

- receptor mechanism,
- the dose response curve,
- the therapeutic index and
- the development of tolerance, dependence and withdrawal phenomena.

The *receptor* site for most psychoactive drugs is also a receptor for an endogenous neurotransmitter. For example, the primary receptor site for chlorpromazine is the dopamine receptor. However, for other psychotherapeutic drugs, this may not be the case.

The *dose response curve* plots the drug dosages against the effects of the drug. The potency of a drug refers to the relative dose required to achieve a certain effect. Haloperidol, for example, is more potent than is chlorpromazine because generally only 5 mg of haloperidol are required to achieve the same therapeutic effect obtained with 100 mg of chlorpromazine. Both haloperidol and chlorpromazine, however, are equal in their maximal efficacies, that is, the maximum clinical response achievable by the administration of a drug.

The side effects of most drugs are often a direct result of their primary pharmacodynamic effects and are better conceptualized as adverse effects. The *therapeutic index* is a relative measure of a drug's toxicity or safety. It is defined as the ratio of the median toxic dose (TD50) to the median effective dose (ED50). Haloperidol, for example, has a very high therapeutic index, as evidenced by the wide range of doses in which it is prescribed. Conversely, lithium salts have a very low therapeutic index, thereby requiring careful monitoring of serum lithium levels when on this drug. There can be both inter- and intra-individual variation in the response to a specific drug. An individual patient may be hypo-reactive, normally reactive, or hyper-reactive to a particular drug. For example, some patients with schizophrenia require 1 mg a day of haloperidol, others require a more typical 10 mg a day, and still others may eventually require a higher daily dosage to achieve a therapeutic response. Idiosyncratic drug responses occur when a person experiences a particularly unusual effect from the drug. For example, some patients become quite agitated when given benzodiazepines.

A person may become less responsive to a particular drug as it is administered over time, which is referred to as *tolerance*. The development of tolerance is associated with the appearance of *dependence*, which may simply be defined as the necessity to continue administering the drug in order to prevent the appearance of *withdrawal* symptoms. However, it should be stressed that tolerance and dependence are not seen with the majority of the drugs which will be discussed below.

PART II

DRUG INFORMATION SHEETS

6. INTRODUCTION TO DRUG INFORMATION SHEETS

In establishing a list of essential medicines for the care of persons with mental disorders the following general principles were followed: (*9*)

1. Adoption of a list of essential medicines for mental disorders implies giving priority to achieving the widest possible coverage of the population, with treatments of proven efficacy and safety, in order to meet the needs for treatment of the most prevalent and severe disorders.

2. Only those medicines for which adequate scientific data are available from well- controlled studies should be selected.

3. Each selected product must meet adequate standards of quality.

4. Concise, accurate and comprehensive information on each different medicine drawn from unbiased sources should accompany each list of essential medicines.

In addition, the following guidelines were also followed, and are recommended, to ensure a process of selection of essential medicines that is unbiased and based on the best available scientific information, yet allowing for a degree of variation to take into account local needs and requirements:

1. The list of essential medicines should be established at a national level by an appointed committee including individuals competent in the fields of clinical psychiatry, psychopharmacology, psychotherapy and social and behavioural sciences, as well health workers at the peripheral level.

2. Cost represents a major selection criterion. In cost comparisons between medicines, the cost of the total treatment, and not only the unit cost, must be considered.

3. Local health authorities should determine the level of expertise required to provide a single treatment or groups of treatments. Consideration should also be given to the competence of the personnel to make a correct diagnosis. In some instances, whilst individuals with advanced training are necessary to prescribe initial therapy, individuals with less training could be responsible for maintaining therapy.

4. The influence on the health status of local physical or psychosocial conditions, or of local diseases, should be considered when making the selections: e.g. nutritional status, climate, housing and employment levels, natural social networks.

5. When two or more treatments or interventions are therapeutically equivalent, preference should be given to:

   i) the treatment which has been most thoroughly investigated;
   ii) the treatment with the most favourable properties, e.g. to improve compliance or to minimize risk in various pathophysiological states;
   iii) the medicine, pharmaceutical product and dosage form that provide the highest benefit/risk ratio;
   iv) medicines, pharmaceutical products and dosage forms with favourable stability, or for which storage facilities exist.
   v) the cheapest medicine with similar pharmacological properties.

6. Preference should be given to the international non-proprietary (generic) names of medicines.

7 The list should be reviewed periodically - at least once every two years and whenever necessary. New treatments should be introduced only if they offer distinct advantages over treatments previously selected; if new information becomes available on treatments already in the list which clearly shows that they no longer have a favourable benefit/risk ratio, they should be deleted and replaced by a safer treatment. It should be remembered that for the treatment of

certain conditions no psychotropic drug treatment at all may be preferable.

For the preparation of WHO List of Essential Drugs (EDL) it was recognized that there was a need to identify the widest range of drugs that can be safely and adequately handled by health workers with minimum training to perform this task at the community level. This implies the development of guidelines for a limited selection of drugs to be used at the primary health care level.

As already mentioned in Chapter 1 (page 2), the WHO EDL includes the following drugs of great relevance for the treatment of psychiatric disorders:

in *Section 24. Psychotherapeutic drugs*:

- amitriptyline
- chlorpromazine
- diazepam
- fluphenazine
- haloperidol
- lithium carbonate

in *Section 9. Antiparkinsonian drugs*:

- biperiden

It must, however, be noted that the square symbol preceding the drugs listed above indicates that those drugs represent *classes of drugs*, rather than a *specific substance*. They are *examples of a therapeutic group* and various drugs could serve as alternatives. Examples of acceptable substitutions include:

- *amitriptyline*: any other *tricyclic antidepressant*;
- *chlorpromazine*: any other *phenothiazine*;
- *diazepam*: any other *benzodiazepine*;
- *fluphenazine*: any other *injectable long-acting neuroleptic*;
- *haloperidol*: any other *butyrophenone*;

and

- *biperiden*: other *antiparkinsonian drugs*.

Considering this as background, after extensive consultations and discussions with experts in different parts in the world, a list of essential psychiatric medicines - as *specific substances* - was compiled and includes:

1. **Amitriptyline** - a standard tricyclic antidepressant;

2. **Biperiden** - a standard antiparkinsonian drug, for the management of adverse reactions caused by neuroleptics:

3. **Chlorpromazine** - a standard phenothiazine neuroleptic;

4. **Clomipramine** - a tricyclic antidepressant, to be used for the treatment of specific disorders, e.g. panic attacks and obsessive-compulsive disorders;

5. **Diazepam** - a standard benzodiazepine;

6. **Fluphenazine decanoate** - a standard long-acting neuroleptic;

7. **Haloperidol** - a standard non-phenothiazine neuroleptic (butyrophenone);

8. **Imipramine** - a standard tricyclic antidepressant, with a profile of adverse effects different from that of amitriptyline, and also used for the treatment of other specific disorders, e.g. panic attacks and obsessive-compulsive disorders;

9. **Lithium carbonate** - a standard drug for the prophylaxis of bipolar and unipolar affective disorders;

10. **Temazepam** - a short-acting benzodiazepine.

It should be noted that during this widespread consultation, the need was felt for only three additional psychotropic drugs as compared to the WHO EDL. This confirms the adequacy and appropriateness of a limited number of psychotropic drugs, sufficient to meeting clinician's needs.

Detailed information on each of these drugs follows.

6.1. Amitriptyline

General information

Amitriptyline, a dibenzazepine derivative, is one of the first antidepressants provided for clinical use. It is still now one of the standard drugs for the pharmacological treatment of depression. Its main metabolite nortriptyline (demethylated amitriptyline) is also an equally potent antidepressant agent. It is well absorbed after oral administration. Its plasma level reaches the peak 2-4 hours after oral intake and its half-life ranges from 10 to 20 hours. The inactivation and excretion occurs over a period of several days. There is a wide inter-patient variation in the metabolism and plasma concentrations of amitriptyline (and other tricyclic antidepressants, including imipramine and clomipramine), to be discussed below. This is due to the fact that the metabolism of these antidepressants is under the control of a polymorphic enzyme. This may lead, in some patients, to excessively high drug concentrations even at normal doses. In particular, this can be true in the case of subjects of specific ethnic background (e.g., Asians).

Storage

Amitriptyline should be stored in well-closed containers protected from light and not be allowed to freeze.

Clinical information

Uses

Treatment of depressive disorders.

Dosage and administration

It is advised to start with a lower dose (45-60 mg/day) the first day and increase the dose gradually to 75-300 mg/day within a few days or weeks. When it is seen that the drug is effective enough and adverse effects are well-tolerated, the dose should be maintained until depressive symptoms are sufficiently improved and then gradually reduced to a lower dose. The treatment should be continued for at least 2 to 4 months even after the symptoms are completely eliminated, and then gradually discontinued (i.e. over 2-3 weeks). In many cases it may be advisable to take it in a single dose at bedtime.

Contraindications

- Closed-angle glaucoma.
- Severe cases of heart, kidney and liver diseases, particularly in the period following an acute myocardial infarction.
- Marked malnutrition.
- Impending danger of suicidal attempt.

Precautions

The dosage should be reduced in elderly patients, and in patients with former cardiac disease. Routine examination of cardiac, hepatic and other functions should be performed during the course of treatment.

Ambulatory patients should take extra precautions while driving or operating machinery during treatment with amitriptyline since reaction times can be impaired by the drug, especially with higher dosages and at the start of the treatment.

Use in pregnancy and in breast-feeding

Amitriptyline should not be used by pregnant women, and non-drug alternatives should be used for treating depression during pregnancy, if needed.

Women taking amitriptyline should not breast-feed.

Adverse effects

Because of its central H_1-alpha$_1$-adrenergic receptor blockade properties, amitriptyline is more sedating than most antidepressants. This may help if insomnia is a problem, but it may also cause daytime drowsiness - especially early in the course of treatment. The most common and troublesome side-effects of amitriptyline are also due to its anticholinergic effects, which may produce dry mouth, gastric discomfort, constipation, blurred vision, dysuria, urinary retention, increased heart rate, precipitation of close-angle glaucoma. Older patients suffer more from these anticholinergic effects. Orthostatic hypotension, dizziness and sleepiness are also observed in some patients. These side-

effects, if not marked, may often be considerably lessened within a few weeks (generally three) while taking the same amount of the drug.

Persistent fine tremor, skin rashes, obstructive jaundice, and mild parkinsonian syndrome may appear occasionally. There may be complaints about sexual difficulties such as erectile difficulties and delayed ejaculation. Delirium can be induced in as many as 6% of patients who get standard doses of this drug.

Drug interactions

Side-effects and sedative effects of amitriptyline are potentiated by neuroleptic, anxiolytic and hypnotic drugs and alcohol in various ways, depending on the pharmacological actions of each drug. Clinically, benzodiazepines are often used in association with amitriptyline to alleviate anxiety and insomnia of depression.

Particularly important is the interaction of amitriptyline with mono-amine oxidase inhibitors (MAOI): this interaction is especially dangerous and must be avoided.

Overdosage

Acute ingestion of amitriptyline (and other tricyclic antidepressants) can be fatal in the dose range of 1-2 g or more. Smaller doses can also be dangerous in children and in those with pre-existing illness. Signs of overdose include difficulty breathing, shock, agitation, delirium and coma.

Gastric lavage should be carried out without delay. Patients should be treated in an intensive care unit, with continuous monitoring of vital signs and electrocardiogram (ECG). It is reported that physostigmine salicylate 1 to 4 mg intramuscularly may reverse the anticholinergic manifestations of severe poisoning, such as coma, delirium and myoclonus.

6.2 Biperiden

General information

Biperiden is one of the antiparkinsonian drugs used to treat Parkinson's disease and to control extra-pyramidal adverse effects (EPSEs) commonly provoked by antipsychotic drugs, which include the classical 'parkinsonian' triad of bradykinesia, rigidity and tremor. Other EPSEs include akathisia, dystonic reactions and excessive salivation. The prevalence of EPSEs seems to vary widely across studies; an overall figure of around 40%, among those in treatment with neuroleptics, seems the most reasonable estimate of the prevalence of EPSEs (*10*).

Biperiden, as other antiparkinsonian drugs, decreases stiffness and tremors and improves muscle control, and this action is obtained through a marked central anticholinergic action; the drug also has peripheral cholinergic blocking effects.

Biperiden is well absorbed after oral administration. It is already ascertainable in the plasma 30 minutes after first administration, and its half-life lasts several hours. The metabolism of this drug occurs through hydroxylation, and its metabolites are largely excreted in the urine.

Clinical information

Uses

Treatment of Parkinsonian side effects associated with the administration of antipsychotic medicines.

Dosage and administration

It is advised to start with 2 mg/day and increase the dose up to a maximum of 6-8 mg daily, depending on response and tolerance. For the treatment of acute dystonic reactions it is possible to administer the drug i.m. or in slow i.v. infusion; in this case the daily dosage is in the range of 5-10 mg/day.

Contraindications

- Known hypersensitivity to biperiden.
- Closed-angle glaucoma.
- Enlarged prostate, mechanical stenosis of the gastrointestinal tract, megacolon, lung atonia.
- Myasthenia gravis.

Precautions

As stated in a WHO Consensus Statement (*11* - see the Appendices), the prophylactic use of anticholinergics in patients on neuroleptic treatment is not recommended and may be justified only early in treatment (after which it should be discontinued and its need should be re-evaluated). As a rule, anticholinergic drugs should be used only when Parkinsonism has actually developed, and when other measures, such as the reduction of neuroleptic dosage or the substitution of the administered drug by another less prone to induce Parkinsonism, have proven ineffective.

This drug should be used cautiously in patients suffering from heart problems (especially patients with a recent myocardial infarction or cardiac arrhythmias), or in patients with urinary problems due to enlarged prostate.

Use in pregnancy and in breast-feeding

Although there are no final data showing that biperiden may increase occurrence of fetal damage, it is advisable, except in highly selected cases, for pregnant women not to use this drug. Women taking biperiden should not breast-feed, since it is still unclear in which quantity biperiden is present in maternal milk.

Adverse effects

As with other antiparkinsonian drugs, biperiden can cause anticholinergic effects, represented by drowsiness, dry mouth, gastric discomfort, constipation, blurred vision, dysuria, urinary retention, tachycardia and dysrhythmias, precipitation of close-angle glaucoma. Older patients suffer more from these anticholinergic effects. In some patients, especially in the

elderly, this drug can cause psychiatric disturbances ranging from mild memory problems to acute confusional states.

Drug interactions

Additive effects may become visible when other drugs having anticholinergic properties, such as tricyclic antidepressants and antihistamines are used at the same time with biperiden.

Overdosage

In cases of gross overdosage an initial acute hyperactivation is followed by depression of the central nervous system. Disturbances of the CNS, resulting in psychosis, hypersensitivity to external stimuli, may be followed by circulatory collapse, hypotension and coma. Death may occur due to respiratory failure. The treatment is only symptomatic and supportive.

