



Psychopharmacological Procedures

HEINZ E. LEHMANN

Douglas Hospital and McGill University, Montreal, Canada

Of all special fields in medicine, internal medicine and psychiatry probably play the most important roles in general medical practice. This has always been so, but there has also always been a gap between the clinical approach to the medical aspects of the total treatment of a person, and to the psychiatric aspects. This gap, which for many years has alienated psychiatry from the other parts of medicine, has only been bridged in the last two decades. Since the early 1950's psychiatric thinking and practice has moved much closer to general medical procedures, so that treatment of many psychiatric patients has become more rational, more understandable and more practical for the non-specialist.

If psychiatric treatment today is a major concern of general medical practice, psychopharmacology has been one of the most important factors in this development. New and effective pharmacological treatments of various psychiatric disorders have made it possible for any physician to treat patients who previously had to be hospitalized and could be treated only by psychiatrists. In making this claim for the pharmacotherapy of psychiatric disorders, I do not wish to imply that the fine arts of interviewing, listening and psychological understanding are no longer needed by the doctor; they still are and probably always will be among the most important skills of any good physician. I simply want to make the point that psychopharmacology

today has grown into a system of empirical and rational procedures which can be studied and acquired by anyone who is motivated to do so. To acquire knowledge and skill of psychopharmacological procedures neither calls for particular assets of temperament or personality nor dedicated immersion into esoteric speculations and polysyllabic terminology.

What is Psychopharmacology?

Psychopharmacology is a new scientific discipline which was born in the first few years of the second half of our century. It is a discipline which deals with psychotropic or psychoactive drugs, i.e., drugs which influence consciousness, mood and behavior. Psychopharmacology, which has played such an important role in bringing psychiatry back into the fold of general medicine, is concerned with four principal aspects of psychotropic drugs: 1) indications for, and dosage of, psychotropic drugs; 2) side effects and complications of these drugs and their management; 3) understanding of the mechanisms of action of psychotropic drugs through the development of operationally defined and measurable research procedures; 4) development and screening of new substances in this field. The first two of these aspects primarily concern the clinician; the latter two lie more within the field of the researcher.

Following the discovery of chlorpromazine, the first of a group of

entirely new drugs for the treatment of mental disorders, it became clear within a few years that the new psychotropic drugs had made a tremendous impact on three areas: 1) the public, for whom—virtually overnight—tranquilizers became a household word and a multimillion-dollar business; 2) research, where the new discipline of psychopharmacology was established in the wake of these discoveries; 3) treatment, where the new drugs made possible an almost revolutionary new approach to the therapy for many psychiatric disorders.

A number of psychotropic drugs have, of course, been known and used by man for a long time. Alcohol, caffeine and certain narcotics are the oldest psychotropic agents known. The discovery of their properties has been lost in the dawn of recorded history. But with the advent of scientific medicine, systematic research during the past century led to the development of anaesthetic drugs and, later, to the introduction of a variety of hypnotic and sedative agents. Thus, after the empirical discovery of intoxicants and stimulants, medical research discovered remedies for some of the universal ills of mankind, i.e., pain, insomnia and anxiety. Effective drugs for more specific uses in the treatment of mental and emotional disorders have been systematically developed since two French psychiatrists, Delay and Deniker (1952), administered chlorpromazine (Thorazine) for the first time to agitated psychotic patients and noted the extraordinary tranquilizing effect of this drug.

Pharmacotherapy in Psychiatric Disorders

Although the title of my paper is "Psychopharmacological Procedures," what I really intend to talk about is pharmacotherapeutics with psychiatric patients. At this point, I would like to remind you that

psychiatry is less fortunate than other branches of medicine, because (with very few exceptions) it lacks objective criteria for diagnosis as well as knowledge about the etiology of most of the conditions for which a psychiatrist has to treat his patients. This does not mean that psychiatric diagnosis is entirely subjective, but it does mean that practically all psychiatric diagnosis is based primarily on the observation of behavioral deviations. The causes of the major psychoses are still unknown, although a great deal of promising research is going on in this area. The origin of neurotic disturbances is better understood but is also still subject to controversy between proponents of psychoanalysis, learning theory and genetic or other somatic factors. In spite of all these theoretical uncertainties, we now have a variety of effective pharmacological treatments in psychiatry, and even if their mechanisms of action are not always clearly understood, many of these treatments have empirically proven their worth.

Rather than involve you in the problems of psychiatric diagnosis and classification, I should like to discuss the four major symptomatic conditions which can be effectively treated with psychotropic drugs. These four conditions are: 1) psychomotor excitement; 2) tension and anxiety; 3) depression; 4) perceptual and cognitive disorders (e.g., hallucinations and delusions). Let me briefly define these well-known behavioral deviations or mental symptoms.

Psychomotor excitement is characterized by restless, overactive, agitated, noisy, boisterous and disinhibited behavior; a feeling of being driven—being under pressure—with the mood being either one of aggressive anger or excessive elation. Usually, pronounced psychomotor excitement is associated with insomnia and sometimes with clouded consciousness, i.e., confusion and delirium.

