HAROLD E. HIMWICH, M.D.*

Galesburg State Research Hospital, Galesburg, Illinois

Psychoactive Drugs

The phenothiazine tranquilizers are highly effective primary therapeutic agents in psychoses and are valuable adjuvants to psychotherapy in the neuroses. Endogenous depression responds readily to the antidepressant drugs of the imipramine type. In atypical depression the monoamine oxidase inhibitors play a prominent therapeutic role. Grave neuroses require the same treatment as do the psychoses. At present, outside the hospitals, one-third of all the prescriptions for psychoactive drugs specify chlordiazepoxide; meprobamate accounts for a slightly smaller proportion.

WE have come now to the end of the first decade of experience with the tranquilizers, time enough for "survival of the fittest" of these psychoactive drugs and for a determination of the effects of their long-term use. This paper is concerned with the applications of psychoactive drugs in four broad fields: treatment of schizophrenia and other severe mental disturbances with phenothiazines, antidepressant therapy, the use of psychoactive drugs in the field of child psychiatry, and the management of the neuroses. My topic is chemotherapy, but psychotherapy and the paramedical arts are essential in the management of the mentally ill patient and cannot be excluded from consideration.

Tranquilizers: the Phenothiazines

The phenothiazines, of which chlorpromazine (THORAZINE®) is the prototype, form the largest, most versatile group of drugs used in the field of mental disorders. Patients with schizophrenia are best managed with these drugs, whether the disease is acute or chronic and whether it is marked by overactivity or underactivity. The phenothiazine derivatives are also used extensively in other mental disturbances, e.g., as adjuvants to psychotherapy for the neuroses.

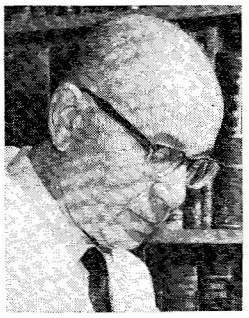
*Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Galesburg, Illinois.

The Improved Climate in Mental Hospitals

The advent of psychoactive drugs initiated a significant decline in the populations of our state mental hospitals and brought about a great improvement in morale. The decline in population has continued, although recently it has been less steep.[1] Insulin hypoglycemia, convulsive therapy and psychosurgery are still valuable forms of therapy for schizophrenia in circumscribed situations. It is true that the barbiturate drugs could be used to stupefy or anesthetize distraught schizophrenic patients, but tranquilizers allow us to treat these patients without a significant interruption of consciousness. Even if a large dose of a tranquilizer must be given for a severe exacerbation, the patient can be awakened relatively easily. This

difference between barbiturates and tranquilizers is attributable to the fact that the latter drugs affect to a greater extent subcortical functions of areas of the brain that are regarded as anatomic substrates of the emotions and affect to a lesser extent the neocortex, which is chiefly involved in discrete awareness.

State mental institutions are now regarded



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as treatment centers rather than as facilities whose chief function is custodial care. A hospital atmosphere has been created. Isolation wards and wet packs have been given up entirely. Mechanical restraints are seldom used. Electroshock is largely relegated to use in severe depressions. Ward doors have been opened, and patients can pursue prescribed activities in a therapeutic community. Greater optimism pervades all the services, resulting in greater effort by the staff and correspondingly better results. While the psychoactive drugs by themselves could not have brought about these improvements, certainly the outlook prior to their introduction was quite dismal.

General and Specific Effects of Phenothiazines

The beneficial effects of the phenothiazines are chiefly the results of a general calming action and a specific antipsychotic action. The calming action is a general toning down of emotional reactions and psychomotor behavior and is achieved mainly by alleviation of anxiety and by a kind of sedation that does not enforce the soporific or hypnotic actions characteristic of the barbiturates. The specific antipsychotic effect corrects the distorted thinking of schizophrenic patients and alleviates or dispels completely their hallucinatory and delusional experiences. These different beneficial effects may occur either together or separately in individual patients.