6.3. Chlorpromazine

General information

Chlorpromazine belongs to the phenothiazine group of antipsychotics and is an aliphatic class phenothiazine. It is generally not so well absorbed from gastrointestinal tract and injection sites, with significant first pass metabolism in the liver following an oral administration. Several metabolites are active. Peak blood levels occur after 1.5-3 hrs of oral administration and 30 minutes of IM injections. Chlorpromazine has a plasma half-life of 6-8 hrs and steady state plasma levels are reached in 5-7 days. It should be noted that the steady state is reached at a slower pace in comparison with the statement made on page 17, section 5, because of the presence of active metabolites with longer half-lives. Chlorpromazine is an enzyme inducer, thereby decreasing its own plasma concentrations after a few weeks of administration and then stabilizing at this lower level. There are also substantial interpatient variations in plasma concentrations and daily variations in the same patient. For these various reasons the correlations between plasma concentration and clinical response have been minimal and not very significant, although generally positive. Thus, currently, plasma antipsychotic concentrations, however measured, do not usefully predict response in psychotic patients and are not to be recommended in routine clinical situations.

Distribution in the body is rapid, with highest concentration occurring in the liver, lungs, spleen and adrenal glands; within the CNS highest concentrations are found in hypothalamus, basal ganglia, thalamus and hippocampus. Chlorpromazine remains bound to tissues for long periods and metabolites are excreted for up to 6 months.

Storage

Chlorpromazine should be stored in well-closed containers protected from light and should not be allowed to freeze.

Clinical information

Uses

Chlorpromazine is a low-potency antipsychotic used in the acute and long-term management of schizophrenia and other psychotic disorders, including acute and transient psychotic disorders, mania and organic mental disorders. It is sometimes used to treat severe psychiatric problems in children. This drug is quite sedating, and often causes hypotension, in particular if administered by IM injection. The sedative properties may be beneficial in calming people with acute agitation or violent behaviour.

The clinical efficacy of chlorpromazine as an antipsychotic agent is probably due to its affinity for dopamine receptors, particularly D2 receptors. It possesses powerful adrenergic receptor blocking properties as well as some cholinergic and histamine receptor blocking properties.

Its other effects include ganglion blocking, quinidine-like, and atropine-like activities and local anaesthetic actions.

Dosage and administration

Acute phase: 300-800 or more mg/per day.

In the acute phase chlorpromazine may eventually be administered by an intra-muscular injection in a dose of 100-200 mg which can be repeated while observing the patient for possible hypotension. However, IM administration may cause sterile abscesses, is acutely painful and is not seen as appropriate by many clinicians; therefore oral administration is to be preferred whenever possible. A maximum daily dose of up to 1,200-1,600 mg may be necessary, although doses above 800 mg per day are rarely required.

Early Treatment: 300-800 mg/per day.

400 mg/day in divided doses is an adequate treatment for most patients. However, dosage of up to 800 mg can be administered provided the patient is closely monitored for hypotension, which can be a serious side effect.

Various patients respond to widely different doses and it is reasonable to start with a lower dose and increase it as necessary. It is important to remember that

maximal effect of a particular dose may only be evident after 4-6 weeks.

Maintenance treatment: 100-500 mg/per day.

In the maintenance phase the drug should be given for at least 6 months following improvement, the dosage then being reduced by 50% gradually over 3-6 months and another 50% after another 6 months. In general, maintenance doses should be as low as possible and still be able to control the psychotic symptoms. All dosages indicated above may be reduced in very hot climates and with special ethnic groups (e.g., Asians).

Contraindications

- Known hypersensitivity to phenothiazine derivatives (since cross-sensitivity may occur).
- Impaired consciousness due to cerebral depression.
- Cardiovascular or liver disease.

Precautions

Chlorpromazine should be used in reduced dosages in the elderly and in patients with cardiovascular insufficiency, Parkinson's disease, hepatic or renal insufficiency.

Ambulatory patients should take extra precautions while driving or operating machinery during treatment with chlorpromazine since reaction times can be impaired by the drug, especially with higher dosages and at the start of the treatment.

Use in pregnancy and in breast-feeding

Chlorpromazine should not be used in pregnant women, unless there is a very urgent need of control of a severe psychiatric psychotic condition affecting the mother for which the need outweighs any possible risk to the fetus.

Women taking chlorpromazine should not breast-feed.

Adverse effects

Orthostatic hypotension is quite common in patients treated with chlorpromazine and is due to the alpha-adrenergic blocking actions of the drug, which also cause delayed or inhibited ejaculation. This adverse effect is more common and may be particularly severe in elderly patients.

Other side effects include acute dystonic reactions, akathisia, drowsiness, ECG changes, anticholinergic effects (e.g., dry mouth, constipation, blurring of vision, difficulty in micturition), weight gain, menstrual irregularities, gynaecomastia, reduced libido and impotence in males, seizures, skin pigmentation. Because of this latter adverse effect, chlorpromazine should be used with particular caution in sunny climates, and eventually other antipsychotic medicines should be preferred.

Parkinsonism is the commonest neurological adverse effect of chlorpromazine, as well as of the other neuroleptics. In its mildest forms it is represented by bradykinesia and akinesia, while in more severe forms it is represented by loss of associated movements, rigidity, stooped posture, mask-like facies, excess salivation and seborrhoea. It is more common in women, in the elderly and in patients who have relatives with idiopathic parkinsonism. It usually appears within the first two months of treatment, and some degree of tolerance to this extrapyramidal effect develops within a few months. At a dosage of 600 mg of chlorpromazine per day, it has an incidence of 15-25 per cent among patients consuming this drug.

Prolonged use of chlorpromazine is associated with increased risk of developing tardive dyskinesia (TD), a potentially irreversible side effect involving disfiguring movements of the face, tongue and limbs (see section on TD).

Idiosyncratic reactions to chlorpromazine include agranulocytosis, cholestatic jaundice, malignant neuroleptic syndrome and light sensitive dermatoses. Cholestatic jaundice is perhaps allergic in nature since fever, eosinophilia, and rashes generally accompany the syndrome. The jaundice is generally benign, and it remits when the drug is stopped. Neuroleptic malignant syndrome is a severe condition provoked by the association of antipsychotic drugs (especially chlorpromazine, haloperidol and fluphenazine) with muscular rigidity, hyperthermia, autonomic dysfunction, leucocytosis and increase in creatine-phosphokinase activity. The incidence of neuroleptic malignant syndrome is less than 0.5 per cent of patients taking antipsychotic drugs but

mortality of this condition is about 20 per cent.

Drug interactions

- Anticholinergics: These drugs decrease the absorption and additive anticholinergic activity may result in anticholinergic toxicity. They further enhance the probability of tardive dyskinesia.

- CNS depressants (Alcohol, opioids, antihistamines and sedatives): Chlorpromazine further potentiates their CNS depressant activity.

- Antidepressants: If administered simultaneously with chlorpromazine, they each decrease the metabolism of the other, resulting in increased plasma concentrations of both. The anticholinergic, sedative and hypotensive effects of these drugs may also be additive.

- Anticonvulsants: Barbiturates increase the metabolism of chlorpromazine and chlorpromazine lowers seizure threshold.

- Antacids and Cimetidine: These reduce the absorption of chlorpromazine.

- Anticoagulants: Chlorpromazine reduces plasma concentration of warfarin.

Overdosage

Symptoms include light-headedness, sedation, confusion, agitation, disorientation, restlessness, convulsions, fever and coma. Treatment is usually symptomatic and hypotension can be especially difficult to counteract, noradrenalin being relatively ineffective because of the alpha adrenergic blockade. The use of drugs acting on the blood vessels, such as angiotensin, has been suggested.

6.4. Clomipramine

General information

Clomipramine is a dibenzazepine derivative: its main metabolite desmethyl-clomipramine (desmethylated clomipramine) is also an equally potent antidepressant agent; it has a half-life of about 3 days and its steady state concentrations are usually 2.5 higher than those of the parent compound. It is well absorbed after oral administration. Its plasma level reaches a peak 2-4 hours after oral intake and the half-life ranges from 10 to 20 hours. The inactivation and excretion occurs over a period of several days. There is a wide inter-patient variation in the metabolism and plasma concentrations of clomipramine (and other tricyclic antidepressants).

Storage

Clomipramine should be stored in well-closed containers protected from light and should not be allowed to freeze.

Clinical information

Uses

Clomipramine, although a tricyclic antidepressant and therefore encompassed within this category under imipramine, has been added to the list of essential drugs because it has been recommended specifically for the treatment of obsessive-compulsive disorders and panic attacks. Like imipramine it can also be used to treat depression and panic attacks with or without agoraphobia.

Dosage and administration

For the treatment of depression, and panic attacks, the same advice holds as for imipramine. should be continued for 2 to 4 months even after the symptoms are completely eliminated, and then gradually discontinued.

For the treatment of OCD, clomipramine may be administered at a higher dosage in order to be therapeutically effective. Therefore, it is usually advisable to start at a dosage of 25-50 mg per day, administered in a single dose at bedtime. The dose then can be increased by 25-20 mg every second day. It seems that the desirable dosage is in the range of 200-300 mg per day, but if the patient cannot tolerate a dose in this range, a lower dosage can be administered. For panic attacks dosage is similar to those indicated for depression.

There are scanty data as regards the length of treatment with clomipramine in OCD. Some authors recommend maintaining the patient for many months (even more than 12 months) before attempting to discontinue the treatment.

Contraindications

- Closed-angle glaucoma.
- Severe cases of heart, kidney and liver diseases, particularly in the period following an acute myocardial infarction.
- Marked malnutrition.
- Impending danger of a suicidal attempt.

Precautions

The dosage should be reduced in elderly patients, and in patients with former cardiac disease. Routine examination of cardiac, hepatic and other functions should be performed in the course of treatment.

This drug should not be used simultaneously with monoamine-oxidase inhibitors or within two weeks after withdrawal of these agents.

Ambulatory patients should take extra precautions while driving or operating machinery during treatment with clomipramine since reaction times can be impaired by the drug, especially with higher dosages and at the start of the treatment.

Use in pregnancy and in breast-feeding

Clomipramine should not be used in pregnant women, and non-drug alternatives should be used for treating depression in pregnancy.

Women taking clomipramine should not breast-feed.

Adverse effects

The most common and troublesome side-effects of clomipramine are represented by its anticholinergic effects, which may produce dry mouth, gastric discomfort, constipation, blurred vision, dysuria, urinary retention, increased heart rate, precipitation of close-angle glaucoma. Older patients suffer more from these anticholinergic effects. Orthostatic hypotension, dizziness and sleepiness are also observed in some patients. These side-effects, if not marked, may often be considerably lessened within a few weeks (generally three) while taking the same amount of the drug.

Complaints of sexual difficulties such as erectile difficulties, delayed ejaculation may sometimes occur. Delirium can be induced in aged patients.

Drug interactions

Side-effects of clomipramine are potentiated by neuroleptics, benzodiazepines and hypnotic drugs, and alcohol, in various ways depending on the pharmacological actions of each drug. Clinically, benzodiazepines are often used in association with clomipramine to alleviate anxiety and insomnia of depression. Particularly important is the interaction of clomipramine with MAO inhibitors: this interaction is especially dangerous and must be avoided. Antidepressants and phenothiazines can also interact between themselves, and under these circumstances TCA concentrations may reach toxic levels.

Overdosage

Acute ingestion of clomipramine (and other tricyclic antidepressants) can be fatal in the dose range of 1-2 g or more. Smaller doses can also be dangerous in children and in those with pre-existing illness. Signs of overdose include difficulty breathing, shock, agitation, delirium and coma.

Gastric lavage should be carried out without delay. Patients should be treated in an intensive care unit, with continuous monitoring of vital signs and ECG. It is reported that 1 to 4 mg of physostigmine salicylate given intramuscularly may reverse the anticholinergic manifestations of severe poisoning, such as coma, delirium and myoclonus.

6.5 Diazepam

General information

Diazepam is a benzodiazepine with anxiolytic and sedative/hypnotic properties, a centrally mediated muscle-relaxant effect and, if used intravenously, an anticonvulsant action. It is metabolized in the liver to several metabolites, which are mainly excreted in the urine as glucuronides.

The response, which persists for 12-24 hours, becomes evident 30-90 minutes after oral administration and 1-5 minutes after intravenous injection. The plasma half-life is 20-50 hours.

Storage

Diazepam should be stored in tightly closed containers protected from light.

Clinical information

Use

In psychiatry diazepam is used primarily to provide short-term relief for mild to moderate anxiety; it is also used to treat symptoms of acute alcohol withdrawal.

Dosage and administration

For the relief of symptoms of anxiety, the drug is used orally at a dosage ranging between 2 and 5 mg per day, with the possibility of increasing the dosage as needed to control symptoms. The maximum daily dosage does not generally exceed 40 mg.

For the treatment of symptoms of acute alcohol withdrawal, diazepam is generally used in i.v. infusion at the dose of 10-20 mg as needed, and is eventually repeated.

Contraindications

- Age less than 12 years.
- Known hypersensitivity to benzodiazepines.

Precautions

In case of i.v. administration, equipment for resuscitation should be immediately available.

Diazepam should be administered with particular caution to patients with myasthenia gravis as well as to patients with obstructive airway disease, who are at risk of respiratory depression. Diazepam should be used with great caution, in substantially lower doses, and only when essential in elderly and debilitated patients, and in patients with chronic pulmonary insufficiency or chronic renal or hepatic disease.

Ambulatory patients should take extra precautions while driving or operating machinery during treatment with diazepam since reaction times can be impaired by the drug, especially with higher dosages.

Tolerance and dependence

Diazepam administration, as for any other BDZ, can be associated with the development of tolerance and dependence phenomena. They are discussed in detail in Section 12.3.

Use in pregnancy and in breast-feeding

Use in pregnancy should be avoided whenever possible. Some studies have reported an increased incidence of malformations among infants born to mothers who were administered diazepam during the first trimester of pregnancy, although other, large-scale prospective studies have failed to confirm these results.

Adverse effects

Paradoxical reactions, including irritability, disinhibition, excitability, hallucinations, increased muscle spasticity and sleep disturbances have been reported, particularly in elderly patients and in children.

Rare but serious adverse reactions include leucopenia, jaundice and hypersensitivity reactions.

Drug interactions

The effects of phenothiazines, barbiturates, monoamine-oxidase inhibitors

and other antidepressants may be potentiated.

Overdosage

Signs of overdosage include somnolence, ataxia, dysarthria, diminished reflexes, confusion and coma. Paradoxical excitement may occur in children. Unless the specific benzodiazepine antagonist flumazenil is available, treatment should be symptomatic and directed to the management of respiratory depression and shock.

6.6 Fluphenazine Decanoate

General information

Fluphenazine decanoate is a depot drug consisting of a pro-drug, an esterase of the active ingredient (fluphenazine) held in an oily vehicle. Its slow release from the vehicle is the step which determines the drug's effective half-life. The drug is injected i.m. into gluteal (or deltoid) muscle, every 2 to 4 weeks. This drug may have three main advantages over oral neuroleptics:

1. avoidance of first-pass hepatic metabolism which may be a source of wide variation in plasma levels;

2. prevention of deliberate or accidental overdose;

3. improved compliance.

The last of these factors circumvents the patient's unreliability and ambivalence at taking tablets, especially when supervision is minimal. However, injections may not be acceptable to all subjects and determined non-cooperation is a barrier to treatment via any route.

Storage

Fluphenazine decanoate should be stored in well-closed containers protected from light and should not be allowed to freeze.

Clinical information

Uses

Fluphenazine decanoate is a high-potency antipsychotic used as maintenance treatment of people with a reliable diagnosis of schizophrenia.