Tension and anxiety are char-

acterized by aimless restlessness and autonomic signs of sympathomimetic (adrenergic) arousal, e.g., tachycardia, sweating, increased blood pressure, mydriasis. At the same time the patient feels uncomfortable, unable to relax and—when not only tension but also anxiety is present—apprehensive and threatened in some undefinable manner. Tense and anxious patients, as a rule, also suffer from insomnia.

Perceptual and cognitive disorders occur mostly in psychotic conditions and indicate impaired contact with reality. Examples of symptoms occurring in this category are: hallucinatory perceptions, in one or several sense modalities, without any corresponding objective stimulation; delusional ideas, i.e., false and persistent beliefs which cannot be corrected by rational proof that they are unfounded; a generalized thinking disorder leading to irrational and bizarre forms of reasoning.

Depression is behaviorally characterized either by agitation or, more typically, by psychomotor retardation, i.e., a general slowing down of all spontaneous and responsive activity, an overall increase of inhibition and reduction of energy output. Most important is the core symptom, a subjective background of an all pervasive feeling of dejection, pessimism and hopelessness which not infrequently leads to attempted or completed suicide.

Classification of Psychotropic Drugs

Having thus classified—though somewhat roughly—the four principal psychiatric conditions which can be effectively treated with psychotropic drugs, let me now give you the brief and simple classification of psychotropic drugs which has been proposed in the report, "Research in Psychopharmacology," published by a World Health Organization scientific group

(1967). The report distinguishes five categories of drugs. The first category is *Neuroleptics*—often referred to as major tranquilizers or antipsychotics—which are represented by the phenothiazines, the butyrophenones and the thioxanthenes, as well as by the reserpine derivatives. The second category is *Anxiolytic Sedatives*—often referred to as minor tranquilizers—which are represented by meprobamate and its derivatives, chlordiazepoxide (Librium) and its derivatives, and barbiturates. The third category is *Antidepressants*, represented by monoamine oxidase (MAO) inhibitors or imipramine and other tricyclic compounds. The fourth category is *Psychostimulants*, represented by the amphetamines, methylphenidate (Ritalin) and pipradrol (Meratran) and by caffeine. The fifth category is *Psychodysleptics* (hallucinogens), which are mainly represented by lysergic acid diethylamide (LSD), mescaline, psilocybin, dimethyltryptamine (DMT) and cannabis (marijuana, hashish or bhong).

Clinical Applications Psychostimulants and Psychodysleptics

Let us first look at the last two categories of psychostimulants and psychodysleptics, because they have few clinical applications and we can rapidly dispose of them. Psychostimulants are specifically indicated for the treatment of narcolepsy. Sometimes they are useful in states of chronic lassitude, such as may be seen following a protracted disease, e.g., a virus infection. The amphetamines may also be helpful in programs of weight reduction because of their anorexogenic effect. In the treatment of depressive conditions, psychostimulants play a very minor role, because a severely depressed patient requires more than a "lift" or "boost." If a depressed patient's state of arousal is increased by a

psychostimulant, he is often rendered more tense and sleepless and may well become more depressed. Sometimes, but rarely, an amphetamine or Ritalin may be helpful in the treatment of certain depressive states, but only when the depression is in its very beginning or already fading out. During a full-blown depression, psychostimulants are contraindicated. Because physical tolerance of and psychological dependence on the amphetamine-like psychostimulants develop rapidly, these drugs should only rarely be prescribed. This is the conclusion reached in the report entitled "Control of Amphetamine Preparations" prepared by a special committee* which had been appointed in Britain to study the place of the amphetamines in clinical medicine.

The psychodysleptics, i.e., LSD and similar drugs which produce strange alterations of consciousness—their current popularity notwithstanding—have no clearly established therapeutic indications. Their use is mainly experimental, although considerable literature exists on the use of LSD in neurotic conditions, behavior disorders and alcoholism. Whether or not these drugs are really effective in these disorders and, if so, in what dosage and under which conditions, will be shown by the outcome of a number of controlled studies, the results of which will not be available for another three to five years. There is also the possibility that the recently isolated active principle of marijuana—tetrahydrocannabinol (THC)—might find some clinical applications, perhaps in the treatment of depressions. At the present time, however, the application of the entire category of psychodysleptic drugs, which manifest their action mainly through disorganization of perceptual, cognitive

and affective processes, is still in the experimental stage.

Therapeutic Applications of Neuroleptics and Anxiolytic Sedatives (Tranquilizers)

States of Excitement

Effective agents in the treatment of acute excitement and acute or chronic states of tension and anxiety are the neuroleptics and the anxiolytic sedatives. Both types of drugs are often referred to as tranquilizers. However, if one chooses to do so, he should make a clear distinction between the major tranquilizers (neuroleptics) and the minor tranquilizers (anxiolytic sedatives). There are distinct clinical and pharmacological differences between the two types of tranquilizers. The only drugs which can effectively reduce specific psychotic symptoms—hallucinations, delusions and psychotic thought disorder—are the major tranquilizers. But both the major and the minor tranquilizers will reduce psychomotor excitement, tension and anxiety, although the minor tranquilizers will do it more effectively.