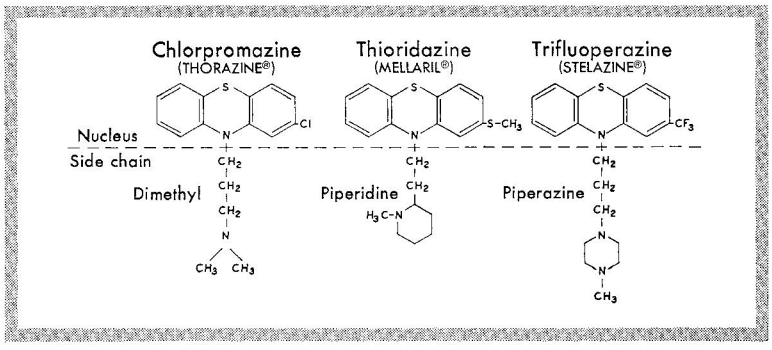
Relative Potency of Phenothiazines

Most of the phenothiazines having psychoactive properties belong to one of three groups distinguished by the side chains in their chemical structures (figure 1). One is the chlorpromazine group which features a dimethylamino configuration. The second group, represented by thioridazine (MELLARIL®), is made up of phenothiazines with a piperidine side chain. The third and largest group consists of the piperazine drugs, represented by trifluoperazine (STELAZINE®). Other members of the chlorpromazine group are triflupromazine (VESPRIN®), promazine (SPARINE®) and methoxypromazine (TENTONE®). Mepazine (PACATAL®) and piperacetazine (QUIDE®) are part of the second or the piperidine group. The third group includes prochlorperazine (COMPAZINE®), perphenazine (TRILAFON®), thiopropazate (DARTAL®), fluphenazine (PROLIXIN®, PERMITIL®), acetophenazine (TINDAL®) and carphenazine (PROKETAZINE®).

The drugs in all three groups are very similar with respect to therapeutic efficacy. A well-controlled double-blind study to compare the effects of chlorpromazine, thioridazine and fluphenazine (representatives of all three groups) in more than 700 acutely ill schizophrenic patients did not demonstrate statistically significant differences in therapeutic efficacy among the three agents.[2] In another double-blind study the effects of reserpine and of five phenothiazine drugs in 512 schizophrenic men were compared. Only reserpine was distinctly less effective. Chlorpromazine, thioridazine, chlorprothixene (TARACTAN®) and trifluoperazine were equally effective.[3]

All these phenothiazine derivatives have

FIGURE 1. Three groups of phenothiazine drugs distinguished by their side chains. The dimethylamino group is represented by chlorpromazine, the piperidine group by thioridazine, and the piperazine group by trifluoperazine. Additional members are listed in the text.



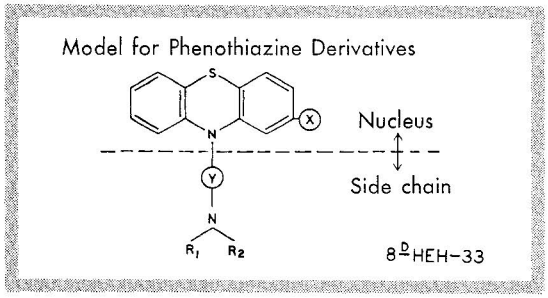


FIGURE 2. In all phenothiazines with psychoactive properties the three-carbon chain is found in the Y position. The X position may be occupied by a hydrogen or chlorine atom or by a trifluoromethyl group.

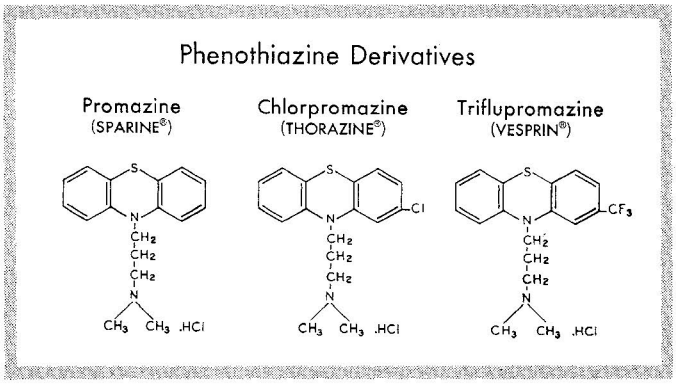


FIGURE 3. Three examples of the dimethylamino group of phenothiazines illustrating differences in structure at the X position (see figure 2). In the promazine structure a hydrogen atom occupies the X position (not shown in the diagram). Chlorpromazine and triflupromazine contain a chlorine atom (–Cl) and a trifluoromethyl group ($-CF_3$), respectively.