Dosage and administration

Fluphenazine decanoate is therapeutically active even at very small doses. Because of a large inter-individual variability in plasma concentrations, doses should be carefully adjusted to the needs and response of each patient. Age, severity of symptoms, and general conditions should be taken into account. There is often the need for an upward titration in the acute phase and a gradual reduction in the maintenance phase. However, since the effective half-life is about 22 days, adjusting the dose by looking at changes in target symptoms actually requires adequate time. It should also be mentioned that it takes some 2-5 months to wash out a person on this depot medication should the physician wish to stop medication.

When used for maintenance therapy, 12.5-50 mg every 15-30 days should be regarded as an average dose.

Recent well-designed studies seem to show that even lower dosages (as low as 2.5 mg every 15-30 days) may represent an effective maintenance treatment.

Contraindications

- Known hypersensitivity to phenothiazines.
- Impaired consciousness due to cerebral depressants or of other origin.

Precautions

Ambulatory patients should take extra precautions while driving or operating machinery during treatment with fluphenazine decanoate since reaction times can be impaired by the drug, especially with higher dosages and at the start of the treatment.

Use in pregnancy and in breast-feeding

Fluphenazine decanoate should not be used in pregnant women, unless there is a very urgent need for control of a severe psychiatric psychotic condition affecting the mother for which the need outweighs any possible risk to the fetus.

Women taking fluphenazine decanoate should not breast-feed.

Adverse effects

The earliest neurological effect arising in the course of a treatment with fluphenazine decanoate is acute dystonia, which may be seen even after a single dose of the drug. It occurs in some 2.5-5% of patients treated with antipsychotic drugs and it is more common in men and children than in women. The features of this side effect include torticollis, retrocollis, facial grimaces and distortion, tongue protrusion, dysarthria, opisthotonus, scoliosis, and oculogyric crises.

Parkinsonism is the commonest neurological adverse effect of fluphenazine decanoate. In its mildest forms it is represented by bradykinesia and akinesia, while in more severe forms it is represented by loss of associated movements, rigidity, stooped posture, mask-like facies, excess salivation and seborrhoea. It is more common in women, in the elderly and in patients who have relatives with idiopathic parkinsonism. It usually appears within the first two months of treatment, although acute EPS can be seen within the first 24 hours of injection - a release peak from the depot site. It is important to be aware of this in order to prevent long term anticholinergic prophylaxis being initiated incorrectly. Some degree of tolerance to this extrapyramidal effect develops within a few months. It has an incidence of 15-25 per cent among patients treated with fluphenazine.

Other adverse effects of fluphenazine decanoate include akathisia, depression, vertigo, confusion, seizures, hyperprolactinemia, lactation, menstrual irregularities, hyperglycaemia, tachycardia, hypotension, dysrhythmias, EEG changes, anorexia, constipation, dyspepsia, skin rashes, photosensitivity, leucopenia.

Idiosyncratic reactions to fluphenazine decanoate include agranulocytosis and malignant neuroleptic syndrome. Neuroleptic malignant syndrome is a severe condition provoked by the association of antipsychotic drugs (especially chlorpromazine, haloperidol and fluphenazine) with muscular rigidity, hyperthermia, autonomic dysfunction, leucocytosis and increase in creatine-phosphokinase activity. Its incidence is less than 0.5 per cent of patients taking antipsychotic drugs but the mortality is about 20 per cent among patients suffering from neuroleptic malignant syndrome.

Prolonged use of fluphenazine decanoate is associated with increased risk of developing tardive dyskinesia (TD), a potentially irreversible side effect involving disfiguring movements of the face, tongue and limbs (see section on TD).

Drug interactions

- Anticholinergics: These drugs decrease the absorption and additive anticholinergic activity may result in anticholinergic toxicity. They further enhance the probability of tardive dyskinesia.

- CNS Depressants (Alcohol, opioids, antihistamines and sedatives): Fluphenazine further potentiates their CNS depressant activity.

- Antidepressants: If administered simultaneously with fluphenazine, they each decrease the metabolism of the other, resulting in increased plasma concentrations of both. The anticholinergic, sedative and hypotensive effects of these drugs may also be additive.

- Anticonvulsants: Barbiturates increase the metabolism of fluphenazine and fluphenazine lowers seizure threshold.

6.7 Haloperidol

General information

Haloperidol is an antipsychotic drug of the butyrophenone series. It functions as a potent neuroleptic which blocks dopamine receptors, particularly D2 receptors, in the CNS. It has a mean plasma half-life of 24 hours and is metabolized in the liver, being excreted in the faeces and urine. In addition to the central dopamine blocking effects, haloperidol also shows antiemetic properties and induces relaxation of gastrointestinal sphincters and increases prolactin release. It does not have antihistaminic or anticholinergic activities.

Storage

Haloperidol should be stored in well-closed containers protected from light and should not be allowed to freeze.

Clinical information

Uses

Haloperidol is a high-potency antipsychotic used to treat people with a reliable diagnosis of schizophrenia or schizophrenia-like disorders. It can also be used for the treatment of organic, including symptomatic, mental disorders, when the clinical picture is characterized by disorganized and/or excited behaviour; for the treatment of manic episodes and finally of acute and transient psychotic disorders.

Dosage and administration

Haloperidol is therapeutically active even at very small doses. It can be given in liquid form as taste-free drops. Because of a large inter-individual variability in plasma concentrations, doses should be carefully adjusted to the needs and response of each patient. Age, severity of symptoms, and general conditions should be taken into account. There is often the need for a higher dosage in the acute phase and a gradual reduction in the maintenance phase. When used as an antipsychotic, the following doses should be regarded as an average:

- moderate symptoms: 1.0-4.0 mg per day;
- severe symptoms: 3.0-15 mg per day;
- maintenance therapy: 2.0-6.0 mg per day.

Even recent trials have shown that dosages higher than 15 mg/day of haloperidol for most patients have no additional beneficial effect in the treatment of acute or exacerbated schizophrenia.

Contraindications

- known hypersensitivity to butyrophenones;
- impaired consciousness due to cerebral depressants or drugs of other origin;
- history of seizures.

Precautions

Ambulatory patients should be warned not to drive or operate machinery during treatment with haloperidol since reaction times can be impaired by the drug, especially with higher dosages and at the start of the treatment.

Use in pregnancy and in breast-feeding

Haloperidol should not be used in pregnant women, unless there is a very urgent need of control of a severe psychiatric psychotic condition affecting the mother for which the need outweighs any possible risk to the fetus.

Women taking haloperidol should not breast-feed.

Adverse effects

The earliest neurological effect arising in the course of a treatment with haloperidol is acute dystonia, which may be seen even after a single dose of the drug. It occurs in some 2.5-5% of patients treated with antipsychotic drugs and it is commoner in men and children than in women. The features of this side effect include torticollis, retrocollis, facial grimaces and distortion, tongue protrusion, dysarthria, opisthotonus, scoliosis, and oculogyric crises.

Parkinsonism is the commonest neurological adverse effect of haloperidol.

In the mildest forms it is represented by bradykinesia and akinesia, while in the more severe forms it is represented by loss of associated movements, rigidity, stooped posture, mask-like facies, excess salivation and seborrhoea. It is more common in women, in the elderly and in patients who have relatives with idiopathic parkinsonism, whereas it is more likely to occur in its severe forms in young males. It usually appears within the first two months of treatment, and some degree of tolerance to this extrapyramidal effect develops within a few months. It has an incidence of 15-25 per cent. Akathisia is another disturbing and serious adverse effects, which often leads to poor compliance.

Haloperidol, compared with other neuroleptics, causes less hypotension, sedation and cardiovascular side-effects; at usual doses it does not have anticholinergic effects. However, it causes more extrapyramidal side-effects due to its blocking activity at the level of the basal ganglia.

Other adverse effects of haloperidol include akathisia, depression, vertigo, confusion, seizures, hyperprolactinemia, lactation, menstrual irregularities, hyperglycaemia, tachycardia, hypotension, dysrhythmias, EEG changes, anorexia, constipation, dyspepsia, skin rashes, photosensitivity, leucopenia.

In addition, sudden and unexplained cases of death have been reported in a few patients receiving haloperidol. It has been impossible to determine the role of the drug in the occurrence of the sudden death.

Idiosyncratic reactions to haloperidol include agranulocytosis and malignant neuroleptic syndrome. Neuroleptic malignant syndrome is a severe condition provoked by the assumption of antipsychotic drugs (especially chlorpromazine, haloperidol and fluphenazine) with muscular rigidity, hyperthermia and autonomic dysfunction. Its incidence is less than 0.5 per cent of patients taking antipsychotic drugs but the mortality is about 20 per cent.

Prolonged use of haloperidol is associated with increased risk of developing tardive dyskinesia (TD), a potentially irreversible side effect involving disfiguring movements of the face, tongue and limbs (see section on TD).

Drug interactions

- Anticholinergics: These drugs decrease the absorption and additive anticholinergic activity may result in anticholinergic toxicity. They further enhance the probability of tardive dyskinesia.

- CNS depressants (Alcohol, opioids, antihistamines and sedatives): Haloperidol further potentiates their CNS depressant activity.

- Antidepressants: If administered simultaneously with haloperidol, they each decrease the metabolism of the other, resulting in increased plasma concentrations of both. The sedative and hypotensive effects of these drugs may also be additive.

- Anticonvulsants: Barbiturates increase the metabolism of haloperidol and haloperidol lowers seizure threshold.

Overdosage

Symptoms include light-headedness, sedation, confusion, agitation, disorientation, restlessness, shock, muscle tremors and coma. Treatment is usually symptomatic. Gastric lavage is of value if undertaken within a few hours of ingestion. Emetics may be ineffective. Oxygen and assisted ventilation are required in the event of a respiratory depression. Seizures may be controlled with diazepam.

6.8 Imipramine

General information

Imipramine was one of the first antidepressants provided for clinical use, and is still widely used for the pharmacological treatment of depression. It is also used for the treatment of panic attacks with or without agoraphobia. Its main metabolite desipramine (demethylated imipramine) is also an equally potent antidepressant agent. It is well absorbed after oral administration. Its plasma level peaks 2-4 hours after oral intake and the half-life ranges from 8 to 20 hours, and between 10 and 30 hours for its main metabolite desipramine. The inactivation and excretion occurs over a period of several days. There is a substantial presystemic metabolism which reduces the systemic availability of the drug to 27-77% of the dosage. There is a wide inter-patient variation in the metabolism and plasma concentrations of imipramine (and other tricyclic antidepressants).

Storage

Imipramine should be stored in well-closed containers protected from light and not allowed to freeze.

Clinical information

Uses

Treatment of depressive disorders. Treatment of panic attacks with or without agoraphobia.

Dosage and administration

It is advisable to start with a lower dose (25-50 mg/day) the first day and increase the dose slowly - in order to reduce adverse effects - to a maximum of 300 mg within a few days or weeks. When it is seen that the drug is effective enough and adverse effects are well tolerated, the dose should be maintained until depressive symptoms are sufficiently improved and then gradually reduced to a lower dose.

The treatment should be continued for 2 up to 6 months after the disappearance of the symptoms, and then gradually discontinued over 1-2 months.

Antipanic dosages are approximately the same to begin with, although they may also be increased to 200 mg or even higher to become effective.

Contraindications

- closed-angle glaucoma;
- severe cases of heart, kidney and liver diseases, particularly in the period following an acute myocardial infarction;
- impending danger of suicidal attempt.

Precautions

The dosage should be reduced in elderly patients, and in patients with former cardiac disease. Routine examination of cardiac, hepatic and other functions should be performed in the course of treatment.

This drug should not be used simultaneously with monoamine-oxidase inhibitors or within two weeks after withdrawal of these agents.

Ambulatory patients should be warned not to drive or operate machinery during treatment with imipramine since reaction times can be impaired by the drug, especially with higher dosages and at the start of the treatment.

Use in pregnancy and in breast-feeding

Imipramine should not be used in pregnant women, and non-drug alternatives should be used for treating depression in pregnancy.

Women taking imipramine should not breast-feed.

Adverse effects

The most common adverse effects of imipramine are represented by its anticholinergic effects, which may produce dry mouth, gastric discomfort, constipation, blurred vision, dysuria, urinary retention, increased heart rate, precipitation of close-angle glaucoma. Older patients suffer more from these anticholinergic effects. Orthostatic hypotension, dizziness and sleepiness are also observed in some patients. These adverse effects, will often decrease within a few weeks (generally three) even while the patient remains on the same dose. If side effects are severe, a lower dose of drug may be tried.

Drug interactions

Side-effects of imipramine are potentiated by neuroleptics, benzodiazepines and hypnotic drugs and alcohol, in various ways depending on pharmacological actions of each drug. Clinically, benzodiazepines are often used in association with imipramine to alleviate anxiety and insomnia frequent in depressive states. Particularly important is the interaction of imipramine with MAO inhibitors: this interaction is especially dangerous and must be avoided. Antidepressants and phenothiazines can also interact between themselves, and under these circumstances TCA concentrations may reach toxic levels.

Overdosage

Acute ingestion of imipramine (and other tricyclic antidepressants) can be fatal in the dose range of 1-2 g or more. Smaller doses can also be dangerous in children and in those with pre-existing illness. Signs of overdose include difficulty in breathing, shock, agitation, delirium and coma.

Gastric lavage should be carried out without delay. Patients should be treated in an intensive care unit, with continuous monitoring of vital signs and ECG. It is reported that 1 to 4 mg of physostigmine salicylate given intramuscularly may reverse the anticholinergic manifestations of severe poisoning, such as coma, delirium and myoclonus.

6.9 Lithium Carbonate

General information

Lithium carbonate (and other soluble lithium salts, active ingredient: the lithium ion) is mainly used for the amelioration or prevention of relapses in bipolar and unipolar affective disorders but can also be employed in the treatment of mania or hypomania..

The mechanism of action may involve modulation of second messenger systems (cyclic adenosine monophosphate and guanosine monophosphate, the phosphoinositide cycle, G-protein).

Lithium is not metabolized in the organism, and it is excreted almost exclusively through the kidneys. Under normal circumstances the renal lithium clearance is about one-fourth of the creatinine clearance, and its half-life is 24-30 hours.

Storage

Tablets should be stored protected from light and out of the reach of children.

Clinical information

Uses

Maintenance treatment in bipolar and unipolar affective disorders with frequent and severe relapses. Treatment of mania and hypomania.

Dosage and administration

Dosage adjustment should be based on clinical response and serum lithium levels (see later). Daily maintenance doses are often 900-1500 mg of lithium carbonate in patients aged under 60 years, 450-900 mg in older patients divided into one or two daily administrations.

Contraindications

- kidney disease with variable glomerular filtration rate;
- severe heart disease;
- disturbance of fluid and salt balance.
- hypothyroidism.

Precautions

Monitoring of serum lithium levels is needed in order to keep lithium at safe blood concentrations.

The recommended range of serum lithium concentrations during maintenance therapy is 0.6-0.8 mmol/l in blood samples drawn 12 hours after the last intake of lithium; lower levels may be indicated in some elderly and higher levels in some young patients.

Lithium should be discontinued or the dosage reduced during "risk situations" especially when there is prolonged loss of liquid from the body (e.g. vomiting, diarrhoea, excessive sweating, dehydration due to various reasons); other risk situations include physical disease with fever, prolonged unconsciousness, surgery with narcosis, low salt intake, rigorous slimming, and concurrent treatment with diuretics, with non-steroidal antirheumatics, or with ACE inhibitory antihypertensives.

