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# ANTIPSYCHOTIC DRUGS

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# Antipsychotic Drugs

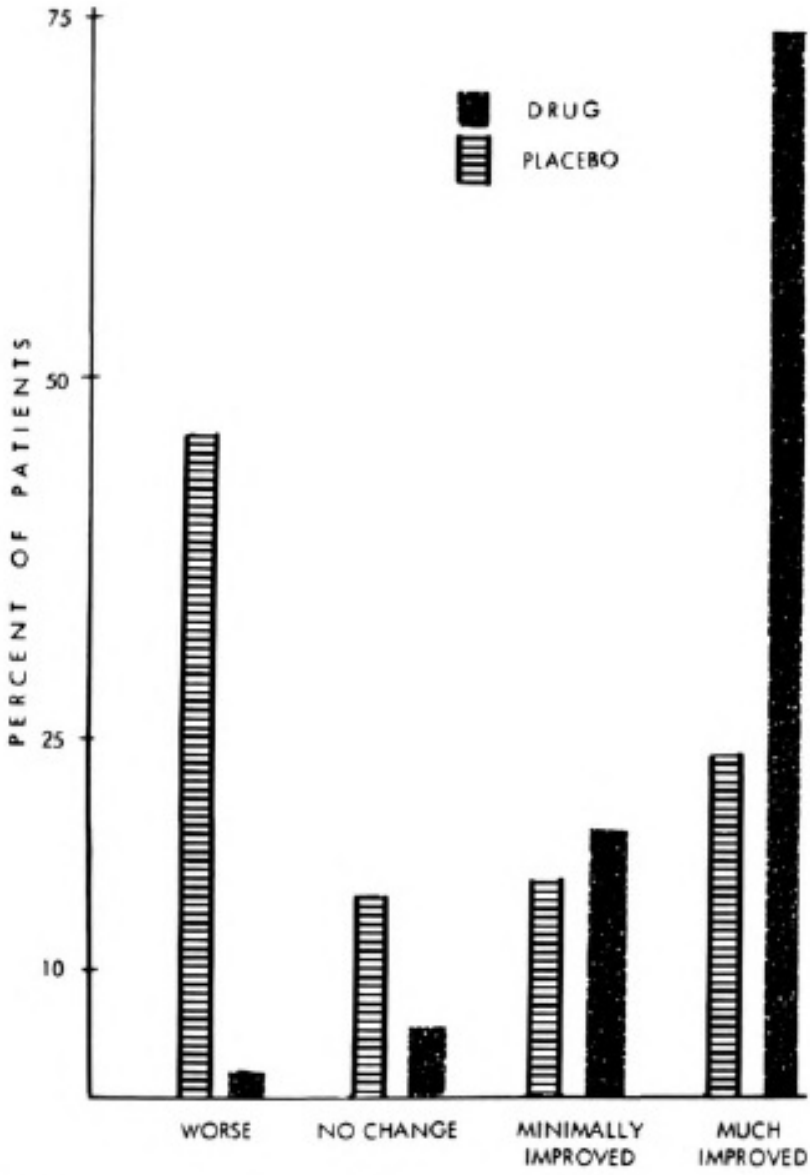
Modern clinical psychopharmacology was ushered in by the almost simultaneous discoveries that two chemically very different drugs were able to alter psychotic behavior in hospitalized psychiatric patients (Shepherd, 1968). The ultimately less important of the two drugs, reserpine, had been observed to have antianxiety effects in hypertensive patients and taming effects in the rhesus monkey. Furthermore, its source, the rauwolfia serpentina root had been used in Hindu native medicine for centuries as a treatment for insanity. Its initial trial on disturbed psychotics in 1952 was well controlled and showed that the active drug caused a statistically larger decrease in hours spent in restraint or seclusion than resulted from placebo treatment (Kline, 1954). The major defect in the design, in retrospect, was the failure of the investigators to establish the effective dose of reserpine before beginning the trial. At the dose used (1 mg. per day) the drug's effect might have been missed had not relatively large numbers of patients been employed in a quantitative experiment. Reserpine's discovery was, therefore, the outcome of a relatively methodical procedure of scientific investigation. Unfortunately, it proved to be slower acting and less effective than chlorpromazine, a drug discovered purely by chance, as have been all new classes of psychoactive drugs discovered since that time.

Chlorpromazine (CPZ) was, in fact, originally synthesized as an

antihistamine. Animal tests revealed it to be rather sedative. Pierre Laborit, a French anesthesiologist was looking for just such a drug to add to the pharmacological agents in his "lytic cocktail," an intravenous mixture with which he was trying to block the overresponse of the human body to surgical stress. He readily obtained it from the French firm which had synthesized it, and soon observed that CPZ produced a behavioral change which might most accurately be described as tranquilization. Soon thereafter, in 1952, two French psychiatrists, J. P. Delay and P. Deniker administered the drug to schizophrenic patients (Delay, 1952). Once again, the tranquilizing effects were observed but, in addition, there seemed to be a striking reduction of psychosis.