in common a chemical structure consisting of the phenothiazine nucleus and a three-carbon chain in the Y position shown in the model in figure 2. The drugs in the piperazine group are more potent, milligram for milligram, than those in the dimethylamino or piperidine group. Potency is also influenced by the chemical configuration in the X position in the model. Promazine, chlorpromazine and triflupromazine represent a sequential increase in potency[4] (figure 3). The promazine molecule contains a hydrogen atom in the X position (not shown in the diagram), chlorpromazine a chlorine atom, and triflupromazine a trifluoromethyl group. Trifluoperazine with a trifluoromethyl group in the X position is five times as potent as perphenazine with a chlorine atom. Trifluoperazine and fluphenazine are by far the most potent of all phenothiazines in general use.

The relative potency may be expressed as a ratio of chlorpromazine dosage. From 200 to 1200 mg. of chlorpromazine per day is usually required to effect psychomotor inhibition in psychotic patients. Taking as unity the chlorpromazine dosage, the comparative dosages of other phenothiazines are as follows: promazine or mepazine, 2 (about twice the chlorpromazine dosage); thioridazine, 1 (same range as chlorpromazine); triflupromazine, 1/2; prochlorperazine, 1/5; thiopropazate, 1/7; perphenazine, 1/12; tri-

TABLE 1

SIDE EFFECTS OF PHENOTHIAZINES

DRUG	COMPARATIVE DOSAGE	SIDE EFFECTS OTHER THAN EXTRAPYRAMIDAL CHANGES*	EXTRAPYRAMIDAL SIDE EFFECTS
Chlorpromazine	1	Stronger	Weaker
Triflupromazine	1/2	↑	↓
Perphenazine	1/12		
Trifluoperazine	1/20		
Fluphenazine	1/40	Weaker	Stronger

*The six principal side effects are dermatitis, jaundice, agranulocytosis, sedation, orthostatic hypotension and convulsions. Thioridazine, with a dosage range similar to that of chlorpromazine, is not included in the table because both types of side reactions to this drug are milder.

fluoperazine, 1/20; fluphenazine, 1/40. Bear in mind that these ratios are not absolute but are merely guides in determining dosage.

Side Effects of Phenothiazines

Thioridazine in the usual dosage range evokes fewer and milder side reactions than any other phenothiazine derivative, yet prolonged administration of amounts greater than 1000 mg. per day[5] will eventually induce transitory retinopathy and temporary blindness; these, however, are reversible and disappear when the medication is stopped.

There are seven principal side reactions to phenothiazines. Three are chiefly allergic: dermatitis, jaundice and agranulocytosis. The others appear to be dose-dependent (occurring with higher dosage levels): sedation, orthostatic hypotension, convulsive seizures and extrapyramidal (neuromuscular) disturbances. Convulsive seizures occur most frequently when there are changes in the brain associated with birth injury or electroshock. The extrapyramidal disorders may be subdivided into three groups: parkinsonian symptoms, motor restlessness and anxiety (akathisia), and spastic contractions and involuntary movements (dyskinesias).

Excessive extrapyramidal reactions may be overcome by reducing the dosage of the phenothiazine drug and by prescribing an antiparkinsonian drug such as benztropine methanesulfonate (COGENTIN®), trihexyphenidyl hydrochloride (ARTANE®) or biperiden hydrochloride (AKINETON®).[6,7] In addition, if akathisia is troublesome, one should give a small dose of a barbiturate daily.

The dimethylamino group of drugs may exert the first six side reactions to a greater extent than do the piperazines. The piperazines, in contrast, evoke extrapyramidal alterations to a greater degree, and they do so in proportion to their potency. The most potent piperazines, trifluoperazine and fluphenazine, are associated with the most pronounced extrapyramidal changes.