Use in pregnancy

Because of evidence of teratogenic action on the heart and large vessels, lithium should generally be avoided during the first trimester of pregnancy, but in the individual case the mother's risk of manic or depressive relapse must be weighed against the child's risk of malformations.

It is advisable to discontinue lithium a few weeks before delivery and to resume treatment a few days after.

Adverse effects

These are usually dose-dependent and can often be prevented or relieved by a moderate reduction of dosage.

Adverse effects may include: hand tremor (counteracted by 10 - 20 mg of propranolol as needed), goitre or hypothyroidism (counteracted by the concurrent administration of thyroxine), lowered renal concentrating ability and polyuria, weight gain (which can be alleviated by moderate dieting, exercise), defecation urge and loose stools (reduction of dosage), and, in a few cases, memory impairment, and reduced reaction speed.

Drug interactions

Lithium may interact adversely with diuretics, non-steroidal antirheumatics, some antihypertensive drugs (calcium channel blockers, e.g. verapamil; conversion enzymes blockers, e.g., captopril) and neuroleptics in high dosage.

Overdosage

Lithium intoxication can be caused by overdosage or by a fall in elimination rate (kidney disease, "risk situations"). Signs of impending intoxication may include: dullness, difficulty concentrating, muscle weakness, unsteady gait, indistinct speech, vomiting and diarrhoea. Fully-developed intoxication (serum lithium usually higher than 1.5-2 mmol/l) resembles narcotic poisoning; it should be treated with correction of water and salt balance and with hemodialysis or arteriovenous hemofiltration.

6.10 Temazepam

General information

Temazepam is a benzodiazepine with anxiolytic and hypnotic properties. It is metabolized in the liver to several inactive metabolites, which are mainly excreted in the urine as glucuronides.

The drug response becomes evident 30-90 minutes after oral administration. The plasma half-life is 6-8 hours, although some recent studies seem to show that the half-life may be longer, about 15 hours.

Storage

Temazepam should be stored in tightly closed containers protected from light.

Clinical information

Uses

Temazepam, although a benzodiazepine, and therefore encompassed within the category under diazepam, has been added to the list of essential drugs because it represents the group of short-acting benzodiazepines, more suitable for use as a hypnotic than diazepam. Like diazepam, it can also be used to treat anxiety but the effects of a single dose is shorter lived.

Dosage and administration

As an hypnotic, temazepam is used at the dosage of 20-30 mg. As an anxiolytic the dose can range from 2-10 mg per day.

Contraindications

- age less than 12 years.
- known hypersensitivity to benzodiazepines.

Precautions

Temazepam, as any other benzodiazepine, should be administered with particular caution to patients with myasthenia gravis as well as to patients with obstructive airway disease, who are at risk of respiratory depression.

Temazepam should be used with great caution and only when essential in elderly and debilitated patients, and in patients with chronic pulmonary insufficiency or chronic renal or hepatic disease.

Ambulatory patients should be warned not to drive or operate machinery during treatment with temazepam since reaction times can be impaired by the drug.

Use in pregnancy and in breast-feeding

Use in pregnancy should be avoided whenever possible. Some studies have reported an increased incidence of malformations among infants born to mothers who were administered benzodiazepines during the first trimester of pregnancy, although other, large-scale prospective studies have failed to confirm these results.

Adverse effects

Paradoxical reactions, including irritability, excitability, hallucinations, increased muscle spasticity and sleep disturbances have been reported, particularly in elderly patients and in children.

Rare but serious adverse reactions include leucopenia, jaundice and hypersensitivity reactions.

Drug interactions

The effects of phenothiazines, barbiturates, monoamine oxidase inhibitors and other antidepressants may be potentiated.

Overdosage

Signs of overdosage include somnolence, ataxia, dysarthria, diminished reflexes, confusion and coma. Paradoxical excitement may occur in children. Unless the specific benzodiazepine antagonist flumazenil is available, treatment should be symptomatic and directed to the management of respiratory depression and shock.

PART III

EVALUATION OF TREATMENT

7. EVALUATION OF PHARMACOLOGICAL TREATMENTS IN PSYCHIATRY[2]

7.1 Non-specific factors affecting the evaluation of pharmacological treatments

The chief problem in evaluating treatment is that four non-specific factors can be associated with a reduction of symptoms and an increase in well-being, and thereby mimic a treatment effect.

Firstly, some disorders, given time, remit completely in the absence of treatment.

Secondly, other disorders, although chronic, vary in intensity; patients tend to present themselves for treatment when their disorder is severe and do not come when it is mild; even without treatment the severity of symptoms will reduce with time. If a treatment is offered when the symptoms are severe, then it may appear more effective than it is, simply because severe symptoms will, in due course, regress back to their mean level of severity.

Thirdly, positive expectations of being treated can bring about improvement in many mental disorders. This non-specific effect of being in treatment can be time limited, and may affect the benefits of a specific treatment in an uneven manner.

Fourthly, the very administration of a medication (regardless of its content) may also produce an effect (placebo effect) which must also be assessed and discounted in the evaluation of a treatment.

The factors, *spontaneous remission, regression to the mean, the non-specific effect of being in treatment*, and the *placebo effect*, can confound results and make treatment evaluation complicated.

In any clinical situation the observed improvement is therefore due to the additive effect of non-specific benefits of being in treatment, together with the benefits which result from the skilled application of specific therapies. Good clinical treatment will seek to *maximize the effects of both*, whereas in treatment outcome research, the magnitude of the effect of the specific intervention must be isolated in a precise manner and assessed, to be compared to the total effect of the treatment in the particular setting, by a particular practitioner to a given patient.

Clinicians should maintain a critical attitude about the "pharmacological" value of the treatment. While it is true that a clinician who is very positive about the likely effects of the treatment will induce a greater non-specific response (and this is to be praised); nevertheless this enthusiasm should not blind the clinician to the fact that the effect may be non-specific rather than specific.

It seems sensible to be wary of treatments with dropout rates that exceed 40%: in fact high drop-out rates are more likely to be seen where the treatment effect, if any, is weak; low drop-out rates (below 20%), on the other hand, often identify good treatments. Patients can be good judges of where value lies, and administrators might usefully adopt drop-out rates as an early indicator of the utility and benefit of various treatment programmes.

7.2 Methodological problems

7.2.1 Levels of evaluation

Techniques for evaluating the *efficacy* of treatment are often based on the assumption that single modes of treatment are the topic of interest. *Efficacy* measures the degree to which a given treatment produces a desired effect; it does not take into effect other aspects such as adverse effects.

In practice, however, treatment is multifaceted and involves several types of intervention aiming to achieve a variety of objectives which include: the removal or reduction of symptoms; stopping the disease process; preventing impairments and disabilities; restoring function; and maintaining or improving the quality of life. Interventions required for adequate management of impairment, disability and disadvantage differ from acute treatment methods, if only in degree. They require continuing involvement on the part of the therapist, and necessitate that this involvement extends more comprehensively over the patient's life and relationships; they demand a slower pace of approach, one with which more action-oriented

practitioners may become impatient. They also require that consideration be given to a host of interacting variables which, although they may have some relevance in acute treatment situations (e.g., cultural considerations) assume much greater importance in the management and rehabilitation of disabilities which may permeate every aspect of a person's life.

Different as they are from one another, conditions which are often chronic, such as schizophrenia and agoraphobia, can be used to illustrate this matter. In both syndromes, there is impairment in the patient's sense of well-being; in both, the impairment can result in patients being disabled, and to a very large extent, housebound; and in both the disability may result in the patient leaving the workforce, and becoming socially isolated. Both conditions have, in randomized controlled trials, responded best to a combination of medication and behavioural therapy. But here the apparent similarity of these two conditions ends; the treatment of each patient, regardless of diagnosis, has to be considered on an individual basis if it is to be optimal.

It is therefore worth distinguishing between the number of different levels at which *effectiveness* can be tested. *Effectiveness* indicates if the results obtained from a given treatment are in accordance with objectives for reducing the disease or improving health; it also indicates the distance between efficacy in an ideal situation (e.g. *in vitro*) and its actual effect in real life situation. The simplest level relates only to whether participants subjectively rate a particular experience as being of value to them. This subjective assessment is a relevant first step in evaluation. Similarly, peer review can contribute to this preliminary step of evaluation.

Two other additional important variables to be evaluated are *efficiency* and *cost-effectiveness*.

Efficiency measures the relationship between cost and results and how to obtain best results from given economic resources. It can be measured by means of process-evaluation, where the roles of various participants are analyzed and their interactions monitored in order to determine how well an attempt to generate improvements worked in terms of its operational functions.

Cost-effectiveness indicates the relationship between cost and effectiveness; it measures the relative cost of alternative ways of achieving an objective. It involves greater attention to comparability, both with other similar programmes and also with some, less arbitrary standard of what the outlay should be (in terms of funding, man-hours, or transfer of resources) in order to achieve a stated outcome. It relies, therefore, on process evaluation as well as a more objective assessment of the inputs which have been made, but also requires a clear understanding of what the outcome is.

To achieve this, an analysis of impact is also necessary. Indeed, there are those who argue that this is the only really important measure of the effectiveness of an intervention.

7.2.2 Indicators of treatment outcome

Occasionally treatments produce such a large effect that no further research seems necessary. Benefits are self-evident. A striking example of this is the impact of streptomycin on tuberculous meningitis; a uniform mortality rate was cut so drastically that it would have been unethical to do a controlled trial. A large treatment effect, whereby the average treated patient is better than 99% of untreated patients, is almost certain to be due to the treatment that has been administered. If this effect can be shown to persist after treatment has concluded, and if the effect can be replicated, this provides robust evidence of the effectiveness of an element in the treatment package.

The issue of replication is important, and the advent of empirical techniques to aggregate the findings of many research studies has allowed the importance of small but significant treatment effects to emerge. *Meta-analysis* is the technique that has been used in psychiatry to add up the benefits to be expected from treatments used in cognitive impairment, schizophrenia, affective disorder, the anxiety disorders and eating disorders. One can estimate from the average benefit, or effect size, and the number of studies, just how likely it is that the finding of significant benefit is real and not a spurious effect.

Furthermore, the magnitude of the effect size is a direct indication of the magnitude of benefit, a property which allows the benefits of different treatments to be compared. Meta-analysis, in a sense, is a method which permits the salvaging of

meaningful results from flawed studies; and one must assume that all studies of treatment effects, on real patients, will be less than perfect.

7.2.3 Randomized placebo-controlled trials

Ideally, any treatment in use should be supported by the results of a randomized, placebo-controlled trial that involved a large enough number of carefully diagnosed patients, and employed reliable, valid, accurate and appropriate measurements made at relevant measurement-occasions and over a period of time appropriate to the known clinical course of the disorder.

Randomization is to make certain that the experimenter did not, consciously or unconsciously, allocate patients with a good prognosis to the treatment group, and those with a poor prognosis to the control group.

The placebo control ensures that the effects of remission, regression and placebo are offset against the improvement observed in the treated group. However, parallel design double-blind trials are often used instead of placebo due to ethical reasons. These trials still allow for natural recovery effects to be evenly distributed between the different study groups.

The number of patients studied should be large enough to permit the study to have the statistical power to detect the superiority expected from the treatment and to avoid missing a real but small effect.

Careful diagnosis ensures that the treatment is being delivered to the disorder likely to be responsive to that treatment.

When an established treatment for a condition already exists, it may be very difficult to use a randomized placebo-controlled trial to demonstrate more than relatively short-term control-of-symptom effects; drop-out rates with placebo treatments that continue for more than eight weeks are unacceptably high. Furthermore, it is unethical to deny active treatment to anyone seriously ill for more than very short periods of time.

PART IV

PHARMACOLOGICAL TREATMENT OF MENTAL DISORDERS

8. F00 - F09 ORGANIC, INCLUDING SYMPTOMATIC, MENTAL DISORDERS

8.1 Principles of treatment

The clinical manifestations of these disorders are broad but fall into two groups. *First* are the syndromes with prominent and invariably present features which are either cognitive disturbances (dysmnesia, intellectual deterioration and learning problems), or disturbances of the sensorium (e.g. disorders of consciousness and attention). *Second* are the syndromes with prominent manifestations in the areas of perception (hallucinations), contents of thinking (delusions), mood and emotion (depression, elation, anxiety), or in overall personality and/or behaviour patterns; cognitive or sensory dysfunction is minimal or hard to assess.

The pharmacological treatment approaches in this area should focus on the following groups:

1. **Dementias** (Chronic Brain Syndromes), including those of the Alzheimer type, Vascular Dementias, and dementias of specific origin;

2. **The organic amnesic syndrome** (Korsakov Syndrome) other than due to drugs or alcohol;

3. **Delirium** (Acute Brain Syndrome or Confusional State) other than deliria due to drugs or alcohol;

4 **Mental Disorders without cognitive impairment, but due to organic pathology of the brain, primary or secondary** (Symptomatic psychoses);

5 **Organic Personality and Behaviour Disorders.**

Treatment options for this entire group of disorders remain limited, apart from the specific treatment of the primary disease or disorder, where it is possible and effective, particularly among the deliria, dementias of specific origin and symptomatic psychoses.

Thus in delirium due to cerebral malaria or typhoid fever, precise and effective treatment is available; the specific dementia of neurosyphilis may dramatically improve with penicillin therapy, and the dementia of hypothyroidism responds dramatically to treatment with thyroxin; organic hallucinatory psychoses due to trypanosomiasis or *Haemophilus influenzae* meningitis, for example, will also usually respond to specific treatment. This reflects the fact that the clinical features of all the organic psycho-syndromes are non-specific, and are secondary to a variety of pathologies, some of which are readily treatable and others are not.

It follows logically that an etiological diagnosis is the fundamental first step in the proper treatment of all of these conditions. This can be difficult and sometimes demands complex investigation. Cost-benefit issues then become relevant. There is evidence from developed countries that the identification and treatment of treatable specific dementias (including normal pressure hydrocephalus, benign cerebral tumours, and infectious, endocrine and vitamin deficiency aetiologies), despite requiring full investigation of all dementias, is cost-effective, the costs of long-term care of persons with treatable (but undiagnosed) dementias outweighing the costs generated by the adequate investigation of every case. Specific pharmacological treatment, however, is only available for a minority of conditions. In the majority of these conditions, attention has to be directed at prevention; at drug and/or behavioural therapies for symptom relief; and at methods for the preservation, maximization and rehabilitation of specific areas of psychosocial and interpersonal function.

8.1.1 The Dementias

The Dementias of the senium (over 65) consist mainly of Senile Dementia of the Alzheimer-type (SDAT) conditions accounting for about 40% of cases; multi-infarct dementias (MID) accounting for about 15-20% of cases, and a mixed group (SDAT + MID) which represent 20-30%. The geographical distribution of different dementia types vary; amongst the Japanese vascular causes of dementia are reportedly

more frequent than Alzheimer-type pathologies.

Specific treatment, especially of SDAT, represents a major international research goal but has yet to be achieved. So far there is no evidence of effectiveness for so-called cerebrovascular dilating drugs, for the use of dietary precursors of acetylcholine (choline, lecithin), nor for the deployment of cholinergic drugs (physostigmine, tetrahydroamino-acridine).