Since the discovery of these drugs and their antischizophrenic effects, psychiatric practice has been profoundly altered. For although the use of CPZ did not usually produce a permanent cure in the schizophrenic, It did produce major benefits in many patients, in a way no other treatment had ever accomplished (Figure 22-1 [Davis, 1969]). The news of Delay's and Deniker's clinical observations spread quickly and resulted in the wide use of CPZ on thousands of schizophrenic patients throughout the world (Childers, 1961; Elkes, 1954; Lehmann, 1965; Mitchell, 1956; Weckowicz, 1960).

*Figure 22-1.*


75
50
25
10
PERCENT OF PATIENTS
DRUG
PLACEBO
WORSE
NO CHANGE
MINIMALLY IMPROVED
MUCH IMPROVED

*Doctors' global rating of improvement in patients after treatment with phenothiazines or placebo.*

The discovery of CPZ heralded the beginning of a therapeutic revolution which extended far beyond the pharmacological actions of the drug (Davis, 1968). For the first time, public mental institutions could be regarded as true treatment centers, rather than as primarily custodial facilities. Since clinically significant therapeutic effects could be produced by this drug, an atmosphere was created in which other therapies, including milieu therapy, psychotherapy, group therapy, and occupational therapy could be applied simultaneously to patients who, prior to drug treatment, were too disturbed and required too much custodial supervision to be offered such treatments on any regular basis (Davis, 1968; Saretsky, 1966; Schiele, 1960; Michaux, 1972). Thus, the widespread use of these social therapies is possible, due to the control, through pharmacological agents, of the more disruptive and destructive aspects of the patient's illness. This has profoundly altered the fate of many patients who would have otherwise languished in the custodial wards of our mental institutions. In fact, some were so improved that they were discharged from the hospital and returned to their communities as functioning members. For other patients whose illness still required inpatient treatment, the hospital became more humane and tolerable. Today schizophrenic patients can often be treated effectively with antipsychotic

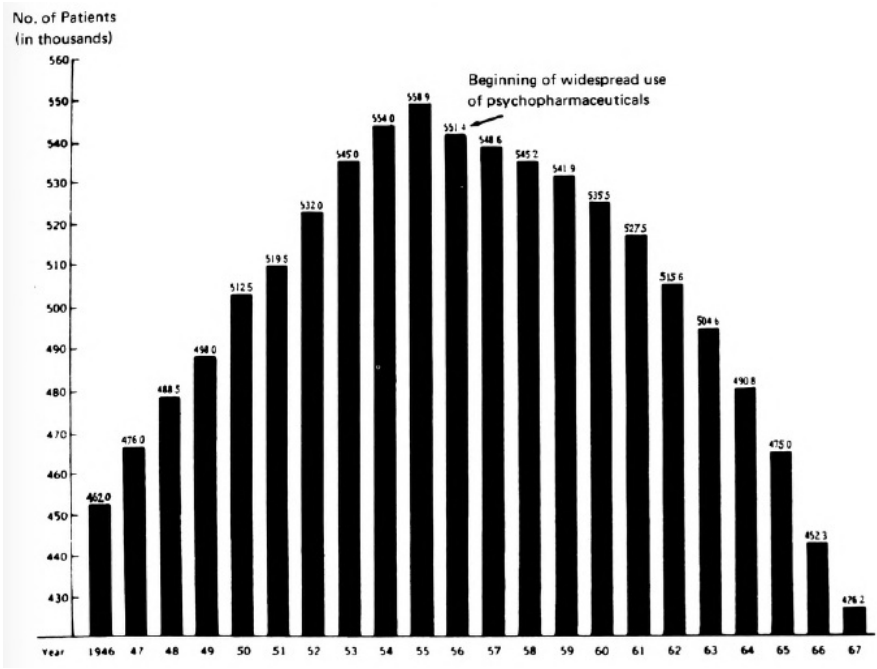
agents without ever being hospitalized. For patients who do need to be hospitalized for a first illness or for recurrent psychotic episodes, the duration of hospitalization is sometimes a few days or, at most, weeks (Cole, 1969; Davis, 1965; Moffat, 1964).

One result of this new therapy has been a major reduction in the number of hospitalized schizophrenic patients. This is an especially remarkable development, because, until the introduction of these new drugs, there had been a steady, large increase in the population of hospitalized mental patients (see Figure 22-2 [Davis, 1968]). This marked change in the fate of mental patients is, perhaps, the most convincing proof of the efficacy of these agents. Indeed, the improvement produced by CPZ and related drugs in schizophrenia is unlike anything produced by earlier somatic or psychotherapies; these drugs represent a major therapeutic breakthrough (Davis, 1968).