Many of the anxiolytic sedatives are highly *toxic* and, thus, can be used for suicidal purposes. The neuroleptics have a much higher margin of safety. Anxiolytic sedatives *raise* the convulsive threshold and, thus, have an anticonvulsant effect, whereas most of the neuroleptics *lower* the convulsive threshold and, in high doses, may induce convulsions. Most of the anxiolytic sedatives can produce tolerance and psychological dependence, and many drugs in this category will produce *physical dependence* when taken in high doses over long periods of time. The neuroleptics produce neither tolerance nor psychological dependence. Only anxiolytic sedatives will produce *disinhibition* of higher nervous processes and, thus, like alcohol, induce a phase of increased and uncontrolled behavioral

* J. Chappell, W. W. Fulton, M. M. Glatt, W. L. Rees and C. W. M. Wilson.

manifestations prior to their inhibitory action. Neuroleptics inhibit only; they do not induce states of transient disinhibition. On the other hand, only neuroleptic drugs can produce *extrapyramidal side effects*, e.g., parkinsonism-like rigidity, tremor or muscular dystonia and dyskinesia.

Since both types of drugs, the minor or the major tranquilizers, can be used for the management of acute excitement or tension and anxiety states, what factors should determine our choice of drugs in these conditions? The physician who is faced with an extremely excited patient is often inclined to choose what he thinks would be the most rapid way of subduing the agitated patient, i.e., by intravenous injection of a sedative drug. It is not advisable to inject neuroleptic drugs intravenously in a patient whose reactions one does not know very well; there may be a sudden marked drop of blood pressure or other undesirable complications. Therefore, the drugs chosen for intravenous administration should be those belonging to the category of anxiolytic sedatives. Barbiturates, e.g., sodium amytal, in doses of 250 to 500 mg; chlordiazepoxide (Librium), in doses of 50 to 100 mg; or diazepam (Valium), in doses of 10 to 30 mg, are often dramatically effective in terminating a state of acute excitement.

However, occasionally the patient does not calm down until very large doses have been administered, thus making the patient toxic and comatose. This difficulty occurs most frequently in states of hysterical excitement. Because of these occasional complications with the intravenous administration of anxiolytic sedatives, and also because this type of drugs in large doses tends to make the patient confused, I feel that it is generally better practice to rely on the intramuscular administration of neuroleptics for the management of acute excitement. Most agitated patients will settle down after an intramus-

cular injection of 50 to 100 mg of chlorpromazine (Thorazine) or thioridazine (Mellaril). Once calmed by these drugs, the patients also tend to become more rational and cooperative rather than confused or comatose, as with the anxiolytic sedatives.

Not every agitated patient can be controlled with one injection of a neuroleptic. The physician should always consider a state of acute excitement as an acute emergency and should no more abandon a patient before his excitement has been brought under control, than he would abandon a patient before shock or hemorrhage had been brought under control. The effects of an intramuscularly administered neuroleptic manifest themselves after about 15 to 20 minutes. If at that time the patient is still excited, another dose of the neuroleptic, either equal to the first dose or somewhat reduced, should be injected. After another 15 minutes a third injection might be given and, sometimes, still a fourth 15 to 20 minutes later. By that time, however, even the most excited patient should be under control with this cumulative intermittent or staggered sedation.

Tension and Anxiety

The treatment of anxiety and tension states by drugs is only a symptomatic approach to the underlying problem—a symptomatic approach which should be limited to the shortest possible period of time. The treatment of choice in all anxiety states is psychotherapy, unless the tension and anxiety is due to physical causes, for instance, hyperthyroidism or congestive failure. It is obvious that any physical causes of tension and anxiety should receive specific treatment, but in the majority of cases, tension and anxiety are due to psychological causes, e.g., environmental stress, personality disorders or intrapsychic conflicts. For these conditions the treatment of choice

is psychotherapy, including the recent modifications of milieu therapy and behavior therapy.

As supportive therapy for a limited period of time, anxiolytic sedatives, or the minor tranquilizers, are very effective in checking symptoms of anxiety and tension. The neuroleptics or major tranquilizers ("major," because they are capable of suppressing psychotic symptoms as well as anxiety symptoms) are less effective in reducing anxiety than the minor tranquilizers. However, the minor tranquilizers tend to produce tolerance and drug dependence and, thus, become dangerous drugs if prescribed in large doses for more than two or three weeks. Tolerance and drug dependence do not develop with the neuroleptics, and for this reason one may sometimes choose to prescribe a neuroleptic drug for a patient suffering from anxiety, even though it is likely to be less effective than an anxiolytic sedative. Such a choice would be indicated if, on the basis of the patient's previous history or his personality structure, one has reason to believe that he might rapidly develop psychological and, also, physical dependence on an anxiolytic sedative. When faced with this hazard it is often wiser to choose the second best drug, e.g., a phenothiazine drug in small doses rather than a minor tranquilizer for sedation.