Another group of drugs, the so-called "metabolic activators", including ergot derivatives (hydergine), naftidrofuryl, piracetam, pyritinol and others, is more difficult to assess. Although many doubt their efficacy, and evidence from well-controlled studies is lacking, there are a number of anecdotal reports indicating some benefit in the short- to medium-term.

The main treatment approach in these dementias remains symptomatic. Neuroleptic drugs are helpful for episodes of agitation or superimposed deliria. The more anti-cholinergic members of this group may, however, have an adverse effect on residual memory; thioxanthine derivatives have been recommended as useful in this context. Insomnia and convulsions are other symptoms which can respond usefully to relevant medication. In the case of sleep problems appropriate neuroleptics may provide more useful help than anxiolytics - providing better sleep and also controlling nocturnal behaviour disorder, whereas benzodiazepines frequently cause paradoxical reactions with increased psychomotor agitation and incoordination, and may worsen memory and intellectual functioning dramatically.

Anti-depressants are extensively used - in part as a response to the possibility that a depressive "pseudo-dementia" might be missed. While they can be of some benefit, tricyclic antidepressants, with their marked anti-cholinergic properties, may add further confusion and cognitive impairment. There is considerable need to evaluate other types of anti-depressants in the management of dementia. Mono-amine oxidase inhibitors[3], in particular, may have an important role in the management of depression; in addition it has been suggested that they may also be of benefit in modifying underlying pathological mechanisms in SDAT.

8.1.2 The organic amnesic syndrome

In these disorders, where pathologies are operating, they must be sought. Specific treatment should be targeted at the primary pathology (e.g. pyloric stenosis with intractable vomiting) and treatment with B Vitamins, especially thiamine. Irrespective of the primary pathology, thiamine has utility, and its administration may reverse deficits in a striking manner. In the other cases, the approaches discussed for dementia are mostly applicable.

8.1.3 Delirium

Acute delirium always represents primary or secondary cerebral dysfunction; etiological diagnosis followed by precise treatment of the causal pathologies is crucial. Multiple pathologies may operate, particularly in the elderly, and drugged states, with interactions, resulting from polypharmacy, superimposed on nutritional or infectious problems, are particularly important. In developing countries similar considerations apply, but the range of nutritional, toxic and infectious pathologies to be considered is greater, and the condition is common in much younger age groups. If background cerebral reserve is diminished due to infantile deprivation or injury or both, very little may be required to trigger a delirium. By the same token, however, mere admission to hospital, with food, hydration, rest and tranquillization, may be all that is required by way of treatment. Otherwise general measures as discussed for dementia are appropriate; neuroleptics have a particular role in quietening agitation and fear resulting from confusion.

8.1.4 Organic psychoses without cognitive impairment - but due to organic pathology of the brain, primary or secondary (Symptomatic psychoses)

These symptomatic psychoses parallel dementia (chronic) and delirium (acute) and treatment is similar. Specific symptoms will dictate choice of approach - e.g. Anti-depressant therapy in organic affective disorder. Acute psychoses of this type, especially in developing countries, are frequently mixed with delirious symptoms,

thus acquiring an amorphous quality, made more confusing by various reactive and/or released emotional symptoms - often hysterical in quality. These atypical acute psychoses should generally be managed as for delirium.

8.1.5 Organic personality disorders

Important issues here relate to the careful evaluation of target behaviours and symptoms which may then be ameliorated or controlled by appropriate drug therapy. Impulsive aggressive outbursts, epileptic phenomena, acute alcoholic excess, and acute depressive episodes are examples of behaviours which may respond well to carefully planned drug treatment interventions.

9. F10 - F19 MENTAL AND BEHAVIOURAL DISORDERS DUE TO PSYCHOACTIVE SUBSTANCE USE

9.1 Principles of treatment

There is an ever increasing range of substances which produce dependence; these can be conveniently categorized into nine groups of compounds which share similar properties:

- alcohol
- amphetamine and other sympathomimetics
- cannabis
- cocaine
- hallucinogens
- inhalants
- opioids
- phenylcyclidine (PCP) and similar compounds
- sedatives, hypnotics and anxiolytics.

Despite the wide coverage given by the press to illegal drugs, most public health problems are associated with abuse of substances more or less easily available such as alcohol, tobacco, volatile organic solvents, amphetamines, sedatives and other "legal" substances. Of these, only three - opioids, sedatives and alcohol - produce a well--defined abstinence syndrome which can be alleviated, in part, by pharmacotherapy; pharmacological treatment of abuse of the other drugs is not recommended.

In general, there are two central components to the management of dependence:

a) Detoxification. This covers the period over which the substance of abuse is completely withdrawn. A compound which exhibits cross-tolerance may be substituted, thereby minimizing the highly noxious, and sometimes dangerous, effects of abrupt withdrawal. The substituted compound is then withdrawn in a controlled manner.

b) Post-detoxification strategies. The difficult period of complete abstinence during the weeks or months following detoxification can be helped by the use of prescribed drugs which offset the lack of pleasurable effects of the substance abused. Alternatively, with opioid dependence, it is common for controlled doses of an opioid to be prescribed if abstinence cannot be achieved.

9.1.1 Opioid withdrawal: detoxification

Because the opioid abstinence syndrome, although distressing, is rarely dangerous, detoxification can be carried out as an outpatient procedure, supervised by trained non-medical staff. However, completion of a withdrawal programme is more often achieved as an inpatient because of the additional support offered by experienced staff.

Methadone[3] is a controversial drug for substitution in opioid dependence, used in some developed countries. This is a synthetic opioid which is inexpensive and similar to morphine in action. However, some properties, different from morphine, render it a most suitable drug for opioid detoxification:

i) Methadone is absorbed well from the gastrointestinal tract and can be given orally, thus extinguishing the secondary reinforcing properties of the injection procedure. It is often wrongly stated that methadone prevents the withdrawal features of other opioids but in itself does not produce euphoria. Methadone is euphorigenic but, because it is taken orally, the opioid "rush" experienced after rapid injection of morphine or heroin is absent.

ii) Methadone has a long half-life and can be administered once a day thus reducing the frequency of withdrawal craving and drug-seeking behaviour.

iii) Withdrawal from methadone is similar in quality but much less intense than from morphine and is therefore better tolerated.

The aim in opioid detoxification is to substitute injectable opioid with oral opioid so that the acute full-blown abstinence syndrome is avoided. Abstinence is ultimately achieved by supervised reduction

of methadone which minimizes, but cannot wholly prevent, the discomfort of withdrawal.

9.1.2 Opioid post-detoxification

Once detoxified, however, many are unable to embark upon rehabilitation without pharmacological intervention.

In cases of very severe distress there is probably no harm in giving pharmacological sedation in the short term. In primary care settings chlorpromazine is likely to be the most useful agent.

9.1.3 Sedative withdrawal

The main drugs of abuse in this category are: the short acting barbiturates (e.g. pentobarbitone), meprobamate, glutethimide, methyprylone, methaqualone and the benzodiazepines. Particularly with shorter acting agents in dependent individuals, an abrupt withdrawal carries the risk of inducing a grand-mal convulsion which may proceed to status epilepticus. For this reason detoxification should be an inpatient procedure using drug substitution and supervised by staff with some medical training. The exception to this is with benzodiazepine dependence, as the risk of withdrawal seizures is very low, when no antecedents have been recorded; in general careful and gradual withdrawal can be accomplished without admission or drug substitution.

The features of the abstinence syndrome are similar for all drugs of this group. The barbiturates have been studied in most detail. It appears that the intensity of the abstinence syndrome depends in part on the amount of drug taken and in part on the rate of clearance from the central nervous system. The short acting barbiturates are cleared rapidly, thus withdrawal features develop quickly and tend to be severe. This is, however, not always the case and fits have been known to occur as late as 12 days after withdrawal from longer acting barbiturates.

9.1.4 Alcohol withdrawal

Whenever a patient presents any of the physical problems often associated with alcoholism or demonstrates a tremor and gives a history of alcohol misuse, the possibility of withdrawal must be carefully considered. Some 95 per cent of alcoholics never evidence severe signs of withdrawal.

Mild reactions, usually lasting up to 48 hours, consist of insomnia, irritability and tremor. More than one half of patients may evidence some level of autonomic nervous system dysfunction, including sweating, an increase in heart rate (100-120/min.) increases in respiratory rate, mild elevations in temperature and elevated blood pressure. Other symptoms are anorexia or nausea and vomiting, emotional complaints including sadness and somatic complaints, headaches and illusions. The severity of the syndrome is related, among other things, to the intensity and duration of the most recent exposure to alcohol.

The most common of the more severe withdrawal symptoms are visual hallucinations involving threat of assault and presence of dangerous animals, and grand mal seizures.

Delirium Tremens, a serious and potentially lethal condition, is characterized by severe autonomic nervous system (ANS) dysfunction, confusion with or without seizures, is reported for fewer than one percent of patients.

The acute and usually mild withdrawal syndrome begins within 12 hours or less of the decrease in blood-alcohol levels, in an individual who has been drinking for days, weeks or months. Symptoms are likely to peak in intensity by 48-72 hours and are usually greatly reduced by 4-5 days.

Many patients with mild withdrawal can be managed safely and effectively at home or in non-medical detoxification centres. In such cases treatment should include thiamine and diazepam in low doses. If possible, a relative or friend should be enlisted to watch the patient during the withdrawal phase. The treatment of the patient is carried out in several stages and includes interventions directed towards life support, prevention of central nervous system damage, control of various medical complications of the condition, and recovery from the alcohol dependence itself.

Oral multiple vitamins should be given for a period of weeks, making sure that folic acid and thiamine are included. It would

be better if the vitamins also contained zinc and magnesium, because some alcoholics can develop deficiencies in these minerals. Hydration may be required, although in milder withdrawal, overhydration is more typical.

Medication is used to decrease overall symptoms, preferably using benzodiazepines, particularly the longer-acting ones, such as diazepam or chlordiazepoxide. The needed dose should be determined on day one, and then decreased by 20 per cent for each day, stopping the drug by day four or five.

Treatment of delirium tremens includes a thorough physical examination and then supportive measures (IV fluids if there is objective evidence of dehydration) as well as the prescription of multiple vitamins including thiamine and folic acid.

9.1.5 Alcohol post-detoxification maintenance

Several compounds have been investigated for their ability to maintain abstinence in alcoholics. Of these disulfiram[3] is the one most widely used. It inhibits liver aldehyde dehydrogenase. As a consequence alcohol intake (as little as 7 ml) causes acetaldehyde to accumulate in the blood which produces a very unpleasant reaction consisting of sweating, nausea, vomiting, palpitations, tachycardia and throbbing headache. This can last from 30 minutes to several hours and can be extremely frightening. Consequently, a form of aversive conditioning occurs preventing further alcohol intake. However, large doses of alcohol on top of disulfiram can produce fatal reactions such as cardiac arrhythmias and hypertensive crises. Also, disulfiram is contra-indicated in patients with a variety of clinical conditions, including liver and brain dysfunctions, which are not rare in alcohol abusers.

9.2 Special issue: benzodiazepine dependence

The large majority of BDZ users - up to two-thirds in some reports - take the drug for 60 days or less. Small but substantial numbers of adults have been found to take the drug for one year or more. According to the A.P.A. Task Force Report on Benzodiazepine Dependence, Toxicity and Abuse, these long-term consumers may represent 1.74% of the population, and they may be divided into four groups:

- the first group includes older, medically-ill patients taking other medicaments as well;

- the second group comprises psychiatric patients with panic or agoraphobia;

- the third group includes patients with mainly dysphoria complaints;

- the fourth group is made up by patients with chronic insomnia or other sleep disorders.

While it is unlikely that there would be any abuse in the first two groups, the indications for long-term prescriptions are less definite in the two remaining groups, since their complaints are vague and ill-defined. Moreover, with regard to long-term users in the fourth group, there are not consistent data about the effectiveness of BDZ for night sedation if taken for periods of over 30 days. Nevertheless many patients claim that they are unable to sleep if they do not take the drug.

Among these long-term users a constellation of symptoms may appear if the drug is stopped abruptly. These symptoms fall within three main categories: rebound, recurrence and withdrawal. Rebound symptoms are the mirror image of the effects of the medicine, and include anxiety, restlessness and insomnia, and may lead to a return to drug administration. Recurrence symptoms are more difficult to define and may be identical to the original symptoms for which the drug was originally prescribed. It is often hard to determine whether these symptoms represent a recurrence of the original symptoms for which the drug was taken, or a manifestation of drug discontinuation or both.

Withdrawal symptoms, on the contrary, were not present when the drug was initially prescribed. The symptoms are generally mild and include anxiety, insomnia, gastrointestinal disturbances and headaches. Rare, but more severe withdrawal symptoms include seizures and

psychosis, and occur after high doses, long duration of treatment and abrupt discontinuation.

All these discontinuance symptoms can occur even at therapeutic dosages, although they are more frequent among people who have used these drugs at higher than usual doses and for prolonged periods of time. There are some data showing that these symptoms may be more frequent among people who used high potency BDZ.

Although it is sometimes stated that BDZ may induce a 'dependence state', it should be clarified that, according to the ICD-10 definition of dependence, the existence of withdrawal symptoms does not necessarily lead to dependence. In fact, a definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year:

(a) a strong desire or sense of compulsion to take the substance;

(b) difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;

(c) a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;

(d) evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opioid-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users);

(e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or recover from its effects;

(f) persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

While it is certainly true that BDZ may induce a withdrawal state, it seems appropriate to avoid the term of dependence to refer to BDZ use.

In any event, the existence of problems associated with long-term use should alert physicians and suggest that BDZ should be prescribed only for limited periods of time; that each prescription should be regularly monitored and re-discussed; that priority should be given to alternative treatment methods for long term use in the case of disorders such as panic, agoraphobia and insomnia; and finally that efforts should be made with long-term users in order to gradually taper off the drug. It is however recommended that BDZ be discontinued gradually (even in a 3-4 month period) and not abruptly.

10. F20 - F29 SCHIZOPHRENIA, SCHIZOTYPAL DELUSIONAL DISORDER AND ACUTE AND TRANSIENT PSYCHOTIC DISORDERS

10.1 Principles of treatment

Drugs used to treat disorders included in ICD-10 category F20-F29 include a number of compounds, belonging to different chemical classes which induce in animals and in men similar biochemical, pharmacological and behavioural effects.

The most important classes of antipsychotic drugs used in the treatment of schizophrenic disorders are:

- phenothiazines (e.g. chlorpromazine);
- butyrophenones (e.g., haloperidol);
- diphenyl butylpiperidine (e.g., pimozide)[3];
- thioxanthens (e.g., flupentixol);[3]
- benzamides (e.g., sulpiride);[3]
- atypical and "new" neuroleptics, including clozapine, piquidone and risperidone.[3]

It is maintained that their therapeutic effect in schizophrenia is exerted through a block of D2 dopamine receptors in limbic areas. Some of these medicaments also exert a sedative action, due to their alpha-adrenolytic and anti-histaminic properties.

No important differences in effectiveness have been demonstrated among the various antipsychotic drugs mentioned above. The differences reported in clinical practice are related to the different incidences of adverse effects.