Skeptics raised the possibility that the improvement might be due to placebo effects, particularly since it was quickly evident that uncontrolled studies of CPZ gave systematically more positive results than controlled studies (Cole, 1966; Davis, 1965; Foulds, 1958; Fox, 1961; Moffat, 1964). Moreover, it was found that false positive findings with other CPZ-like drugs had been obtained—findings in which some drugs (e.g., mepazine) which were later found to be therapeutically ineffective were thought initially to be

effective because of favorable results obtained in early uncontrolled evaluation. In addition, false negative results also occurred, in which skeptical investigators found CPZ-like drugs to be ineffective when they were later proven to be effective. Results such as these led to considerable controversy in psychiatry as to the real efficacy of these agents. Some physicians, regarding these tranquilizers as merely fancy sedatives, had little use for them, or thought they might actually be harmful, whereas other doctors endorsed them without critical reservations. Well-controlled studies using adequate drug dosages, appropriate treatment periods and criteria of change have proved like drugs of the CPZ type to be highly effective. In conjunction with this we should point out that development of the methodology to carry out the controlled trials of these drugs was, in itself, an important advance in psychiatry.

*Figure 22-2.*




*Population of public mental hospitals in the United States, 1946-1967. Note the progressive decline in the number of patients beginning in 1956 corresponding to the widespread introduction of the phenothiazines, followed shortly thereafter by other psychoactive agents. Based on data from the United States Public Health Service.*

Heretofore, radically new treatment approaches in psychiatry within a wide range of modalities, e.g., psychoanalysis, insulin coma therapy, or behavior therapy, have generally been greeted with a mixture of popular enthusiasm and professional skepticism, or even outright and hostile rejection. New treatments were evaluated by a mixture of testimonials by

proponents and criticism by opponents. Such evaluations sometimes resembled religious controversies more than objective scientific assessments of efficacy.

However, during the past twenty years it has become standard practice in psychopharmacology to have drugs tested by controlled randomized double-blind trials in which the drug is compared to placebo or a standard comparison drug. This is reflected in the widespread use of this methodology, the funding of such studies by both drug companies and the National Institute of Mental Health, and the insistence on controlled studies by the Food and Drug Administration. Indeed, the practice of treatment evaluation in psychiatry has been profoundly altered. An increasing number of controlled studies of psychological and social therapies in psychiatry have been completed since the mid-1960s. The paradigm for treatment evaluation, particularly in psychopharmacology, has changed from testimonial to controlled trial. This is a consequence of the discovery of chlorpromazine. In our judgment, this new paradigm of the controlled clinical trial is itself a psychiatric advance of major significance.

In this context, the concept of placebo effect requires discussion. The placebo (or inert medication) is used in clinical drug studies to eliminate several phenomena, one or more of which might influence the outcome of a drug study. The patient might get better simply because he believes the pill

helps him. This is the conventional, narrow conception of the placebo effect. In addition, however, a placebo-treated group can be used to control spontaneous improvement as well as the effects of other treatments (e.g., milieu or psychotherapy) upon the patient's status. It can remove also or reduce the effects of observer bias, i.e., the expectation of the doctor or nurse that the drug *must* be helpful, leading to objectively unwarranted ratings of improvement. The other aspects of rigorous treatment evaluation are the random assignment of patients to treatments—so that all the good prognosis patients are not placed in the drug (or in the placebo) treated groups—and, the double-blind technique—whereby neither the elevators nor the patients know which patients are receiving the drug and which the placebo (Cole, 1966; Davis, 1965; Foulds, 1958; Fox, 1961; Moffat, 1964; Shepherd, 1968).

## General Considerations of Efficacy

Chlorpromazine and the other antipsychotic drugs have now been examined in hundreds of double-blind studies, the results of which are summarized in Table 22-1. The vast majority of these studies indicate, as the table clearly shows, that antipsychotics are superior to placebo in the treatment of both acute and chronic schizophrenic patients. In some of the smaller studies, which failed to show a reliable drug-placebo difference, it becomes clear, on detailed evaluation that the dosage was too low for a demonstrable effect. Such results occurred most frequently in the earlier

studies of chlorpromazine. However, when adequate doses were administered, chlorpromazine was consistently shown to be superior to placebo, the magnitude of improvement being quite considerable. An NIMH study showed that approximately 75 percent of the phenothiazine-treated patients involved improved significantly under phenothiazine therapy; only 5 percent failed to be helped to some degree and only 2 percent worsened (Cole, 1964; Cole, 1966; Goldberg, 1965).[1] This is certainly in marked contrast to the placebo-treated group in which only one fourth of those involved showed moderate to marked improvement, while half of the group failed to improve or became worse (see Figure 22-1). In addition, this same study showed that new schizophrenic symptoms often emerged in the placebo-treated group, even when these patients were simultaneously receiving individual psychotherapy, group therapy, or other social therapies. This worsening was prevented by phenothiazines (Goldberg, 1965). Lehman (1965) has used the word "psychostatic" to describe the effects of the phenothiazines because they seem to prevent the emergence of new psychotic symptomatology as well as suppressing the preexisting symptom of schizophrenia.