Of all psychiatric conditions which a physician is called upon to treat, anxiety is undoubtedly the most common. It is difficult to resist the urgent demands of an anxious patient for immediate relief from his symptoms. The doctor must learn to brace himself against these demands and persuade his patient to settle for less than complete relief, particularly if tranquilizing drugs have to be prescribed for periods exceeding two or three weeks. Patients who present anxiety symptoms are often highly sensitive to side effects which may be associated with the use of major tranquilizers, and they will make every

effort to convince the doctor that they *ought* to receive a drug which does not cause them any discomfort. However, patients should learn to accept the comparatively mild inconveniences of side effects, e.g., dry mouth, stuffy nose, even some drowsiness and lack of energy. It is probable that major tranquilizers produce less dependence, precisely because they tend to produce more unpleasant side effects than the minor tranquilizers. When the dangers of drug toxicity, development of tolerance and dependency are threatening, the therapeutic "elegance" of prescribing a drug with no unpleasant side effects should definitely be disregarded.

Although barbiturates are the principal offenders in producing drug dependence and toxic symptoms, it is a fact that almost every minor tranquilizer has these potentials. There is no pharmacological reason for making a distinction between hypnotic drugs and anxiolytic sedatives. Every drug which is used primarily for sleep induction can also be used in smaller doses as a daytime sedative, and every daytime sedative (or minor tranquilizer) in larger doses will produce drowsiness and sleep. The distinction between hypnotics and sedatives is, thus, only a question of dosage. Minor tranquilizers other than barbiturates, e.g., methypylon, or Nolidar (Jensen, 1960; Peters, 1966), and glutethimide, or Doriden (Ossenfort, 1957; Lingl, 1966), are just as likely to produce psychological and physical dependence with dangerous withdrawal symptoms as are the barbiturates. To a lesser degree this is also true for meprobamate (Equanil) and even chlordiazepoxide (Librium) and diazepam (Valium), although physical dependence on the latter two drugs is rarely seen. Librium has the best safety record of all minor tranquilizers; no death has been reported with this drug, although, with large doses, a number of suicidal attempts have been made.

The only minor tranquilizer which seems to be free of the potential hazard of inducing physical drug dependence is tybamate. With this drug it has been impossible to induce physical dependence in animals or humans under experimental conditions, and dependence on the drug has not been reported under clinical conditions. This may be due to the fact that tybamate has an unusually short half-life in the organism; its rapid degradation may prevent the development of dependence through the absence of any cumulative effects (Shelton and Hollister, 1967). Looking for a drug to be less likely to induce psychological dependence, we have noted that one of the new minor tranquilizers, hydroxyzine (Atarax), is less likely than other sedatives to be taken in larger doses or for a longer time than prescribed—possibly because it causes euphoria and disinhibition less frequently than most of the other minor tranquilizers.

In summing up the salient features regarding clinical use of anxiolytic sedatives, we arrive at the following conclusions. Anxiolytic sedatives, which are also called minor tranquilizers, differ from hypnotic drugs only in dosage. Pharmacological and psychological effects of all drugs in this category are very similar, regardless of the chemical nature of the drug. Many of the drugs in this category are highly toxic; therefore, no patient should be given a prescription for more than 15 doses of a barbiturate or meprobamate at one time. With very few exceptions, all anxiolytic sedatives tend to produce tolerance and psychological and physical dependence. There is cross-tolerance between all drugs in this category, e.g., between alcohol and paraldehyde, or alcohol and Librium, or barbiturates and Librium. Once physical dependence on a minor tranquilizer has developed, abrupt withdrawal is potentially dangerous and should always be undertaken in a hospital setting. The safest

drug from the toxicity point of view seems to be chlordiazepoxide; from the point of view of physical dependence, tybamate; and from the point of view of psychological dependence, hydroxyzine. Pharmacotherapy of anxiety and tension symptoms is always symptomatic and should only be used as an adjunct to other more specific therapy. One should avoid prescribing the same minor tranquilizer for more than two weeks, unless the patient receives only small doses. It is advisable for a doctor to become familiar with three or four minor tranquilizers at the most and to alternate their use if anxiety-relieving drugs have to be prescribed for more than two weeks or if special indications, e.g., danger of suicide or addiction are present.

Acute Psychotic States

Acute psychotic episodes frequently improve within a few days with the use of neuroleptic (antipsychotic) drugs. In previous years these states usually lasted for months, and even with shock therapy more time was required for a successful resolution of symptoms than is required today with pharmacotherapy.

The prototype of neuroleptic drugs is Thorazine, which still serves as a standard against which newer drugs in the neuroleptic category are evaluated. Thorazine is a phenothiazine derivative, as are most of the other antipsychotic drugs on the market today. In recent years, the butyrophenones and thioxanthenes, derivatives of two other chemical structures, have joined the phenothiazines as powerful neuroleptic agents.