10.1.1 Acute phase treatment

The antipsychotic medicaments reduce or eliminate 'positive' symptoms of schizophrenic disorders, e.g. delusions, hallucinations and psychomotor disturbances. In as many as 80 to 90% of all patients, they seem also to reduce the impact of acute and chronic stress in the every-day living environment. Although these drugs reduce florid symptoms particularly in acute phases of schizophrenia, some 10 percent of acutely ill patients will show little response to these drugs. Some of these patients whose symptoms fail to respond to one of the antipsychotic drugs will respond to another. The reasons for this are obscure, since all of them are believed to act by blocking D-2 dopamine receptors. 'Negative' symptoms, (e.g. lack of motivation and interest, inactivity, lack of emotional display, and restricted speech) do not seem to respond as well to treatment with classical neuroleptic drugs. There are however some reports showing that clozapine (a drug not discussed in this document) might be effective for negative symptoms. The interaction and reinforcement between negative symptoms and sedation caused by maintenance drug treatment is insufficiently explored.

The general strategy for acute treatment involves the administration of an antipsychotic drug such as chlorpromazine or haloperidol. In the acute phase chlorpromazine may be administered by an intra muscular injection in a dose of 100-200 mg which can be repeated while observing the patient for a possible hypotension. In most cases, however, the intra-muscular administration is not needed and the patients can be treated with a simple oral dose. A maximum daily dose of up to 1,200-1,600 mg may be necessary, although doses above 800 mg per day are rarely required.

Regarding haloperidol, the dosage generally used for the management of acute cases ranges between 3.0 and 10 mg per day. There is often the need for an upward titration in the acute phase. Combinations of two or more antipsychotic drugs should not be administered.

Treatment strategies centred on the use of very high dosages of antipsychotic drugs (up to 100 mg of haloperidol a day), administered at very short intervals, called 'rapid neuroleptization', have not proved to be more effective than more conservative and gradual treatment strategies, while they seem to increase the overall risks associated with the administration of neuroleptics.

10.1.2 Maintenance treatment

The effectiveness of antipsychotic drugs in maintenance therapy of schizophrenia has

been established by numerous studies. However, protection against relapse is incomplete, with about 30-40 percent of patients relapsing by the end of a year after commencing treatment. Exacerbations of illness in patients on maintenance drug therapy is often precipitated by acute stress, (e.g. stressful life events), and chronic stress occasioned by living circumstances. The addition to the drug regime of stress management procedures can reduce this relapse rate. Reported success rates of rehabilitation programmes for long-term schizophrenic patients show remarkable variation from one third to three quarters of all patients according to different authors, techniques and populations.

Optimum long-term drug management appears to be maintenance on the lowest possible dose of neuroleptics that will prevent major exacerbations of florid symptoms. Controlled studies in countries with well-developed services, over a period of one year after a florid acute episode, comparing oral with intramuscular depot preparations used for maintenance, have not demonstrated any significant advantages for the depot preparation. However, in individual, non-compliant cases depot medications may have some advantages over oral medications. On the other hand, prevention of relapse by reintroducing drug treatment when prodromal symptoms of the relapse appear, (so-called "targeted medication") has also been reported as an effective strategy useful in particular to reduce side effects likely to be more frequent in long-term maintenance therapy. However, recent studies have failed to confirm the effectiveness of this medication strategy.

In all cases, it has been recommended to foster the education of patients and immediate caregivers, about the illness; about factors that promote relapse; about the costs and benefits of drug therapy; as well as about the early recognition of signs of major exacerbations.

The main disadvantage of antipsychotic drugs is their adverse effects involving movements, autonomic nervous functions, haematopoiesis and other vital functions. Among the most serious of these irreversible side effects is tardive dyskinesia, which can be extremely disabling and disfiguring.

A substantial proportion of patients with schizophrenia will recover completely after a first episode and remain well. The proportion of these patients seems to be significantly higher in developing countries, as shown by two major WHO international collaborative studies (*12, 13*). There are no clinically useful predictors of good prognosis for individual patients; for groups of patients features associated with a good outcome include female sex, married status, acute onset, nutritional deficiencies, puerperal status, significant co-existing affective symptoms, a good premorbid personality, a preceding life event, and living in low stress households. In this group of patients many clinicians recommend the interruption of long-term medication, especially in order to prevent adverse, possibly irreversible effects (e.g., tardive dyskinesia), with the prevention of relapse by reintroducing drug treatment when prodromal symptoms of the relapse appear.

All patients receiving long-term treatment require periodic evaluation and documentation of continued need and benefit. The benefits and risks of long-term neuroleptic treatment should be discussed with patients and families and their informed consent to treatment, documented. Patients should also be routinely examined for signs of tardive dyskinesia.

10.1.3 Special problems: Tardive dyskinesia

Tardive dyskinesia (TD) is a syndrome of choreoathetoid and/or other involuntary movements that may affect mouth, lips, tongue, arms, legs or trunk; TD is associated with the long-term (usually greater than 6 months) use of neuroleptics. There is a wide variation in reports of the incidence of tardive dyskinesia in patients on long-term neuroleptic therapy (0.5 to 56%), with an average prevalence rate of 20% among patients continuously exposed to neuroleptic treatment for at least one year. It is likely that part of this variation can be attributed to the differences among criteria used for assessing abnormal involuntary movements, ranging from minimal sinuous movements

of the lips to a gross motor disability impeding breathing and swallowing.

The proportion of patients developing abnormal involuntary movements is believed to increase with increasing length of treatment or total exposure to neuroleptics. The syndrome can develop after relatively brief (3 to 6 months) treatment periods at low dosages. However, it is impossible at present to identify which patients are at risk.

In cross-sectional studies, the majority of cases are judged to be mild (i.e., not obvious to the untrained observer or subjectively troublesome to the patient). Identification and diagnosis are complicated by the fact that neuroleptic drugs may mask TD symptoms. Drug discontinuation or dosage reduction may reveal previously masked symptoms.

Although there are few long-term follow-up studies, the condition does not appear to be generally progressive. The incidence of tardive dyskinesia does increase with age.

The course of the condition is difficult to predict in individual patients. In a substantial proportion of cases symptoms will disappear within 2 to 5 years, if the neuroleptic medication is discontinued. However, a proportion of patients (in the range of about 30%) will show persistent dyskinesias even after drug discontinuation.

There is no established treatment for tardive dyskinesia. Antiparkinsonian drugs are ineffective for tardive dyskinesia and there have been reports that giving them in the absence of extrapyramidal signs to prevent their occurrence in fact facilitates the occurrence of tardive dyskinesia. Antiparkinsonian drugs are advised *only* for the treatment of extrapyramidal side effects when they actually appear. They should be gradually discontinued over time. Appendix V reports the WHO Consensus Statement on the prophylactic use of anticholinergics in patients on long-term neuroleptic treatment.

11. F30 - F39 MOOD (AFFECTIVE) DISORDERS

11.1 Principles of treatment

The current ICD 10 classification of affective disorders includes:

a) Manic episode
b) Depressive episode:
   severe depressive episode
   mild depressive episode
c) Bipolar affective disorder
d) Recurrent depressive disorders
e) Persistent affective states
f) Other mood (affective) episodes

These conditions occur with high prevalence and cause remarkable morbidity in all ethnic groups and cultures so far studied. Prevalence varies somewhat from place to place, but not as much as was once believed. Regardless of the cut-off point (symptom severity) chosen, depressive disorders affect a large proportion of the population at some stage of their lives.

Mood disorders are very often recurrent and chronic (50% relapse after a first episode, and 20% develop a chronic course after a first episode). They are under-diagnosed and under-treated world-wide. Because of their guises, and particularly because of the frequency with which sufferers complain of fatigue, weakness and anergia, with multiple somatic and painful complaints, they are most commonly first encountered by primary care workers, general practitioners, and physicians. Studies suggest that depressive episodes may comprise 10% - 15% of illnesses seen in general medical practice and these figures may be an underestimate. Many cases are not initially diagnosed, or are misdiagnosed as anxiety states in primary care practice. All too frequently, they are treated with tranquillizers - drugs which may provide some initial symptomatic relief of agitation and insomnia. A depressive illness is a major risk factor for suicide.

Appendix VI shows the WHO Consensus Statement on pharmacotherapy of depressive disorders.

11.2 Depressive episodes

11.2.1 Treatment options

Tricyclic and allied antidepressants (imipramine, amitriptyline, doxepin[3], dothiepin[3]) are the most widely used drugs in the treatment of depressive disorders. Controlled clinical trials have established their effectiveness in these states, but have not demonstrated significant differences in efficacy between individual drugs. Administration in adequate dosage is essential for a good response in patients with a severe depressive episode. Non-psychiatrist physicians often employ too low a dosage. Although it has been claimed that the dose level needed varies from culture to culture, there is no firm evidence on this point. Response to antidepressant drugs is usually delayed, with a lag up to 3-8 weeks, although the sedative and anxiolytic properties of some (especially doxepin and dothiepin) may provide partial relief of insomnia and anxiety from the beginning - to the encouragement of the patient in many cases.

The use of more than one tricyclic drug has not been shown to enhance effectiveness, nor is the delay in onset of action shortened by parenteral administration.

Anticholinergic *side-effects* occur with all the tricyclic drugs, dryness of the mouth, blurring of vision (**cave** glaucoma which can be worsened), difficulty in micturition (**cave** retention of urine, particularly in males with prostatic disease), constipation (**cave** faecal impaction and intestinal obstruction, especially in the elderly), and partial impotence and anorgasmia are common. The patient's compliance with therapy is usually much better if he/she (and the family) is informed of these possible effects - in detail. Toxic effects on cardiac conduction (slowing) and myocardial contractility (increased irritability with enhanced potential for dysrhythmias) are a feature of all the tricyclics. These effects are not troublesome in normal dosage, except in persons with myocardial disease, where dysrhythmias and cardiac arrest can occur. In overdosage, intended or accidental, these toxic effects make tricyclic drugs potentially lethal.

11.2.2 Acute phase treatment

The pharmacologic treatment of a depressive episode should involve the administration of an antidepressant. Practitioners should become familiar with the properties of two or three compounds, particularly with regard to the effective dose. The effective dose may vary from one population to another, and in general older patients need lower doses than younger ones. If a patient does not respond within 3 weeks, increasing the dosage or changing to an alternative medication should be considered. Side effects, which may be particularly pronounced with higher doses, should always be discussed with the patient. In prescribing, it should always be borne in mind that depressed patients, especially those with severe depression, may be at risk of suicide and the total amount of medication prescribed or given to the patients at one time should not be high.

As regards the optimal dose, in the case of clomipramine it is advised to start with a lower dose (25-50 mg/day) on the first day and increase the dose gradually up to a maximum of 300 mg within 2-3 weeks.

11.2.3 Maintenance treatment

Antidepressant medication should be continued up to 6 months after recovery. It should then be discontinued gradually and the patient should always be seen about 3 weeks after cessation of all antidepressant medication to assess the psychological state. If well, the patient should then be seen at no more than 2-month intervals for up to a 6-month period. From the beginning, the patient and the family should be involved in the treatment and it should be explained that the best time to end treatment can only be ascertained through trial discontinuation of the medication.

11.3 Special issue: Treatment resistance in depression

Assessing the issue of treatment resistance in these episodic disorders requires the study of such questions as:

i. Is treatment being delivered efficiently and with skill?

ii. Is treatment at this stage of the natural history of an affective episode being given at the wrong time? There is evidence for differing efficacy of treatments at different points in the waxing and waning of an affective cycle. Might not the same treatment work if given later?

iii Is apparent response of a "resistant case" to a special regime, an observational artefact; i.e., a spontaneous improvement occurring at this point in time?

iv. Is "resistant depression" in some cases the results of adverse effects of the drug, plus emotional reactions to such side-effects (e.g. impotence), worsened by marital discord resulting from enforced celibacy, continuing day-time sedation, hypersomnia, and excessive drug-induced weight-gain etc.? Might not recovery occur simply as a result of stopping medication?

v. When this occurs, might not some "new" treatment which has been introduced in the meantime, and which lacks both efficacy **and** side-effects, be given undeserved credit, and written up as a useful method of dealing with treatment "resistance"?

Lithium carbonate, MAOIs, ECT, carbamazepine[3], regular physical exercise, and various psychotherapies have all been considered worthy of a trial in treatment-resistant depression, as well as treatment by the combination of lithium with an antidepressant which some consider as a treatment of choice in these situations. It is important to be aware that *stopping* all treatment is sometimes effective.

11.4 Prevention of depressive episodes

If a depressed patient has had more than one severe episode of depressive illness, (especially if there has been one or more episodes in the last five years), long-term prophylactic therapy should be considered. This can take the form of long-term treatments with antidepressants or lithium salts. Some experts advocate the use of carbamazepine as a prophylactic treatment with those patients for whom, for

various reasons, lithium administration is unfeasible.

11.5 Manic episodes

Lithium salts are effective in the acute management of manic episodes. Haloperidol, as well as other neuroleptics, are also effective in controlling these acute states and act faster than lithium salts, especially for the control of agitation and hyperactivity, but cause more side-effects (confusion, over-sedation, slurring of speech, ataxia, extra-pyramidal symptoms, etc).

For patients with *affective disorders*, who are particularly likely to suffer recurrences, extensive studies support the efficacy of lithium in preventing such recurrences, whether depressive or manic. Some experts advocate the use of carbamazepine as a prophylactic treatment with those patients for whom, for various reasons, lithium administration is unfeasible. The tricyclic antidepressants have been shown to be effective as long-term preventive treatments for recurrent unipolar disorder.

12. F40 - F48 TREATMENT OF NEUROTIC, STRESS-RELATED AND SOMATOFORM DISORDERS

12.1 Principles of treatment: panic, agoraphobia, generalized anxiety disorders and obsessive-compulsive disorder

The main disorders which will be discussed in this section are panic and agoraphobia, generalized anxiety disorders and obsessive compulsive disorders.

Agoraphobia without panic is rare and, like specific phobias, seldom produces sufficient disability to warrant medical attention. Panic disorder, with or without agoraphobia, is a potent reason for seeking medical attention simply because of the fear that panic may end in a medical emergency. Despite medical attention, avoidance of situations for fear of panic frequently follows a chronic course simply because of the absence of avoidance learning.

There has been extensive research on the drug treatment of this disorder, demonstrating that imipramine, clomipramine and alprazolam[3] will produce improvement. Antidepressant drugs are recommended as the treatment of choice in panic disorder. Some tolerance to high doses seems to develop so that after a few weeks on the drug the dose can be raised further if the therapeutic effect is inadequate. It may take four to six weeks on a full dose before suppression of panic attacks occurs. Maintenance therapy should be continued for a minimum of six months (at an usual dosage of 100-125 mg at night) for the tricyclics, and the drug should then be withdrawn. Should symptoms recur treatment can be re-instituted. Drug therapy should only rarely be continued beyond 18 months. If symptoms recur after this period one should consider a more systematic application of alternative approaches (e.g., behaviour therapy techniques) and family, interpersonal, or dynamic factors that may be perpetuating the panic disorder should be investigated.

About 20% of panic disorder patients experience a reaction after one or two tablets of imipramine, causing increased anxiety, unsteadiness, and feeling very ill in some unspecifiable way. Even those who persist with the drug need a clear waning about the side effects like dry mouth, hypotension, or tremor if they are not to misinterpret these symptoms as evidence of a worsening of panic. It is usual to begin with a 50 mg dose of imipramine, increasing by one 25 or 50 mg tablet every few days until the patient is taking 150-200 mg in divided doses in the early evening and before retiring.