General Guides to Phenothiazine Therapy

The response to a phenothiazine derivative will vary from patient to patient. A patient who does not exhibit a beneficial response to one phenothiazine may improve when another is given. Some generalizations may be useful as guides. Many hyperactive patients are more effectively treated with chlorpromazine or triflupromazine than with a piperazine. On the other hand, the piperazines produce greater psychomotor stimulation[4,8] and therefore may be more effective in apathetic, underactive patients. Susceptibility to side reactions also varies, but again some general comments may be made, especially with respect to extrapyramidal disturbances. Older persons are more likely to exhibit parkinsonian changes. Dyskinesias are more com-

mon among younger patients. Akathisia occurs in patients of all ages. Women are more sensitive to the side effects than are men.

Thorough familiarity with a few phenothiazine drugs is recommended. The Department of Mental Health of Illinois has suggested that its members should concentrate on six drugs, by no means implying thereby that others are not equally efficacious. Chlorpromazine, thioridazine, trifluprομazine, perphenazine, trifluoperazine and fluphenazine have been stressed (table 1).

Long-Term Effects

Experience has amply demonstrated that long-term therapy with phenothiazines can maintain clinical improvement[9-11] without significant danger to the liver, bone marrow and kidneys. Recently, however, skin pigmentation and fine particulate matter in the cornea and lens of the eye have been observed in hospitalized patients, primarily women, who have received large doses of chlorpromazine for four to eight years.

Opinions differ as to the addictive effects of the phenothiazines,[12-15] but tolerance does not develop. In fact, smaller rather than larger amounts are required to maintain improvement. These drugs are not curative but they continue to alleviate undesirable symptoms after patients are discharged from the hospital. Like insulin, they may be given indefinitely, the dosage being adjusted according to the severity of symptoms.

A survey of six years' experience with tranquilizers furnishes dramatic evidence that drug therapy is only one component of the treatment that must be given to patients with severe mental disease.[16] The study group was composed of 1000 combative, destructive, incontinent, denudative female patients. Over the six year period, 277 were discharged from the hospital and 91 returned. Only 24 of these readmissions, however, were prompted by relapses in patients who had been taking the drugs as prescribed. Adjustment of dosage or substitution of another phenothiazine again brought about a good therapeutic response in these cases. Thirty-one of the patients who returned had failed to take the prescribed medication regularly or at all, and 36 re-entered the hospital for reasons unrelated to drug therapy; e.g., one patient's bedroom at home was needed because of the birth of a child in the family. It is obvious that teamwork of the hospital staff, counseling of patients and their families, and steps to re-establish patients in their communities are necessary.

Antidepressant Drugs

Endogenous depressions respond readily to a group of antidepressant drugs whose prototype is imipramine (TOFRANIL®). In atypical depressions marked primarily by anxiety or hysteria, the monoamine oxidase inhibitors (MAOI) occupy a prominent therapeutic position. A third form of depression, reactive in type, usually is secondary to an environmental change, e.g., personal bereavement or long-standing chronic illness, and is an expression of an excessive response to stress. In contrast to endogenous depression, which is a psychotic reaction, reactive depressions are termed neurotic. Severe neurotic depression cannot always be distinguished from psychotic depression and requires the same treatment. Milder depressions, commonly seen in private practice, are managed in the same way as the neuroses.

Features of Endogenous Depression

Among the endogenous depressions are the involutional forms observed in older persons, the climacteric type, and the depressed phase of a manic-depressive reaction. Depression also may be superimposed on a chronic brain syndrome and on a schizophrenic reaction. Endogenous depressions are characterized by gross physiologic changes: insomnia, gastrointestinal alterations, amenorrhea,

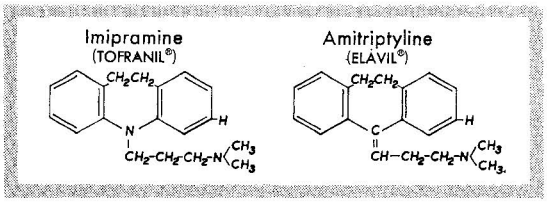


FIGURE 4. Two antidepressants, imipramine and amitriptyline. While both drugs resemble promazine in structure, they also represent significant changes from the phenothiazines: an ethylene chain (CH_2CH_2) in place of the sulfur (S) and, in the amitriptyline structure, substitution of a carbon (C) for the nitrogen (N) in the nucleus.