The neuroleptic drugs, which are mainly used in the treatment of psychotic conditions, may be divided into two groups: 1) those with side effects manifesting themselves mainly in *disturbances of autonomic functions* (hypertension, miosis, tachycardia, dry mouth, excessive perspiration and other

symptoms of adrenergic-cholinergic imbalance); and 2) those with side effects expressed mainly in the *extrapyramidal system* (parkinsonism, akathisia, muscular dystonia and dyskinesia). If the drug is a phenothiazine derivative, the nature of its side effects can usually be predicted from the side chain which is attached to the phenothiazine nucleus. Drugs containing a piperazine ring in the side chain are more potent, milligram for milligram and produce extrapyramidal symptoms more frequently than drugs with an aliphatic side chain which, in turn, are more likely to produce changes in autonomic functions and sedation and must be given in larger doses. Despite their designation as major tranquilizers, not all neuroleptic drugs produce sedation. Some of them have distinctly stimulant effects and may even increase tension in the patient if one of their side effects is akathisia, i.e., the inability of the patient to remain still. The hyperkinetic extrapyramidal symptom of akathisia, as well as the hypokinetic symptom of rigidity, may be so disturbing to the patient that antiparkinsonism drugs must be employed to counteract these symptoms. The most frequently used drugs for this purpose are: trihexyphenidyl hydrochloride (Artane), benzotropine methanesulfonate (Cogentin) and procyclidine hydrochloride (Kemadrin). All of these antiparkinsonism drugs have a strong anticholinergic action. We have found that they may produce toxic psychotic symptoms if they are given in daily doses exceeding six or eight mg of Artane or Cogentin, or 15 mg of Kemadrin.

Most neuroleptic drugs have remarkably low toxicity and an extraordinarily wide therapeutic margin, but they also have an unusually broad range of unpleasant side effects, such as somnolence, apathy and restlessness, extrapyramidal symptoms, dryness of the mucous membranes, tachycardia, hypotension, disturbances of accommoda-

tion, constipation, obesity, menstrual irregularity and photosensitization. Skin rashes, edema, leucopenia and cholestatic jaundice may occur as symptoms of idiosyncratic hypersensitivity. Rarely, agranulocytosis and venous thrombosis are seen. With very large doses of neuroleptics—over 1000 mg of Thorazine a day or its dose equivalent—convulsions may occur.

Mellaril, the neuroleptic with the lowest incidence of extrapyramidal side effects, should not be prescribed in doses exceeding a daily maximum of 400 to 500 mg for more than two or three weeks, since under those conditions it might produce irreversible retinal changes or dangerous cardiac arrhythmias. Doses of the drug up to 400 mg/day seem to be well tolerated for an indefinite time.

The following is a list of the most frequently used neuroleptics:

1) Phenothiazine derivatives with an aliphatic structure in the side chain: chlorpromazine (Thorazine); triflupromazine (Vesprin); promazine (Sparine).

2) Phenothiazine derivatives with a piperazine ring in the side chain: perphenazine (Trilafon); trifluoperazine (Stelazine); prochlorperazine (Compazine); thiopropazate (Dartal); fluphenazine (Prolixin; Moditen).

3) Phenothiazine derivatives with a piperidyl ring in the side chain: thioridazine (Mellaril).

4) Butyrophenone derivative: haloperidol (Haldol).

5) Thioxanthene derivatives: chlorprothixene (Taractan); thiothixene (Navane).

This list is not complete, but refers only to the more frequently used drugs in the United States. Specific doses for each drug can best be obtained from the information provided by the manufacturer, although dosage information given on the package inserts by the manufacturer invariably tends to be on the conservative side and frequently has to be exceeded in individual cases. Fortunately, this can

be done in most cases without particular risk because of the wide safety margin of all neuroleptic drugs.

Which of the many neuroleptics should one choose? Years of careful clinical investigation have made it very clear that for all practical—i.e., clinical—purposes, no specific indications or specific therapeutic properties exist for any of the neuroleptic drugs. Therefore, it is probably best for a physician to become thoroughly familiar with two or three neuroleptic drugs and then restrict himself to their use. What is essential is that adequate doses are given over an adequate period of time. Such specific differences between the actions of various neuroleptic drugs as were found to exist were only of statistical significance and so slight that they probably have no importance for the clinician (Goldberg et al., 1967).

What is an adequate dose? The table on the opposite page shows approximate therapeutic equivalences of doses of various neuroleptic drugs in comparison to Thorazine. If 1 mg of Thorazine is taken as 1 phenothiazine unit, the clinical approximations shown in the Table are obtained. For example, the table indicates that 10 mg of Trilafon are equivalent to 100 mg of Thorazine, and 1 mg of Haldol is equivalent to 70 mg of Thorazine.

The therapeutic daily dose for the treatment of an acute psychotic reaction is between 400 and 1000 phenothiazine units (mg of Thorazine or the dosage equivalent of other neuroleptic drugs). Sometimes higher daily dose levels are required, e.g., 1000 to 2000 phenothiazine units and, occasionally, up to 3000 or 4000 units a day. But 400 to 1000 phenothiazine units a day will be effective in the treatment of most acute psychotic breakdowns. If the dose is adequate, the symptoms of restlessness and insomnia should have subsided after one week of pharmacother-

apy; after two weeks of treatment the patient's anxiety, irritability, depression, suspiciousness and social withdrawal should be significantly reduced. Only after 8 to 12 weeks may one expect the disappearance of hallucinations, delusions and thought disorder. In some patients resolution of all symptoms may, under adequate pharmacotherapy, be telescoped into a few days, particularly if the breakdown has been very sudden in onset. On the other hand, if the above timetable indicates that the patient's symptoms are not subsiding within the expected periods of time, it may be necessary to increase the dose of the neuroleptic (Lehmann, 1965a).