In the average patient, most of the therapeutic gain occurs in the first six weeks of phenothiazine therapy, although further gains are made during the subsequent twelve to eighteen weeks as well (Cole, 1969; Cole, 1966; Davis, 1965). Individual differences do occur, with some patients showing a very

rapid improvement in a single day or a few weeks, and some patients exhibiting a very gradual rate of improvement over several months. The course of improvement for the average patient is illustrated in Figure 22-3.

*Table 22-1. The Comparative Efficacy of Antipsychotic Drugs*

| | PERCENTAGE OF STUDIES IN WHICH DRUG WAS | | | | |
|---|---|---|---|---|---|
| DRUG | MORE EFFECTIVE THAN PLACEBO | EQUAL TO PLACEBO | MORE EFFECTIVE THAN CHLORPROMAZINE | EQUAL TO CHLORPROMAZINE | LESS EF THAN CHLORP |
| Chlorpromazine | 82.00% | 17% (66)* | — | — | — |
| Acetophenazine | — | — | O. | 100.0 ( 1 ) | 0.0 |
| Butaperazine | 100.0 | 0.0 (4) | 0.0 | 100. (2) | 0 |
| Carphenazine | 100.0 | 0(2) | 0. | 100.0 ( 2 ) | 0. |
| Fluphenazine | 100.0 | 0(15) | 0.0 | 100.0 (9) | 0.0 |
| Mepazine | 40 | 60(5) | 0.0 | 0.0 (4) | 100.0 |
| Mesorizadine | 100.0 | 0(3) | 0. | 100. (7) | 0. |
| Perphenazine | 100.0 | 0.0 (5) | 0.0 | 100.0 (6) | 0.0 |
| Piperacetazine | — | — | 0 | 100.0 (3) | 0. |
| Prochlorperazine | 77.8 | 22.2 (9) | 0.0 | 100.0 (10) | 0.0 |
| Promazine | 43 | 57 (7) | 0.0 | 33.3 (6) | 66.7 |
| Thiopropazate | — | — | 0. | 100.0 (1) | 0. |
| Thioridazine | 100.0 | 0.0 (7) | 0.0 | 100.0 (12) | 0.0 |
| Trifluoperazine | 88.9 | 11.1(18) | 0.0 | 100.0 (11) | 0.0 |
| Triflupromazine | 90.0 | 10.0 (10) | 0.0 | 100.0 (10) | 0.0 |

| | | | | | |
|---|---|---|---|---|---|
| Chlorprothixene | 100.0 | 0.0 (4) | 0 | 100. (6) | 0 |
| Thiothixene | 100.0 | 0.0 (2) | 0 | 100. (4) | 0 |
| Haloperidol | 100.0 | 0.0 (9) | 0 | 100. (3) | 0 |
| Phenobarbital | 0.0 | 100.0 (3) | 0 | 100. (6) | 0 |
| Reserpine | 69.0 | 31.0 (29) | — | — | — |

| | MORE EFFECTIVE THAN THIORIDAZINE | EQUAL TO THIORIDAZINE | LESS EFFECTIVE THAN THIORIDAZINE |
|---|---|---|---|
| Carphenazine | 0.0% | 100.0 (1) | 0.0 |
| Haloperidol | 0.0 | 100.0 ( 2 ) | 0.0 |
| Mesoridazine | 0.0 | 100.0 (2) | 0.0 |
| Piperacetazine | 0.0 | 100.0 (3) | 0.0 |

| | MORE EFFECTIVE THAN TRIFLUOPERAZINE | EQUAL TO TRIFLUOPERAZINE | LESS EFFECTIVE THAN TRIFLUOPERAZINE |
|---|---|---|---|
| Acetophenazine | 0.0% | 100.0 (1) | 0.0 |
| Butaperazine | 0.0 | 100.0 (3) | 0.0 |
| Carphenazine | 0.0 | 100.0 (3) | 0.0 |
| Chlorprothixene | 0.0 | 100.0 ( 1 ) | 0.0 |
| Haloperidol | 0.0 | 100.0 (4) | 0.0 |
| Mesoridazine | 0.0 | 100.0 ( 1 ) | 0.0 |

* The numbers in parentheses indicate the number of studies on which the percentages are based.