Regarding the management of generalised anxiety disorders, the efficacy and safety of benzodiazepines has led them to become the dominant anxiolytic drug group. They should, however, preferably be used for short-term management, that is for less than four weeks, because of the tolerance and dependence that often develops with longer use. In terms of withdrawal symptoms, short-acting benzodiazepines are more problematic than the long-acting compounds. However, if they are slowly tapered, there is no difference between long and short-acting compounds.

Benzodiazepines may be used in two ways in the short-term management of uncomplicated generalised anxiety disorder. First, short-acting compounds may be prescribed either for occasional and intermittent treatment of acute symptoms or in specified situations where an individual is subject to a particularly potent stressor. Second, where the patient suffers severe anxiety over a substantial part of the day, low doses of the long-acting compounds may be employed adjunctively with both behaviour therapy and psychotherapy. The use of anxiolytic drugs in larger doses may impair the ability of the patient to benefit from the behavioural or dynamic psychotherapies.

There is no evidence to suggest any significant role for beta-blockers in this condition. Similarly, the use of major tranquillizers in otherwise uncomplicated generalised anxiety disorder is not indicated. A few elderly patients taking benzodiazepines may show excessive sedation and confusion. If drug therapy

appears obligatory in such cases, then there may be a limited role for low and intermittent doses of major tranquillizers otherwise not indicated in this condition.

Regarding obsessive-compulsive disorders, tricyclic antidepressants, especially clomipramine, have been reported to have a specific effect in their management and a therapeutic trial of a tricyclic antidepressant is worthy of consideration in patients with significant compulsions. Resistance to drug taking is high in this group of patients and may reflect a predominant personality conflict over self control versus control by others. These patients do not tolerate changes in state easily, and even patients who have benefited from the drug often discontinue voluntarily, then relapse and have to begin taking the drug again. Some patients may have difficulty in tolerating the adverse effects of tricyclic antidepressants; in some cases non-tricyclic antidepressants (e.g., MAOI, SSRI, or others) can be better tolerated. The demand for or refusal of a prescribed drug can become a focus for debate in therapy, the issues of domination and submission becoming the main topics. Prescribing therefore has to be done with a high level of psychological sensitivity. Obviously, the combination of drug and psychological therapy is frequently indicated, especially when there is evidence of depression.

Anxiolytic drugs have a very limited role in the treatment of obsessive-compulsive disorders. These drugs can produce suppression of the anxiety associated with the disorder, but this may rapidly lead to dependence so that even though patients obtain no lasting benefit, they may have great difficulty in discontinuing benzodiazepines.

Clomipramine has also been shown to be effective in the management of social phobia.

12.2 Principles of treatment: Post-traumatic stress disorder (PTSD), adjustment disorder, dissociative disorder, somatization disorder

A small number of recently controlled trials seem to indicate that tricyclic antidepressant (imipramine or amitriptyline) may be effective in the management of PTSD; antidepressants have been employed for eight-week treatment periods, with doses up to 300 mg. It is worth noting the lack of any placebo response in PTSD:

The use of benzodiazepines in adjustment disorders is not supported by the results of well controlled trials; moreover, drug treatment may involve risks because prescription of a drug (or of another intervention) can 'legitimize' the symptoms as illness, convincing the patient of the seriousness of the state and may present an obstacle to recovery.

There is to date no adequate scientific information about the pharmacological treatment of dissociative disorders. Medication should generally be avoided in somatization disorder.

13. F51.0 NON-ORGANIC INSOMNIA

In many cases a disturbance of sleep is one of the symptoms of another disorder, either mental or physical. Even when a specific sleep disorder appears to be clinically independent, a number of associated psychiatric and/or physical factors may contribute to its occurrence. Whether a sleep disorder is an independent condition or simply one of the features of another disorder should be determined on the basis of a careful assessment by the clinician.

It should also be noted that the actual amount of hours of sleep is not necessarily related to the patient's complaints, as there are so-called short sleepers who do not consider themselves as insomniacs while there are people who suffer greatly from the poor quality of their sleep, and yet their sleep quantity is considered subjectively and/or objectively within normal limits.

Treatment of nonorganic insomnia should be highly individualized, as it is in any disorder in which lifestyle and learning patterns interact with different physiological parameters.

Before starting any pharmacological treatment, the patient should be carefully educated for a proper sleep hygiene. Appendix VII lists twelve rules for a better sleep hygiene (16). It is surprising how frequently some, or most of these simple rules are violated, and nevertheless the patient complains of a poor sleep. These rules should also serve as a guide for the clinician to explore the behavioral patterns of the patient concerned and find ways to improve them.

A chronic, nightly use of hypnotics and sedatives is hardly justified, because of the risk of withdrawal and rebound symptoms when the patient stops taking the medicine. However, in selected circumstances the prescription of an hypnotic is justified, especially when sleeping is a primary need for the patient, for instance because of a very important upcoming day or other selected situations. For temazepam, the usual dosage is in the range of 10-50 mg.

In these cases, temazepam (and similar short-acting benzodiazepines) are to be preferred, since they are rapidly metabolized and there are smaller hang-over symptoms the day after.

14. F60.0-F60.7 TREATMENT OF DISORDERS OF ADULT PERSONALITY AND BEHAVIOUR

14.1 Principles of Treatment

Personality disorders (PD) are usually present from adolescence onwards. They often lead to (chronic) difficulty maintaining employment or meaningful relationships.

Despite the shortage of randomised controlled trials, it is becoming apparent that the treatment to be preferred differs between the various personality disorders.

Given the chronic, long-term course of these disorders, it is difficult to think in terms of acute treatment as opposed to maintenance treatment. However, patients suffering from PDs can have acute decompensation which may require the administration of targeted pharmacotherapy. The choice of the drug, its dosage, and the length of the administration will depend on the specific nature and characteristics of the disorder and of the acute decompensation.

F60.0 Paranoid Personality Disorder: There are no controlled studies about the pharmacological treatment of this condition but clinical wisdom suggests that neuroleptics at low dosage may lead to increased trust and decreased suspiciousness that may improve the social and occupational functioning of some of these individuals, at least in periods of worsened social adaptation.

F60.1 Schizoid Personality Disorder: There are no studies of effective treatment in this condition but especially case reports suggest that neuroleptics at low dosage can help in the management of acute decompensations; acute anxiety or depressive episodes can also be treated pharmacologically, using benzodiazepines at low dosage.

F60.2 Dyssocial Personality Disorder: There is a large amount of literature on this disorder that points out its relationship to behavioural disorder in childhood, and to criminality and drug and alcohol abuse in adulthood. There is no acceptable evidence that the disorder can be ameliorated by drug treatment.

F60.3 Borderline Personality Disorder: There are three double-blind drug studies from which one might conclude that benzodiazepines are not to be recommended because they can lead to difficulties in emotional and behavioural control. There are suggestions from some controlled clinical trials that low dose neuroleptics may have some short-term limited usefulness in selected severely ill patients, notably those with transient psychotic ideation, anxiety and somatization. Major depressive episodes may complicate the disorder and may necessitate an adequate treatment using tricyclic antidepressant drugs.

F60.4 Histrionic Personality Disorder: There is no research-based information available about the drug treatment of this disorder.

F60.5 Anancastic personality disorder: There is no evidence about the effectiveness of current pharmacological treatments.

F60.6 and F60.7 Anxious and Dependent Personality Disorders: Also for these personality disorders, there are very few data concerning effective pharmacological treatment approaches. In dependent personality disorders, the need to avoid drug dependence has been stressed.

15. F70-F79 MENTAL RETARDATION

Mental retardation (MR) as such is not amenable to drug treatment: however, psychiatric disorders often associated with mental retardation can be treated pharmacologically. Neuroleptics are used in schizophrenia and schizophrenia-like states; and in severe behaviour disorder. Tardive dyskinesia is a common toxic effect, particularly in persons over the age of 50 years. The neuroleptic malignant syndrome has also been reported. Care is necessary to avoid excessive dosage, particularly in this population. These patients are frequently not of sufficient competence to be involved in treatment decisions about themselves, and are usually compliant with treatment instructions.

Antidepressants are used in affective disorders; lithium carbonate in manic and depressive disorders; and more recently to reduce aggression in MR. Stimulant drugs (e.g., methyl amphetamine[3]) are used for hyperactivity, and anticonvulsants for the treatment of epilepsy, often associated with MR. Consent to treatment with medication should be sought from a person authorized to give it, when the patient is unable to give informed consent. Such treatment should be reviewed on a regular basis with special attention to adverse effects since these patients are often poor informants.

16. F80 - F99 BEHAVIOURAL AND EMOTIONAL DISORDERS WITH ONSET USUALLY OCCURRING IN CHILDHOOD

This section will deal with only a few behavioural and emotional disorders with onset usually in childhood (e.g. hyperactivity, conduct disorders, and enuresis) (ICD F80-99).

16.1 Current treatments

Dietary approaches for *hyperactivity* have been popularized, but evidence as to their efficacy is conflicting; they may be of some value in cases of hyperactivity due to sensitivity to specific food substances. However, it is not clear how to identify such patients. With regard to the treatment of hyperactivity with stimulants, however, effectiveness in reducing some of its associated symptoms, such as attention deficits, has been well established, as are rational indicators for the selection and timing of this treatment approach.

In the management of *enuresis*, although tricyclics have been shown in randomized control trials to be effective, relapse after termination is common and drug side effects may be significant.

Little attention has been given to childhood psychiatric disorders in developing countries, particularly with regard to the evaluation of the effectiveness and the appropriateness of various therapies used in different cultural and ethnic setting. This is particularly important in child psychiatry because of the extent to which disorders *and* treatments are influenced by cultural, developmental, and ambient disease variables.

PART VI

APPENDICES

APPENDIX I

CLASSIFICATION OF PSYCHOACTIVE DRUGS

1. ANXIOLYTICS

1.1 Benzodiazepines

1.1.1 1,4 Benzodiazepines

Pro- and Nor-diazepam derivatives

Bromazepam
Clorazepate
Chlordiazepoxide
Diazepam[4]
Flurazepam
Ketazolam
Medazepam
Prazepam

Nitro-derivatives

Flunitrazepam
Nitrazepam

3-hydroxy substituted derivatives

Lorazepam
Lormetazepam
Oxazepam
Temazepam[4]

1.1.2 1,5 Benzodiazepines

Clobazam

1.1.3 Triazolo-benzodiazepines

Alprazolam
Midazolam
Triazolam
Brotizolam

1.1.4 Thiodiazepines

Clothiazepam

1.2 With a different chemical structure

Buspirone
Meprobamate
Zoplicone
Zolpidem

2. ANTIDEPRESSANTS

2.1 Tricyclic antidepressants

2.1.1 Iminodibenzilic

Clomipramine[4]
Desipramine
Imipramine[4]
Lofepramine

2.1.2 Dibenzocicloheptadienic

Amitriptyline[4]
Nortriptyline

2.1.3 Dibenzocicloheptatrienic

Butriptyline
Protriptyline

2.1.4 Other

Amineptine
Amoxapine
Dibenzepine
Dothiepin
Doxepin
Dosulepine
Melitracen

2.2 Mono-Amine Oxidase Inhibitors

2.2.1 Irreversible

Phenelzine
Isocarboxazid
Nialamid
Tranylcypromine

2.2.2 Reversible (RIMA)

Moclobemide
Toloxatone

2.3 With a different chemical structure

Bupropione
Maprotiline
Mianserine
Minaprine
Trazodone

2.4 Serotoninergic selective re-uptake inhibitors

Fluoxetine
Fluvoxamine
Paroxetine
Citaprolam
Sertraline

3 ANTIPSYCHOTICS

3.1 Phenothiazines

Aliphatic phenothiazines
Chlorpromazine[4]
Levomepramazine
Promazine
Trifluopromazine
Piperidine phenothiazines
Pipotiazine
Thioridazine
Piperazine phenothiazines
Fluphenazine[4]
Perphenazine
Trifluoperazine

3.2 Thioxanthenes

Clopenthixol
Clorprothixene
Flupenthixole
Tioxanthene

3.3 Dibenzoxazepines

Clothiapine
Loxapine

3.4 Butyrophenones

Haloperidol[4]
Droperidol
Trifluoperidol

3.5 Biphenylbutylpiperidines

Pimozide

3.6 Benzamides

Sulpiride

3.7 Dibenzodiazepine

Clozapine

3.8 With different chemical structure

Molindone
Risperidone

APPENDIX II

Tables of equivalency of selected psychiatric drugs

TABLE 1. EQUIVALENCY OF SELECTED ANTISPYCHOTIC DRUGS

DRUG	Relative potency
Chlorpromazine	100
Droperidol	2
Fluphenazine	4
Haloperidol	2
Levomepromazine	120
Perphenazine	12
Pimozide	2
Pipothiazine	2
Promazine	100
Thioridazine	120
Trifluoperazine	5

TABLE 2. COMPARATIVE FEATURES OF THREE ANTIPSYCHOTIC DRUGS

	CHLORPROMA-ZINE	HALOPERIDOL	FLUPHENAZINE DECANOATE
Dose equivalency	100 mg	2 mg	2 mg
Half life	15-30 hrs	24 hrs	7-10 days
Steady state	5-7 days	several days	several days
Acute phase doses	300-800 mg/day	3-10 mg/day	25-50 mg every 2-4 days
Maintenance treatment doses	100-500 mg/day	2-6 mg/day	12.5-25 mg every 2-4 days

TABLE 3. EQUIVALENT AVERAGE DOSES OF SELECTED ANTIDEPRESSANT DRUGS

Drug	Average dose (mg)
Amitriptyline	150
Clomipramine	150
Dothiepin	100
Imipramine	150
Lofepramine	140
Nortriptyline	100
Fluoxetine	20
Fluvoxamine	200
Mianserin	90
Trazodone	150
Isocarboxazid	30
Phenelzine	45
Moclobemide	300

TABLE 4. THERAPEUTIC AVERAGE DOSES OF SELECTED BENZODIAZEPINES

Drug	Anxiolytic effect	Hypnotic effect
Alprazolam	0.50	-
Bromazepam	2	6
Chlordesmethyldiazepam	1	5
Chlordiazepoxide	15	75
Desmethyldiazepam	2.5	10
Diazepam	5	20
Flunitrazepam	-	4
Flurazepam	-	30
Lorazepam	1	5
Oxazepam	15	60
Temazepam	6	25
Triazolam	-	0.25

TABLE 5. APPROXIMATE COMPARATIVE COST OF SOME ESSENTIAL DRUGS*

Drug	US$/FOB (approx.)	Unit quantity supplied for quoted price	Average cost of 4 weeks maintenance treatment
Amitriptyline HCl tabs 25 mg	7	per 1,000	2.10
Biperiden HCl ** tabs 2 mg Biperiden lactate inj. 5mg/ml	4 2	per 50 per 5	4.80 -
Chlorpromazine HCl tabs 100 mg inj. 50 mg/2 ml	11 6	per 1,000 per 100	1.15
Diazepam tabs 5 mg inj. 10 mg/2 ml	3 6	per 1,000 per 100	0.18 -
Fluphenazine decanoate inj. 25 mg/ml	8	per 10 vials of 1 ml	0.80
Haloperidol tabs 1.5 mg	7	per 1,000	0.63
Imipramine HCl tabs 25 mg	7	per 1,000	2.10
Lithium carbonate tabs 300 mg	4	per 60	6.00
Disposable 5 ml syringes with needles	5	per 100	-

* Average prices quoted by several WHO suppliers, whose addresses are available on request.