An acute psychotic condition is treated preferably with intramuscular injections, at least for the first few days; then a change to oral administration may be instituted. The risk of giving too much of a neuroleptic drug is small if the general framework of the recommended dosage is followed and one or two test doses are given to observe the patient's initial reaction to the drug.

Maintenance Therapy of Schizophrenics in Remission

Chronic psychotic patients and schizophrenic patients in remission frequently require maintenance therapy with neuroleptic drugs for many months—sometimes for years. The maintenance dose in most cases is from one-sixth to one-fourth of the acute treatment dose. If main-

tenance therapy is interrupted, the risk of a relapse is between 30% and 50%. This risk can be reduced to 5% or 10%, provided the patient remains on regular follow-up therapy. At times of increased stress, family conflicts, job changes and similar problems, the maintenance dose may have to be increased for a short time; the same applies if the patient shows signs of increasing tension or instability. The clinical situation is similar to that of an epileptic patient on anticonvulsant treatment or of a diabetic on insulin, i.e., the treatment is neither merely symptomatic nor curative, but corrective or compensating in nature.

A long-acting, injectable phenothiazine drug is now available in the form of Fluphenazine Enanthate. The usual dose is 1 cc, containing 25 mg of the drug. For individual patients it is, of course, sometimes necessary to increase or decrease the dose, but the great advantage of this preparation is that the effects of one injection in most cases last for two weeks or longer, thus freeing the patient from the responsibility to take medication himself every day. All he needs to do is return every two or three weeks for his injection. Since Fluphenazine has a piperazine structure in its side chain, the compound is likely to induce extrapyramidal symptoms, and antiparkinsonism drugs might be required to counteract these side effects.

It is true that probably 50% or 60% of former schizophrenic patients are today receiving neuroleptic drug therapy for months or years without needing it. The trouble is that we cannot tell, by any criterion, which of the patients are the 40% or 50% who will relapse if they do not receive maintenance therapy. If we have seen once that a patient who did not take any maintenance medication had a relapse, we can assume with a high degree of probability that this patient will again relapse unless he receives maintenance therapy. Usually, we do not have this information, because the patient is put on maintenance therapy after the first psychotic breakdown. In these cases one should continue with maintenance therapy for at least six months and then carefully try to withdraw the maintenance medication. Once it is known that an individual patient requires maintenance therapy, this treatment should have considerable priority over all other considerations. The question one would have to ask of oneself is whether it is more advantageous for the patient to stop taking his medication and be hospitalized in a psychotic state or to continue taking his medication and remain a normally functioning member of the community suffering the inconvenience of certain unpleasant side effects.

Serious complications, i.e., agranulocytosis or jaundice, very rarely occur after the first two months of pharmacotherapy. Unfortunately, regular blood counts and biochemical tests have hardly more than legal value, unless they are repeated every two days. Skin pigmentation and lens opacities (usually without effect on visual acuity) have been described after more than six months' medication with high doses of Thorazine, and recently attention has been drawn to extrapyramidal symptoms, usually involving muscles of the tongue and the mouth, which occur after long-term therapy with piper-

Dose Equivalence of Various Neuroleptic Drugs

Neuroleptic Drugs	Phenothiazine Units
Trifluoperazine (Vesprin)	3
Promazine (Sparine)	$\frac{1}{2}$
Perphenazine (Trilafon)	10
Trifluoperazine (Stelazine)	20
Prochlorperazine (Compazine)	6
Fluphenazine (Prolixin; Moditen)	70
Thioridazine (Mellaril)	1
Haloperidol (Haldol)	70
Chlorprothixene (Taractan)	1
Thiothixene (Navane)	20

zine derivatives of the phenothiazines. (Unlike the extrapyramidal symptoms occurring under acute treatment conditions, these late involuntary movements are usually irreversible. Fortunately, they occur only in a comparatively small percentage of patients, mostly in the older age group, and only after more than a year of continued drug therapy.)

Therapeutics of Antidepressants

The physician who has diagnosed his patient as being depressed and is considering the choice of treatment must first determine how threatening the patient's condition is. Is the patient acutely suicidal? Does he refuse to take food or medication? Is he psychotic and uncooperative? These features may determine whether the patient can be treated at home or must be hospitalized; they may also indicate whether the patient should receive immediate electro-convulsive therapy or can be treated with an antidepressant drug. In acutely suicidal patients electro-convulsive treatment is often indicated, since most antidepressant drugs take from one to three weeks to produce notable improvement.

A differential diagnosis between endogenous and reactive depression is often helpful, because endogenous depressions mainly require physical treatment, either electro-convulsive treatment or pharmacotherapy, whereas reactive depressions, which may also respond to physical treatments, usually require psychotherapy in addition to other treatments. Today, the extent to which one can really distinguish between purely endogenous and purely reactive depressions is becoming more and more questionable. The concept of "endoreactive" depression, which is used in the German psychiatric literature, reflects the state of affairs which is frequently encountered in depressive states, i.e., one with endogenous as well as reactive components.