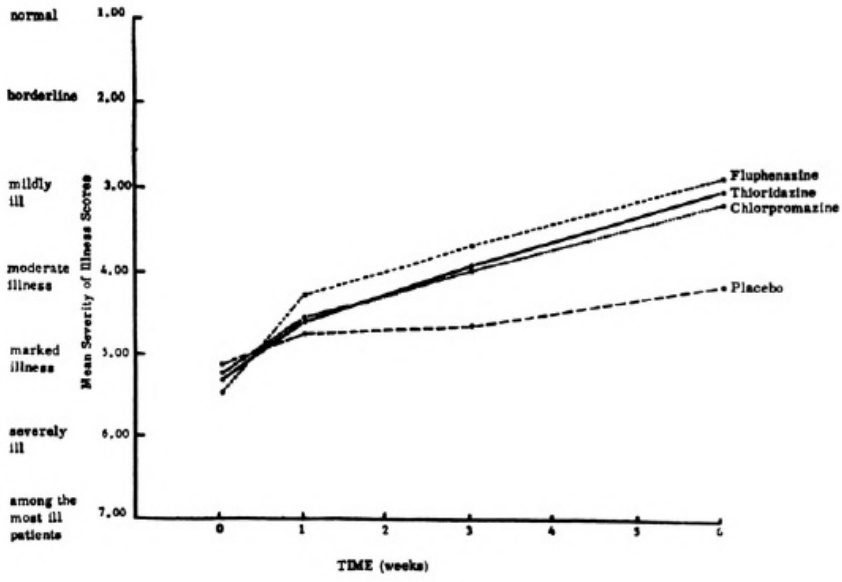
While it is important to know that the phenothiazines benefit

psychotics, it is equally important to know the quality and nature of this effect. This information, combined with an increased understanding of the etiology and pathogenesis of schizophrenia, should lead to a more rational pharmacotherapy of this illness.

The data available show that phenothiazine therapy brings about a cognitive restoration with a decrease in psychotic thinking, projection, suspiciousness, perplexity, and ideas of reference, as well as a normalization of psychomotor behavior in slowed and retarded, as well as hyperactive, patients (Cole, 1964; Cole, 1969; Cole, 1966; Goldberg, 1967; Goldberg, 1967; Killam, 1965; Simpson, 1972). Rating scales show a reduction of both the fundamental symptoms of schizophrenia (i.e., thought disorder, blunted affect, indifference, autistic withdrawal, psychotic behavior, and mannerisms) and in accessory symptoms (i.e., hallucinations, paranoid identification, hostility, belligerence, resistiveness, and uncooperativeness). Specific aspects of schizophrenic thought disorder, such as overinclusive thinking (as measured by categorizing tasks), and in bizarre, inappropriate responses have been shown to respond to these drugs (Gorham, 1961; Shimkunas, 1966). This is so particularly in process schizophrenia (Leff, 1971; Lehmann, 1965; Lehmann, 1954). Thus, the symptoms which are reduced by the phenothiazines are typical of schizophrenia in particular and psychosis in general, and, therefore, these agents are most correctly called "antischizophrenic" or "antipsychotic" drugs (Cole, 1964; Cole, 1969; Cole,

1966). They do not, in any real sense, produce a state of tranquility in either normal or psychotic individuals (DiMascio, 1963; DiMascio, 1963). The term "tranquilizer" is, therefore, inappropriate. Normal subjects usually dislike the effects of these drugs which tend to produce unpleasant sedation and fatigue.

*Figure 22-3.*




*Improvement over time of patients treated with phenothiazines, measured by the severity of illness scores. Data from NIMH-PSC Collaborative Study I.*

## Comparative Effects

The advent of chlorpromazine as a novel and effective antipsychotic

agent stimulated the search for better antipsychotic drugs with fewer side effects and, as a result, a number of new phenothiazine derivatives were synthesized. In addition, animal screening for chemically unrelated but pharmacologically similar drugs resulted in the development of a number of new classes of antipsychotic compounds. These include the thioxanthene derivatives, which are structural analogs of the phenothiazines, and the butyrophenones, a class of effective antipsychotic compounds with very different chemical structures (Lefave, 1967), as well as several other classes of currently experimental agents with antipsychotic properties. Inasmuch as we can now choose from a variety of drugs with antipsychotic properties, the question arises as to whether any of these drugs are better than chlorpromazine in treating the average schizophrenic patient or any particular schizophrenic symptoms, or any subtype. Furthermore, we must ask whether these agents all produce the same quality of improvement.

In response to these questions we can say that, with the exception of Promazine and mepazine, all the phenothiazine drugs are clearly superior to placebo. Controlled trials have shown that both mepazine and Promazine are clearly inferior to chlorpromazine (see Table 22-1) and, in addition, that all the other antipsychotic agents are equal to chlorpromazine in their therapeutic efficacy. There is considerable evidence, then, from many controlled studies that the antipsychotic drugs, excepting Promazine and mepazine are equal to chlorpromazine in therapeutic efficacy.