** Other anticholinergic antiparkinson drugs are available more cheaply, e.g. benzihexol/trihexyphenoxyl 5 mg: US$ 6.00 per 1,000.

APPENDIX III

PSYCHOACTIVE DRUGS IN PREGNANCY

Special precautions should be used whenever a psychotropic drug is prescribed during pregnancy. The first point to be considered is to what extent the pregnant woman needs a pharmacologic treatment, and whether it is possible to use alternative non-pharmacologic treatments. Should the drug prescription be absolutely needed, it is necessary to know the following data concerning psychotropic drugs in pregnancy; they will dealt with under four headings: hypnotic and anxiolytic drugs, neuroleptic drugs, antidepressants, and lithium carbonate.

1. Hypnotic and anxiolytic drugs

Benzodiazepines, the most widely used anxiolytic drugs, cross the placenta and may cause hypotonia, respiratory depression and hypothermia in the newborn. These drugs, owing to their pharmacological effects, have caused, or may be suspected of causing, harmful effects on the human fetus or neonate **without causing** malformations. **These effects may be reversible.**

Long-term treatment and administration of high dosages in connection with the delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.

2. Neuroleptic (anti-psychotic) drugs

2.1 Phenothiazines

These drugs, owing to their pharmacological effects, have caused, or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

In some cases in which they have been administered in high dosages during late pregnancy, phenothiazines have caused prolonged extrapyramidal symptoms in the newborn.

2.2 Butyrophenones

Although there have been isolated case reports of birth defects following fetal exposure to haloperidol and droperidol in combination with other drugs, no definite cause and effect relationship can be confirmed for the butyrophenones. In some cases in which they have been administered in high dosages during late pregnancy, butyrophenones have caused prolonged extrapyramidal symptoms in the newborn.

3. Antidepressant drugs

Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Therefore these drugs should be taken only in selected cases needing an urgent pharmacologic treatment.

As regards other antidepressants including MAOIs, the evidence available about their safety is scanty, and therefore they are best avoided in pregnancy.

4. Lithium carbonate

Several studies have shown the teratogenic effect of lithium taken in the first months of pregnancy. The cardiovascular system is especially affected, in particular the tricuspid valve. Other studies have shown other teratogenic effects possibly due to lithium.

Moreover lithium enters the fetal circulation and cases of disturbance of thyroid function of the newborn infant have been reported. For all these reasons, lithium should be avoided during pregnancy.

For more detailed information on this very sensitive and specific issue, the reader should to consult up-to-date textbooks of pharmacology.

APPENDIX IV

PSYCHOACTIVE MEDICINES IN OLD AGE

There are no psychiatric disorders that are absolutely specific to old age. The various syndromes that are discussed in this document, except age specific conditions of childhood, adolescence, and the reproductive period of life, are all found in the elderly. However old age is a period of life in which diseases and disorders occur more frequently than in younger age groups. These conditions not only interact with one another, but also with environmental and treatment variables to produce a group of characteristic management and drug treatment problems which deserve attention.

Psychiatric conditions which show increased rates in the elderly include organic psycho-syndromes and depressive illness of all types. Paranoid, neurotic and hypochondriacal disorders are also frequent, and often complicate the treatment of somatic illnesses, themselves prevalent in the elderly. The pharmacological management of these states does not differ greatly from those dealt with elsewhere in this report. However, mental disorders in the elderly do have certain unique features affecting drug treatment.

Mental disorders in the elderly are superimposed on diminishing physiological capacities and functions. Cerebral neuronal reserve is diminished, making the emergence of organic psycho-syndromes more likely when minimal additional insult occurs; hence the elderly are more at risk for minor states of illness, toxicity, or deprivation to set off a delirium or other acute organic state. Reduced renal clearance and diminished efficiency of hepatic and other detoxification mechanisms, make them peculiarly vulnerable to the consequences of high blood levels of drugs, and also to interactions between drugs; this is further influenced by the fact that their numerous ills lead to the accumulation of prescriptions for different types of medications. Drugs are added to this list more often than they are removed; removal is often stubbornly resisted by patients because of the false security medicaments may provide.

Polypharmacy thus constitutes a major source of secondary mental disorder. Added to this, infectious or toxic states, themselves of minor consequence, are common, and cerebral oxygenation is often compromised by inefficient cardiopulmonary and oxygen transport systems. Neglect of adequate nutrition because of (a) reduced appetite, (b) the effect of living alone and on a reduced income, and (c) less efficient intestinal absorptive mechanisms, contributes to this overall picture of cerebral vulnerability.

The net result is an increase in the rate of occurrence of organic psycho-syndromes. These are frequently mild; unfortunately, their manifestations are often dismissed as simply those of old-age and senescence. These mild states of cerebral dysfunction are typically characterised by organic affective symptoms, resembling personality features (particularly paranoia, anxiety, irritability and querulousness, low frustration tolerance, affective disinhibition and lability, and hypochondriacal preoccupation with minor discomforts). More frank states of delirium can emerge with suddenness. Management requires that the practitioner be sensitive to these circumstances, and tailor his drug prescribing, and his dosages, accordingly.

As with other diseases in the elderly, depressive illness may respond well to lower doses of anti-depressants; but there is a risk of side effects due to anticholinergic properties of many of the currently used antidepressants.

APPENDIX V

Prophylactic Use of Anticholinergics in Patients on Long-Term Neuroleptic Treatment: a Consensus Statement (14)

The heads of centres collaborating with the WHO in biological research on mental disorders decided to develop a series of consensus statements on key issues in biological research and treatment of psychiatric problems. The statement on prophylactic use of anticholinergics in patients on neuroleptic treatment is the second of the proposed series.

Anticholinergics (that is, agents which antagonise the action of acetylcholine at muscarinic receptor sites) are not only commonly used for the treatment of early neuroleptic-induced extrapyramidal side-effects (Parkinsonism, dystonia), but are also sometimes administered from the onset of antipsychotic therapy, with the aim of preventing the occurrence of such effects.

The prophylactic use of anticholinergics has been claimed to be particularly useful in order: (a) to avoid the appearance of neurological manifestations (such as akinesia and akathisia) which may mimic psychopathological symptoms and therefore, may lead to an inappropriate increase of the neuroleptic dosage; and (b) to improve the patient's compliance, since patients who experience neurological adverse reactions are more prone to become non-compliant.

Nevertheless, several arguments against the prescription of anti-Parkinsonian preventive medication can be advanced:

(a) The long-term use of anticholinergics may predispose to tardive dyskinesia (in fact, the administration of these agents exacerbates the syndrome in affected patients and has been used as an aid to its early detection).

(b) Anticholinergic medication may induce autonomic side-effects, which may be sometimes serious (urinary retention, paralytic ileus).

(c) The long-term use of anticholinergics is likely to affect memory functions, thus further compromising the already impaired cognitive performance of schizophrenic patients.

(d) It has been suggested that anticholinergics may contribute to the development of hyperthermic episodes, some of which may be fatal.

(e) The consumption of an excessive dose of anticholinergics may produce an acute toxic state, with agitation, disorientation in time and space, delusions and hallucinations.

(f) In some cases, anticholinergics may be abused as euphoriants, so that their discontinuation may be difficult.

(g) There are some indications that anticholinergics can decrease the therapeutic activity of neuroleptics, although early reports of pharmacokinetic interactions between the two classes of drugs have not been confirmed by more recent studies.

(h) Many patients on antipsychotic therapy do not develop Parkinsonism, so that anti-Parkinsonian preventive treatment is sometimes unnecessary.

On the basis of these considerations, the prophylactic use of anticholinergics in patients on neuroleptic treatment is not recommended, and may be justified only early in treatment (after which it should be discontinued and its need should be re-evaluated. As a rule, these components should be used only when Parkinsonism has actually developed, and when other measures, such as the reduction of neuroleptic dosage or the substitution of the administered drug by another less prone to induce Parkinsonism, have proven ineffective.

APPENDIX VI
Pharmacotherapy of depressive disorders: a consensus statement
(15)

WHO Mental Health Collaborating Centres

The heads of centres collaborating with WHO in biological psychiatry and psychopharmacology decided to develop a series of consensus statements on key issues in biological research and treatment of psychiatric problems. This statement on Pharmacotherapy of Depressive Disorders is the first of the proposed series.

Acute treatment. Treatment of depressive disorders will be initiated with antidepressants. Practitioners should become familiar with the properties of two or three compounds, particularly with regard to the effective dose. The effective dose may vary from one population to another. In general, older patients need lower doses than younger ones. If a patient does not respond within 3 weeks, changing dosage or alternative medication should be considered. Electroconvulsive therapy may be considered in some cases of severe depressive illness and those not responding to treatment with antidepressant drugs and psychotherapy. Potential side-effects should always be discussed with the patient. In prescribing, it should always be borne in mind that depressed patients may have suicidal thoughts and the total amount of medication prescribed or given to the patients should not be too large.

For all patients suffering from depressive disorders psychotherapy may be useful in conjunction with pharmacotherapy.

Continuation treatment. Antidepressant medication should be continued for at least six months after recovery. It should then be discontinued gradually and the patient should always be seen about 3 weeks after cessation of all antidepressant medication to check the mental state. If well, the patient should then be seen at no more than 2-month intervals for up to a 6-month period. From the beginning the patient and the family should be involved in the treatment and it should be explained that the best time to end treatment can only be ascertained through trial discontinuation of the medication.

Prophylaxis. If the patient has had more than one severe episode of depressive illness and especially if there has been one or several other episodes (apart from the present one) in the last 5 years, long-term prophylactic therapy should be considered. This can take the form of long-term treatment with antidepressants (particularly with an antidepressant the patient is known to have responded to) or with lithium salts. Lithium has the advantage of also preventing manic attacks and is known to be effective in lower doses than previously used (a plasma lithium concentration 12 h after the last dose of 0.5-0.7 mmol/l is sufficient). It is useful to check plasma levels every 2 months after the patient has been stabilised on the appropriate dose. Whenever possible long-term lithium or antidepressants should be given in a single dose (usually at bedtime) so as to ensure maximum compliance. All long-term therapy should be accompanied by regular check-up visits at least once every 2 months.

A special facility for systematic and regular follow-up of patients and for monitoring plasma lithium (e.g. an affective disorder clinic) can greatly assist the management of these patients.

Prophylactic medication should always be carefully discussed with the patient and family. If the patient does not wish to receive long-term medication, it is particularly important to make clear to the patient and the family that they should seek help at the first sign of a recurrence of the illness.

Patients maintained on long-term medication will often request (especially after a period of good health) to discontinue treatment. If the patient presses to discontinue prophylactic medication after appearing well for 2 years or more, it is reasonable to undertake a trial discontinuation of treatment. In these cases the patient should still be followed up as before, i.e., at 2-month intervals, and warned of the danger of future episodes and the need to return immediately for treatment if the symptoms return.

APPENDIX VII

Rules for Better Sleep Hygiene

(16)

1. Lie down intending to go to sleep only when you are sleepy. But have a consistent time when you plan to go to sleep.

2. Never use the bedroom for anything but sleep or sex. No activities in bed like reading, watching television, eating, talking on the telephone or discussing problems.

3. Set your alarm and get up at the same time every morning, regardless of how much sleep you get during the day.

4. Do not nap during the day.

5. Do not drink alcohol within several hours of bedtime.

6. Do not consume caffeine beverages or medications that contain caffeine within several hours of bedtime.

7. Do not smoke within several hours of bedtime.

8. Exercise in the late afternoon or early evening. Light stretching or a short walk may be sufficient .

9. Allow yourself a transition period. During the hour before you go to bed, gradually decrease your activity level. Do things that are quiet and relaxing

10. Develop a routine before going to bed. Include activities like personal hygiene, checking lights, and locked doors. Do things that make you feel safe and secure.

11. Make sure no excessive light or sound will disturb you, and that your room is at a comfortable temperature.

12. Going to bed hungry or after a large meal can inhibit sleep. However, if you feel hungry, a light snack or a glass of warm milk is appropriate.

18. NOTES

[1] For instance: WHO, **The selection of essential drugs**. Geneva, WHO, 1977; WHO, **The selection of essential drugs. Geneva, WHO 1992;** Ghodse H. & Khan I. **Psychoactive drugs: improving prescribing practices.** Geneva, WHO, 1988; WHO, **Benzodiazepines and therapeutic counselling.** Geneva, WHO, 1988; WHO, **The introduction of a mental health component into primary health care.** Geneva, WHO, 1990; WHO, **Evaluation of methods for the treatment of mental disorders.** Geneva, WHO, 1991.

[2] This section is adapted from WHO Scientific Group on the Treatment of Psychiatric Disorders. **Evaluation of methods for the treatment of mental disorders** (TRS 812). Geneva, WHO, 1991.

[3] Not discussed in this document.

[4] Described in some detail in this document.

19. REFERENCES

1. WHO. **The selection of essential drugs.** Geneva, World Health Organization, 1977.

2. WHO. **Evaluation of methods for the treatment of mental disorders** (TRS No. 812). Geneva, World Health Organization, 1991.

3. Harding T & Chrusciel TL. The use of psychotropic drugs in developing countries. **Bulletin of the World Health Organization**, 52: 357-367, 1975.

4. WHO. **Essential Treatments in Psychiatry.** (Doc. WHO/MNH/MND/93.26). Geneva, World Health Organization, 1993.

5. American Medical Association. Council Report: Quality of Care. **Journal of the American Medical Asociation**, 256(8):1032-1034, 1988.

6. Ghodse H & Khan I. **Psychoactive drugs: improving prescribing practices.** Geneva, World Health Organization, 1988.

7. Gutheil TG. Drug therapy: alliance and compliance. **Psychosomatics**, 19: 219-225, 1978.

8. Smith GT. Keep on taking the tablets? **Office of Health Economics Briefing**, 21, 1-6, 1983.

9. WHO. **The selection of essential drugs.** Geneva, World Health Organization, 1992.

10. Mallett P. Anticholinergic drugs in psychiatry. **International Journal of Clinical Psychopharmacology**, 4(4):261-71, 1989.

11. WHO. **The introduction of a mental health component into primary health care.** Geneva, World Health Organization, 1990.

12. WHO. **The International Pilot Study of Schizophrenia.** Chichester, Wiley, 1979.

13. Jablensky A, Sartorius N, Ernberg G et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization Ten-Country Study. **Psychological Medicine Monograph Supplement**, 20, 1992.

14. WHO Mental Health Collaborating Centres. Prophylactic Use of Anticholinergics in Patients on Long-Term Neuroleptic Treatment: a Consensus Statement **British Journal of Psychiatry**, 156:412, 1990.

15. WHO Mental Health Collaborating Centres. Pharmacotherapy of Depressive Disorders: a Consensus Statement **Journal of Affective Disorders**, 17:197-198, 1989.

16. WHO. **How to use the teaching package on "Insomnia in General Practice".** (Doc.: MNH/PSF/93.10). Geneva, World Health Organization, 1993.