However, it is still useful to attempt an assessment of the varying degrees to which each of these two components is present in a given depression (Lehmann, 1965b, 1968).

Once the decision to use antidepressant drug therapy has been made, the choice lies between drugs belonging to the class of monoamine oxidase inhibitors and drugs which are often referred to as tricyclic antidepressants, because their chemical structure is characterized by a three-ring nucleus. Examples of the first type are: phenelzine (Nardil); isocarboxazide (Marplan); nialamide (Niamid); tranylcypromine (Parnate). Examples of the second group are: imipramine (Tofranil); amitriptyline (Elavil); desipramine (Pertofrane, Norpramin); nortriptyline (Aventyl); protriptyline (Vivactil, Triptil). The monoamine oxidase inhibitors have approximately the same therapeutic effectiveness as the tricyclic antidepressants, although there is gradually increasing evidence that the tricyclic antidepressants are slightly more effective than the MAO inhibitors. On the average, about 60% to 65% of depressed patients show a satisfactory improvement within two to three weeks when treated with antidepressant drugs.

The physician who prescribes a MAO inhibitor must remember that the effect of this enzyme inhibitor is reaching farther than ordinary drug action, because the inhibition of monoamine oxidase is not easily reversed. Monoamine oxidase is the enzyme that degrades serotonin and noradrenaline, and when this enzyme is inhibited, the biogenic amines are allowed to accumulate. A similar effect is produced by the tricyclic antidepressants, but through a different mechanism; they prevent excessive noradrenaline, which has been freed at the neuronal synapses, from being reabsorbed into the cell body. Both classes of antidepressant drugs, thus, lead to an increase of available

serotonin and noradrenaline at neuronal synapses. This has been advanced as an explanation of their antidepressant action, since current neurochemical theories of depression propose that the underlying physical substrate of a depressive state is a reduction of the biogenic amines at the synapses of the central nervous system.

Some MAO inhibitors, e.g., tranylcypromine (Parnate), have an immediate amphetamine-like stimulating and euphorizing effect in addition to their principal antidepressant action, which can be observed only after one to three weeks. Such stimulation is often desirable, but in some cases it might be contraindicated. The side effects of MAO inhibitors are more difficult to manage than those of the tricyclic antidepressants, because MAO inhibitors are incompatible with many other drugs and with certain food substances, e.g., cheese, which may contain the pressor substance tyramine. It is essential that patients receiving a MAO inhibitor abstain from these food items and from most other drugs, particularly adrenaline, amphetamines, thyroid and Demerol which, in combination with a MAO inhibitor, may precipitate very alarming toxic complications. MAO inhibitors and tricyclic antidepressants should not be administered simultaneously, and at least a week should elapse after discontinuation of a MAO inhibitor before treatment with a tricyclic antidepressant is instituted.

Tricyclic antidepressants produce mainly anticholinergic side effects; hence, care should be exercised when ordering these drugs for patients in whom urinary retention or glaucoma may be precipitated. A tricyclic antidepressant should never be administered concurrently with both an antiparkinsonism drug and a neuroleptic, since all three drugs—particularly the first two—have anticholinergic properties and may act synergistically to produce dangerous and even fatal complica-

tions, e.g., adynamic ileus (Warnes, Lehmann and Ban, 1967). Some caution is also indicated in patients with myocardial damage in whom tricyclic antidepressants may produce reversible cardiac arrhythmias.

Some antidepressant drugs, e.g., amitriptyline (Elavil), also have anxiety-reducing effects. Patients suffering from an anxious or agitated type of depression often respond favorably to minor or major tranquilizers, e.g., Equanil, Librium or Mellaril. Anxiety is very frequently associated with depression, and since the manifestations of anxiety are far more conspicuous than the manifestations of depression, there is a danger that the lessening of anxiety in response to a drug is mistaken for an overall improvement in the depressed patient's condition. If this happens, one may relax one's vigilance when treating a patient who, in initial response to therapy, may sleep better, look better and display less anxiety, but may still feel depressed and hopeless and may also still be suicidal. The core symptom of depression is a feeling of sadness, despair, pessimism and hopelessness and the inability to get involved with things or people. Until these core symptoms have subsided, a depressed patient's improvement is far from complete.

After the depressed patient's symptoms have disappeared, drug therapy should be continued for at least two to three months at the same dosage; after this time the dose of the antidepressant might be reduced to about one-half or one-third for another month or two.

For patients with frequently recurrent depressions or patients who have many recurring manic or depressive episodes, lithium has recently been shown to offer valuable prophylactic action. The therapeutic effects of lithium carbonate in states of manic excitement have been known for 20 years. However, the drug seems to have few, if any, therapeutic effects in depres-

sive states. Recently, Baastrup and Schou (1967) have shown that lithium carbonate, in doses of about one-third or one-half of the therapeutic dose in manic conditions, can be given as successful maintenance treatment to prevent the recurrence of both manic or depressive episodes. This is a considerable step forward, because maintenance treatment for affective disorders previous to the introduction of lithium treatment has by no means been as effective as maintenance treatment of schizophrenic patients in remission. However, before treatment with lithium carbonate is instituted, a careful history should be taken and the differential diagnosis should be well established, since this form of therapy does not seem to be effective in schizophrenic conditions and would not be indicated for manic or depressive episodes which occur only at long intervals. Since lithium may cause dangerous toxic complications which may be fatal, it is essential for patients on lithium therapy to have their lithium blood level monitored at regular intervals.