It would, of course, be possible for one drug to be slightly superior to another in several studies, while showing statistically significant difference in no single study. We therefore inspected all the original studies to see if, indeed, there were any trends. This inspection revealed that if a given antipsychotic compound were slightly better than another in one trial, it would be likely to be less effective in a second trial. There was no consistent trend for any drug to be superior to any other drug. Inspection of the changes of the symptoms of schizophrenia brought about by the various drugs revealed that all the antipsychotic compounds produced changes consistently on the same dimensions. We found the similarity of these results to be quite striking and supportive of the hypothesis that these drugs act through a common and specific mechanism of action. Differences exist between the drugs, of course, but these lie primarily in the nature of the side effects produced. For example, some may produce more sedation than others, but they all reduce psychotic retardation to a significant extent. In fact, even the most sedating agents reduce psychotic retardation and produce normalization which, in this context, means increased activity and apparent alertness. Similarly, even the least sedating of the drugs produces a calming of psychotic agitation, and does so to an extent equal to that of the most sedating member of this class (see Table 22-2). In summation, then, all the antipsychotic compounds exhibit this paradoxical effect through which they normalize patient behavior: psychomotor activity is *increased* in the retarded

patient but *reduced* in the agitated patient.

*Table 22.2 Comparison of Sedative Properties and Antipsychotic Activity*

| DRUG | SEDATIVE ACTION | ANTIPSYCHOTIC EFFECT |
|---|---|---|
| Chlorpromazine | + + | + + + + |
| Promethazine | + + | 0 |
| Phenobarbital | +++ + | 0 |
| Trifluoperazine | + - | +++ + |

Legend: + to + + + + indicate varying degrees of sedative or antipsychotic activity, with ++++ indicating the greatest and + indicating the least amount of activity. H indicates that the effect may or may not be sedating depending upon the circumstances.

All antipsychotic drugs being about equally efficacious, we now face the problem of individual differences among patients in attempting to choose the best drug for a given patient (Galbrecht, 1968; Goldberg, 1967; Goldberg, 1967; Klein, 1967; Klein, 1969). That is, can we predict how a given patient will react to a specific antipsychotic medication? Certainly, it could be argued, since the antipsychotic action of the drug is related to those features of the molecule which are shared by all the antipsychotics. There is no reason, therefore, to expect that a subtype of patient would respond better to a particular phenothiazine. Nevertheless, the possibility does exist that subtypes of patients may indeed respond better to a particular phenothiazine than to others, due to differential absorption, accumulation at neuronal receptor sites, or differences in the metabolism of one derivative or another.

It is further hypothesized that the patient's psychological response to side effects, such as sedation, could play a role in differential responsiveness. For example, there is some clinical evidence that a patient who uses activity as a defense mechanism may become quite alarmed if he is sedated and should do better on a nonsedating drug. In any case, determining whether a subtype of patient responds differentially to a given drug is a legitimate empirical question, but one which cannot be answered positively given the existing relevant clinical data.

A myth presently extant in psychiatry is that hyperexcitable patients respond best to chlorpromazine (Thorazine) because it is a sedating phenothiazine, while withdrawn patients respond best to an altering phenothiazine, such as fluphenazine (Prolixin) or trifluoperazine (Stelazine), but this has never been proven to be true (Goldberg, 1967). In fact, evidence from NIMH multihospital collaborative studies suggests that a second-order factor labelled "apathetic and retarded" predicts a differentially *good* response to chlorpromazine (Goldberg, 1972; Goldberg, 1967). Even though attempts to replicate this finding have failed, it is noted since the trend runs against the popular clinical impression of chlorpromazine's special properties. It is particularly important to remember, when evaluating predictive studies, that with many predictors, variables, and outcome measures, a statistical analysis of the data often yields statistically significant predictions by chance alone. It is therefore most important that results be

cross-validated before they be accepted as gospel truth. This statement is confirmed by the fact that most reported predictions in this field have failed to survive cross-validation. Specifically, several systems have been developed to predict which class of schizophrenic will respond best to which antipsychotic drug (Goldberg, 1972). But subsequently, studies which tested these empirically defined predictions have invalidated them. However, it should be noted that despite the absence of clear differential indications for one or another antipsychotic in a particular patient or class of patients, psychiatrists continue to observe clinically that patients who fail to respond to one phenothiazine occasionally do show a good response to another. Of course it is unwise to change antipsychotic drugs every few days. Certainly one must try to find the optimal dosage of a single drug and, having found said dosage, allow the drug a reasonable time to exert its behavioral effect. However, after a reasonable period of administration—perhaps a few days in a severely disturbed acute patient, a few weeks in a less dramatically impaired patient—a trial with a different antipsychotic agent is warranted.

The aim of drug treatment is to achieve the maximum therapeutic improvement in the patient. Thus, one must treat the whole patient, including the underlying disease process, and not merely a given symptom. This is particularly noteworthy when treating a depressed schizoaffective or retarded schizophrenic patient, for these patients often respond dramatically to antipsychotic drugs even though troublesome target symptoms, such as

agitation or aggression, are completely absent. Luckily, existing antipsychotic drugs tend to produce a generalized reduction in a broad range of schizophrenic psychopathologies rather than working only on a specific isolated target symptom. In sum, the therapeutic goal is for maximum cognitive reorganization and a lessening of the underlying schizophrenic process and, hence, of all symptoms.