retardation of both mental and physical processes (psychomotor inhibition). Delusional ideas and depersonalization are frequently noted. Excessive sadness also occurs in association with agitation, anxiety and increased motor activity (agitated depression). These persons have feelings of guilt, unworthiness, hopelessness and helplessness which carry with them the danger of suicide. Whereas normal persons are sometimes depressed and sometimes elated, the person with an endogenous depression has a fixity or persistence of mood; he may, however, undergo swings to hyperactive states with manic reactions. The course of the disorder usually is self-limited but we have good evidence to support the conclusion that psychoactive drugs shorten the depressive episodes.

Drug Therapy of Endogenous Depression

In the treatment of endogenous depression, electroshock acts most rapidly and may be lifesaving for the patient with suicidal tendencies. Because electroshock is distasteful to patients, drugs have assumed a dominant position in therapy. The drugs of the imipramine group include amitriptyline (ELAVIL®) (figure 4), desimipramine (PERTOFANE®), nortriptyline (AVENTYL®) and protriptyline (VIVACTIL®). When drug therapy is successful, the depression usually is lifted in one to two weeks. Improvement may be evident as early as the third day or may be delayed until the end of the third week. During this period the patient should be hospitalized to prevent suicide.

Side reactions to these antidepressant drugs are moderate in degree and include orthostatic hypotension, sweating, dryness of the mouth, and blurring of the vision. Imipramine is usually given in an initial dosage of 25 mg. three times a day (after meals). The maximum dosage of imipramine is 200 mg. a day; larger dosages cause noticeable side reactions. Amitriptyline imposes some sedation. The dosage of amitriptyline is 40 to 150 mg. a day. It is safe to give these drugs in combination either with another antidepressant of the same group or with a phenothiazine. For example, if a patient receiving imipramine has insomnia, amitriptyline may be substituted as the evening medication. When anxiety is difficult to control with an antidepressant alone, a phenothiazine may be added.

It is encouraging to observe improvement in a patient following the institution of drug therapy for endogenous depression, but this is not a sign to stop the medication. In fact, a patient with psychomotor retardation is more likely to commit suicide when the depression begins to lift and he becomes more energetic. Drug therapy should be continued for some time after maximum benefit has been achieved. Then it should be withdrawn cautiously and the patient observed closely to determine whether or not improvement is maintained. Supportive psychotherapy is necessary throughout the course of the disorder. The depressed patient has great need for continuous reassurance.

Therapy of Atypical Depression

In an atypical depression the sad reaction is secondary in importance to the more prominent anxiety and hysterical features. Usually neither electroshock nor the imipramine group of drugs is as beneficial as the MAOI class of drugs.[17] The depressed patient who will benefit from therapy with the MAOI drugs may be described as one who has a good personality, is kind and conscientious,

and exhibits neither the psychomotor retardation nor the agitated indecision of the patient with endogenous depressive illness. Unlike those with endogenous depressions, these patients blame others rather than themselves for their predicament. They are overconscientious and sensitive, and for long periods they complain of vague and variable depression, increased emotionality and anxiety. Fatigue is a prominent and disabling symptom.

The enzyme monoamine oxidase facilitates the oxidation of serotonin and norepinephrine, neurohormones present in the brain and elsewhere. Therapeutic doses of the MAOI drugs prevent the oxidation of these neurohormones and cause their accumulation in the brain.[18]

The dosage range of nialamide (NIAMID®) for treatment of the depressed patient is 100 to 300 mg. per day. Taking this dosage as unity, the corresponding dosages of phenelzine (NARDIL®) and isocarboxazid (MARPLAN®) are 1/4 and 1/10. It is safe to use the drugs of the MAOI group in combination or interchangeably but it is dangerous to give a drug of the imipramine group simultaneously. Such combinations may produce dizziness, tremulousness, psychomotor excitement, convulsions and even death. If an MAOI drug is given first and found to be inadequate, a drug of the imipramine type may be added with complete safety after a week has elapsed. If an imipramine drug is used first, an interval of only one day is sufficient. The discerning physician will use an imipramine drug first and will add an MAOI drug only if the first agent is unsuccessful. Despite the characterization of different drugs for each of these types of depression (endogenous, atypical), the differential diagnosis is not always clear.