Alcoholism and Antabuse

Drugs are of no value in the treatment of most personality disorders, for instance, antisocial behavior and sexual deviation. Some drugs can play an important role in the rehabilitation of opiate addicts, e.g., methadone, which, in the first few years of a large-scale trial in New York City, has shown remarkable results (Dole, Nyswander and Warner, 1968; Methadone Maintenance Evaluation Committee, 1968). However, the treatment of addicts has not yet progressed to the point where the non-specialist may be advised to undertake it. But there is one kind of addiction, i.e., alcoholism, which is so widespread—there are over two million alcoholics in the United States—that non-specialist physicians must accept a major part of the responsibility for treating this group of

patients. Treatment of the alcoholic is a complex problem and involves the application of almost every medical skill, but in the framework of this discussion, I want to draw your attention to one pharmacotherapeutic approach which is specifically applicable to the treatment of alcoholism. I am referring to the use of disulfiram (Antabuse) as a maintenance treatment for alcoholics who are motivated to give up drinking.

Antabuse is an enzyme inhibitor which blocks the breakdown of alcohol in the organism at the acetaldehyde stage. Since acetaldehyde is a highly toxic substance, people who have taken Antabuse and later take alcohol become very ill within a matter of minutes. The alcoholic who takes his Antabuse medication regularly will usually be deterred from taking alcohol by his knowledge of the ordeal he would have to endure. The drug thus serves as a chemical straitjacket, a most valuable aid to those who are seriously motivated to give up drinking, but is not of much value to those who simply stop taking Antabuse when they feel the desire to drink.

Summary

Psychopharmacology has opened the door to many previously blocked parts of psychiatric therapy. It has been a welcome catalyst for a long awaited rapprochement between psychiatry and the rest of medicine. Even if psychopharmacological research is not likely to produce another revolutionary "breakthrough" type of drug in the near future, there is good reason to expect many more useful therapeutic tools to issue from such research in the years to come.

References

- BAASTRUP, P. C. AND M. SCHOU.
Lithium as a prophylactic agent. Its effect against recurrent depressions and manic-depressive psychosis.

- Arch. Gen. Psychiat.* 16:162-172, 1967.
- Control of amphetamine preparations. *Brit. Med. J.* 4:572-573, 1968.
- DELAY, J. AND P. DENIKER. Le traitement des psychoses par une méthode neurolytique dérivée de l'hibernothérapie. (Le 4560 RP utilisé seul en cure prolongée et continue.) Congrès des Psychiatrie des Langues Française, Luxembourg, 22-26 July, 1952.
- DOLE, V. P., M. E. NYSWANDER AND A. WARNER. Successful treatment of 750 criminal addicts. *JAMA* 206:2708-2711, 1968.
- GOLDBERG, S. C., N. MATTSSON, J. O. COLE AND G. L. KLERMAN. Prediction of improvement in schizophrenia under four phenothiazines. *Arch. Gen. Psychiat.* 16:107-117, 1967.
- JENSEN, G. R. Addiction to noludar. A report of two cases. *New Zealand Med. J.* 59:431-432, 1960.
- LEHMANN, H. E. Drug treatment of schizophrenia. In *Psychopharmacology*. N. S. Kline and H. E. Lehmann (eds.). Boston: Little, Brown, 1965a, pp. 717-751.
- . Problems of differential diagnosis and choice of therapy in depressive states. *Psychosomatics* 6:266-272, 1965b.
- . Clinical perspectives on antidepressant therapy. *Am. J. Psychiat.* 124 (Suppl.):12-21, 1968.
- LINGL, F. A. Irreversible effects of glutethimide addiction. *Am. J. Psychiat.* 123:349-351, 1966.
- Methadone Maintenance Evaluation Committee. Progress report of evaluation of methadone maintenance treatment program as of March 31, 1968. *JAMA* 206:2712-2714, 1968.
- OSSENFORT, W. F. Drug addictions. *Dallas Med. J.* 43:229-232, 1957.
- PETERS, U. H. Kombination von Noludar und Alkohol. Sucht und einmalige Vergiftungen. *Med. Klin. (Munich)* 61:1455-1458, 1966.
- Research in psychopharmacology. Report of a WHO scientific group. *World Health Organ. Tech. Rep. Ser.* 371:1-39, 1967.
- SHELTON, J. AND L. E. HOLLISTER. Simulated abuse of tybamate in man. Failure to demonstrate withdrawal reactions. *JAMA* 199:338-340, 1967.
- Tranquilizer Proves Non-Addictive in Study, editorial. *Medical World News* 6:66, 1965.
- WARNES, H., H. E. LEHMANN AND T. A. BAN. Adynamic ileus during psychoactive medication: A report of three fatal and five severe cases. *Can. Med. Assoc. J.* 96:1112-1113, 1967.