## Dosage

Different patients respond to different dosage levels, hence there is no set dose for any given antipsychotic agent. Table 22-3 gives an idea of the clinical dose used in some of the better controlled studies, as well as the cost of the various antipsychotic medications. Columns 1 and 2 are based on empirical data drawn from double-blind studies, in which the different drugs were given in identical appearing tablets to samples of schizophrenic patients. From these results the number of mg. of a given neuroleptic that produces the same therapeutic response in comparison to 100 mg. of chlorpromazine can be calculated. Thus, in column 1 are the number of mg. of each drug equivalent to 100 mg. of chlorpromazine. These double-blind studies were generally based on severely ill hospitalized patients. The average dose of chlorpromazine was 734 mg. a day. In column 2 the average daily dose of all the neuroleptics are given. Thus, column 1 gives the equivalent dose to 100 mg. of chlorpromazine and column 2 gives the

equivalent daily dose of the various drugs. Since equivalent doses are known one can compute the cost of the drugs from retail pharmacy catalogs. This is expressed as the total cost for a typical patient of the average daily dose of the given drug in the largest possible tablet size. One could also think of it as the total cost of treating thirty patients for one day where the group receives the average daily dose.

*Table 22-3. Comparable Doses of Antipsychotic Drugs*

| GENETIC NAME | TRADE NAME | EMPIRICAL DEFINED DOSE IN MG. EQ. TO 100 MG. CHLORPROMAZINE | AVERAGE DAILY DOSE, MG. | AVERAGE COST FOR ONE MONTH AT ACUTE DOSE SCHEDULE |
|---|---|---|---|---|
| Chlorpromazine | Thorazine | 100 | 734 | $15.31 |
| Thioridazine | Mellaril | 97±7 | 712 | 37.29 |
| Mesoridazine | Serentil | 56 ±6 | 411 | 30.68 |
| Chlorprothixine | Taractan | 44 ± 8 | 322 | 18.03 |
| Trifluprom azine | Vesprin | 28 ± 2 | 206 | 38.71 |
| Carphenazine | Proketazine | 25 ± 2 | 184 | 20.55 |
| Acetophenazine | Tindal | 23 ± 1 | 169 | 23.34 |
| Prochlorperazine | Compazine | 14 ± 2 | 103 | 30.09 |
| Piperacetazine | Quide | 11 | 81 | 22.27 |
| Butaperazine | Repoise | 9±1 | 66 | 19.63 |
| Perphenazine | Trilafon | 9 ± 0.6 | 66 | 27.11 |
| Molindone | Moban | 6 ± 0.9 | 44 | 12.06 |
| Thiothizene | Navane | 4.4 ± 1 | 32 | 22.39 |

| | | | | |
|---|---|---|---|---|
| Trifluoperazine | Stelazine | 2.8 ± 0.4 | 21 | 16.91 |
| Haloperidol | Haldol | 1.6 ± 0.5 | 12 | 28.04 |
| Fluphenazine | Prolixin, 5 mg. | 1.2 ± 0.1 | 9 | 15.84 |
| Fluphenazine | Permitil, 10 mg. | 1.2 ± 0.1 | 9 | 6.92 |
| Fluphenazine | Prolixin Enanthate | 0.67 | | 20.91 |
| Fluphenazine | Prolixin Decanoate | 0.61 | | 18.24 |

It should be pointed out that these dose figures are averaged dose. For reasons explained in the text, one must adjust the dose to the individual patient. The average dose or the dose compared to 100 mg. chlorpromazine is as only a guide to the average dose. This should not be confused with maximal dose. It should also not be confused to suggest that the average dose is appropriate for every patient. With psychotropic drugs the average dose is just that and indeed is not appropriate for most patients, since a little less than half the patients require a slightly smaller dose and roughly half the patients require a slightly higher dose.

A number of points should be made about dosage regulation in the acute patient (Appleton, 1965; Goldman, 1958; Molcan, 1971; Parks, 1972; Simpson, 1968). There is a wide therapeutic range between effective dose and toxic overdose with the antipsychotic agents. In research studies, patients

have been safely treated with between ten and 100 times the recommended therapeutic dose. Although we do not advocate routinely treating patients with 100 times the dose recommended in the company brochure (e.g., 700 mg./day of perphenazine, or 1000 mg./day of fluphenazine), we wish to go on record as having stated that one can administer a substantially higher dosage of such agents than that recommended, without danger to the patient (Itil, 1966; Molcan, 1971; Simpson, 1968). Consequently, the physician should not be concerned about increasing the dose of an antipsychotic drug for good clinical reasons. Evidence for the efficacy of very high dose therapy will be discussed below.