Unfortunately the MAOI group exhibits many side effects,[19] which include dizziness, blurred vision, gastrointestinal disorders, delayed micturition, altered erotic desires, edema, sweating, muscle tremor, dermatitis and insomnia. Orthostatic hypotension is a relatively frequent occurrence, and rarely a paradoxical hypertensive episode is seen. These drugs are cumulative in action. Side effects may persist for several days after they are withdrawn. Untoward reactions are more severe in older than in younger patients and are more frequent in women than in men. As an additional disadvantage, the MAOI drugs may potentiate the actions of amphetamine, tranquilizers, opiates, atropine derivatives, ganglionic blocking agents, corticosteroids, antirheumatic compounds, anesthetic agents, hypnotics and alcohol. Nevertheless they are employed successfully both in hospital situations and in private practice and have provided immeasurable benefits for many patients with atypical depressions.

Applications of Psychoactive Drugs in the Field of Child Psychiatry

The effects of psychoactive drugs in children are similar in many respects to those in adults, but striking differences are being recognized. The actions of phenothiazines and antidepressants are similar in both age groups. On the other hand, new uses have been found for reserpine, amphetamine, methylphenidate (RITALIN®) and diphenhydramine (BENADRYL®) in disorders characteristic of the earlier years of life. A surprising response to LSD-25 has been reported. Children with psychiatric disorders, like their adult counterparts, require an integrated therapeutic approach consisting of familial, social, psychologic and psychopharmacologic aspects. The disturbed child is often the expression of a disturbed family complex.

Phenothiazines in schizophrenia—The phenothiazines occupy a prime position in the management of schizophrenic children. The remarks made earlier in regard to treatment of this disease in adults are generally applicable. Fish,[20] studying 28 schizophrenic children, found that those who had an I.Q. lower than 70 and were withdrawn and apathetic responded better to prochlorperazine and perphenazine than to chlorpro-

mazine but responded best to trifluoperazine. Chlorpromazine was too depressing for the apathetic group but was helpful in the treatment of hyperactive children with an I.Q. lower than 70. The average daily dosage of chlorpromazine is 2 mg. per kilogram of body weight. Taking this dosage as unity, comparative dosages of other phenothiazines are as follows: prochlorperazine, 1/10; perphenazine, approximately 1/35; trifluoperazine, 1/100. These ratios reflect a much steeper rise in potency than the respective figures for adults, which are 1/5, 1/12 and 1/20.

Side reactions to phenothiazines are generally the same in children but occur less frequently than in adults,[21] except for extrapyramidal disturbances. In Ayd's[12] series the youngest patients with dyskinesia, akathisia and parkinsonism were 4, 12 and 18 years of age, respectively.

Other severe disturbances—Chlorpromazine can be beneficial to the emotionally maladjusted child who is acutely disturbed and exhibits chronic acting-out behavior. He will become calmer, more cooperative and communicative, and rapport with the therapist can be established.[22] Children with primary brain disorders due to environmental changes and emotional difficulties in the developmental process as well as conflicts of various kinds respond well to prochlorperazine, perphenazine, chlorpromazine and trifluoperazine. It is difficult to predict which patient will respond to a particular phenothiazine derivative.[20] If one fails, another is likely to succeed.

Another prominent problem in pediatric psychiatry is the hyperactive brain-injured child. Drugs are necessary to prevent such a child from injuring himself and others as well as to limit his destructiveness. Chlorpromazine should be used first, but the other phenothiazines have also brought improvement. If reasonably large doses of phenothiazine fail to suppress the ceaseless activity, the addition of reserpine is helpful. Reserpine is effective in the management of the overactive autistic child, but its greatest usefulness in the field of child psychiatry lies in management of the nonpsychotic (but mentally disturbed) hyperactive brain-injured child. It is especially useful for institutionalized children. Self-abuse, aggressive behavior, and property damage have diminished when reserpine has been employed in these cases. Behavior improves, but intellectual capacity and I.Q. are unaffected. For an infant, 0.1 mg. of reserpine may be given three times a day initially, this amount being increased or decreased according to the severity of the symptoms.[23] For an older child the dosage is 1 to 4 mg. per kilogram of body weight.

Antidepressants—The antidepressants promise to be helpful in the treatment of withdrawn, depressed adolescents as well as autistic children. Imipramine is effective in making young patients more alert, in facilitating attempts to speak, and in helping them relate to their environment. Phenelzine and nialamide also have proved useful. The dosage of any of these antidepressant drugs is 75 to 100 mg. per day given in two or three divided doses. Small children should receive smaller initial dosages, to avoid excessive excitement.

Amphetamine—Amphetamine evokes beneficial alterations in emotional reactions to distressing situations and is chiefly effective in behavior disorders in children, especially in more mature children. It helps to reduce the apathy and to allay the fantasies and fears that accompany the phobias and hypochondriacal symptoms at this age. Fear, depression, sexual tension and hyperkinesia are alleviated. The average dosage is 0.2 mg. per kilogram of body weight per day.[20]

Methylphenidate for hyperkinesia—Knobel[24] and co-workers studied the effects of methylphenidate in a large number of pa-

tients with the syndrome of hyperkinesia, with clinical features including low tolerance for frustration, aggressiveness, impulsiveness, poor school performance, and hostility. Hyperactivity and aggressiveness decreased in 82 per cent. The average dosage was 20 to 40 mg. per day. The drug was given with breakfast and lunch to minimize insomnia.

Diphenhydramine—Diphenhydramine is particularly useful in children with behavior disorders and moderate anxiety who exhibit unorganized motor activity and immature behavior. In such children with primary brain disorders, diphenhydramine reduces anxiety and hypermotility and increases the attention span. The drug is of little value in organic brain disorders. Side reactions are insignificant, consisting chiefly of fatigue and irritability. The average dosage employed by Fish[20] was 4 mg. per kilogram of body weight per day. Diphenhydramine is an effective drug for the treatment of mental disorders only in children under 10 years of age. When it is given to older children or adults it acts simply as a sedative.

LSD-25 in schizophrenia—Bender, Faretra and Cobrinik[25] reported a surprising response to LSD-25. A group of 45 hospitalized schizophrenic children under 12 years of age received LSD-25 or methysergide maleate (SANSERT®) for 14 months. About half the children were autistic, regressed and essentially nonverbal; the others were psychotic but verbal and alert. The salutary response to LSD-25, which is hallucinogenic in adults, included an increase of contact, awareness of the environment, and improved ability to understand directions and language. A remarkable feature was the absence of side effects.[26, 27] The initial dosage of LSD-25, 50 mcg. per day, was increased gradually to 150 mcg., given in two divided doses. Dosage of methysergide maleate was 4 to 12 mcg. in two divided doses.

Management of the Neuroses

It is easy to find statistical evidence of the value of psychoactive drugs in the psychoses. Placebos are greatly inferior to the tranquilizers in schizophrenia.[28] It can be anticipated that most patients with grave neuroses and deep-seated disturbances will be helped by drugs. In psychoneurotic patients, improvement was maintained for an average of four months by administration of a placebo and for two and one-half years by administration of chlorpromazine.[28] In the milder neuroses the placebo effect is much more pronounced, but even a mild tranquilizer such as meprobamate will maintain improvement far longer than a placebo.[29]

Tranquilizers—Patients with grave neuroses should be given the same drugs as psychotic patients, and sometimes in larger doses.[28] For the milder forms of neurosis we have the minor tranquilizers: chlordiazepoxide (LIBRIUM®), meprobamate (MILTOWN®, EQUANIL®) and hydroxyzine (ATARAX®, VISTARIL®). In general the major tranquilizers combat grave symptoms more effectively but also exhibit the most severe side reactions. Chlordiazepoxide is the most active of the minor tranquilizers and at the same time produces the largest number of side effects. Hydroxyzine is the least potent and exhibits almost no side reactions.

Chlordiazepoxide not only relieves anxiety and tension and the psychosomatic manifestations of anxiety but also serves as an effective adjuvant to psychotherapy of neuroses, involutional reactions, and depressions of all kinds. Side reactions consist of drowsiness, ataxia, increase of appetite and weight, dizziness, and confusion. Loss of libido, menorrhagia, urinary frequency, and headache are rare. There is no intellectual impairment even when large doses are given, and extrapyramidal symptoms are notable by their absence. The usual dosage range is 30 to 400 mg. per day.

Meprobamate, which calms the tense, nervous or emotionally depressed patients seen so frequently in general practice, is also used to allay anxiety in the exogenous or reactive depression. Side effects are uncommon, but drowsiness may occur, particularly early

in the treatment. Addiction is observed, however, although rarely (these patients frequently are addicted to other drugs as well). In a controlled study of the addictive potential of meprobamate, 47 patients were given an initial dosage of 3200 or 6400 mg. per day, an amount far greater than the recommended limit. Addictive changes were observed in 44 patients after the drug was abruptly withdrawn.[30] The recommended dosage range for patients with depression is 1200 to 2400 mg. per day.

Hydroxyzine is of value in overcoming the anxiety, tension and psychomotor agitation so frequently associated with psychoneuroses but is not recommended for use in psychoses or severe depressive states. It has a low order of toxicity. Even excessively large doses produce only a mild depression with stupor and vomiting. The recommended dosage range is 75 to 400 mg. per day.

The milder tranquilizers not only diminish tension and anxiety but also relieve insomnia. They aid the therapist by alleviating apathy and lack of drive and combating the depressive features. At present, outside the hospitals, one-third of all the prescriptions for psychoactive drugs are prescriptions for chlordiazepoxide; meprobamate prescriptions account for a slightly smaller proportion.

Psychic stimulants—For mild depressions attended by little or no anxiety, we have still another series of drugs, the stimulants. This group includes methylphenidate, pipradrol (MERATRAN®) and amphetamine; the latter is preferably used in combination with a barbiturate, as in DEXAMYL®. The stimulants exert a global effect involving all elements of behavior, desirable or otherwise. In addition to combating lethargy and psychomotor retardation, they increase anxiety and may produce motor restlessness. Their use in psychotic depressions is not recommended, since they may activate psychotic symptoms. In mild depressions they are useful either alone or in combination with a phenothiazine drug.

Roles of Chemotherapy and Psychotherapy in Mental Disorders

Drugs do not initiate behavior. Behavioral processes are initiated by the patient. Psychoactive drugs may, however, alter the intensity of these processes. This quantitative effect may be a decisive factor in the success of treatment. For example, in a neurotic patient with overwhelming anxiety, therapeutic progress may come to a standstill with psychotherapy alone. Adding a mild tranquilizer (chlordiazepoxide, meprobamate, hydroxyzine) may, by reducing anxiety, permit headway to be made again. Many psychoneurotic patients are better able to adapt to their environment when both chemotherapy and psychotherapy are given, and the duration of therapy may thereby be shortened.[31] To what extent each form of treatment is used must be decided for each patient. If drugs impair a patient's motivation, they should not be used at all. However, if conflicts are overpowering and well-nigh intolerable, the administration of a drug which will quickly reduce anxiety is a humane act. Drugs should not be given for extended periods in treatment of the neuroses. Rather they should be given temporarily to aid in overcoming an anxiety crisis and alleviating the disorganizing symptoms. The patient and his family should be fully apprised of the drug's action.

The psychoactive drugs exert specific antipsychotic actions which can directly counteract abnormal behavior and therefore are effective primary therapeutic agents in the psychoses. We do not have drugs which are specific for the neuroses. Therefore, psychotherapy is of primary importance and drugs occupy a secondary position in the management of neuroses, but their adjunctive role must not be underestimated.

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