Institution of antipsychotic drug therapy varies widely, in both manner and level, from one psychiatric setting to another. Generally, crisis-oriented facilities start drug therapy in the emergency room, using IM medication freely in turbulent or severely withdrawn patients. The dosage is rapidly increased over two or three days to a high level (perhaps 1200 mg./day of chlorpromazine), and reduced only after the patient is clearly much less aroused and agitated and is beginning to look quiet and even sleepy. In better staffed, more selective, private facilities, a more thoughtful drug free evaluation period of days or even weeks may precede a rather gradual initiation of drug therapy, with levels of 600 mg./day of chlorpromazine being much more common than levels of 1200 mg./day. However, there is really no reasonable evidence to indicate which regimen leads to a better longterm

remission, and regardless of the procedure, the goals of therapy remain unchanged, i.e., reduction of overt psychotic symptoms and gradual cognitive reorganization. However, it should be recognized that the dosage level attainable is sometimes limited by the side effects and may necessitate shifting to another drug.

The most common side effects concomitant with administration of antipsychotic drugs are sedation and extrapyramidal symptoms. However, the appearance of these effects does not usually necessitate shifting to another drug.

The patients generally develop tolerance to the sedative properties so that this side effect disappears after a few days or weeks. Persistent sedation can be handled by dosage reduction or giving most of the drug at bedtime. But neurological side effects present a bigger problem. Generally it is clinically necessary to treat the psychosis with phenothiazines so that one controls the extrapyramidal side effects by antiparkinsonian medication. When there is a question as to whether one needs such a high dose of antipsychotic medication, one can control the extrapyramidal side effects by dosage reduction.

In general, clinicians gradually reduce the dosage of the antipsychotic drug once the patient appears maximally improved, raising the dose again if

the symptoms recur. In addition, the dosage is often elevated prophylactically when the patient is about to undergo a special stress, such as returning home or starting a new job.

There are some practical matters relevant to dosage which deserve special attention. The antipsychotic effect of the phenothiazines is of relatively long duration, on the order of days rather than hours, while the sedative effect generally lasts only a few hours. For this reason the common medical practice of administering medication three times a day may leave the patient over sedated when he should be working, learning, or participating in psychotherapies. The same total dose given at bedtime may well promote better sleep while leaving the patient calm, though not sedated, during the day.

Another argument in favor of once-a-day dosage is that the cost of these drugs is not a function of dose, a 25-mg. chlorpromazine tablet costing almost as much as a 100-mg. tablet (see Table 22-4).

There are substantial differences in the cost per mg. of the various drugs depending on the size of the tablet or capsule which was prescribed. For example, if a physician prescribed twenty xo-mg. tablets of Thorazine a day to one patient, it would cost the patient essentially ten times as much (or 1060 percent) as the same amount in one 200 mg. tablet (100 percent) would cost.

Similarly, if one prescribed a patient one 200-mg tablet of Thorazine at bedtime vs. 25 mg. chlorpromazine tablets (two tablets four times a day) it would cost the patients five times as much (or 500 percent). Table 22-4 gives the comparative cost figures for different tablet or capsule sizes of the various neuroleptics. The largest tablet size marketed is given the arbitrary rating of 100 percent and the percent figure of the other tablet sizes are calculated. It should be pointed out that different pharmacies have different pricing policies. Just as auto dealerships in different parts of the country might sell cars at slightly different average prices, so different pharmacies might sell the same drug at slightly different prices. The information given in Table 22-4 is from a general pricelist and is only an approximation of what a given pharmacy may charge.

Thus, giving the largest available indicated dosage form once a day will save considerable money over a long time, substantially reducing nursing time and cost to the hospital. For patients in aftercare, a bedtime or evening dose, once it becomes routine, should be harder to forget and easier for the family to monitor, than a three-times-a-day regimen. Finally, although spansules or other delayed-release oral forms are available for some of the phenothiazines, there is no evidence that these more expensive formulations have any advantage over the standard tablet preparations.

*Table 22-4. Cost per mg. for Different Tablet Size in Percent of Cost of Most*

*Inexpensive Tablet Size*

| TABLET SIZE | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 200 | 100 | 50 | 25 | 16 | 125 | 10 | 8 | 5 | 4 | 25 | 2 |
| Chlorpromazine | 100 | 180 | 300 | 500 | | | 1060 | | | | | |
| Trifluprомazine | | | 100 | 150 | | | 250 | | | | | |
| Thioridazine | 100 | 138 | 231 | 415 | | | 762 | | | | | |
| Prochlorperazine | | | | 100 | | | 210 | | 323 | | | |
| Perphenazine | | | | | 100 | | | 149 | | 246 | | 35 |
| Fluphenazine | | | | | | | | | 100 | | 154 | |
| Trifluoperazine | | | | | | | 100 | | 153 | | | 35 |
| Carphenazine | | 100 | 165 | | 277 | | | | | | | |
| Butaperazine | | | | 100 | | | 197 | | 310 | | | |
| Mesoridazine | | 100 | 167 | 289 | | | 545 | | | | | |
| Piperacetazine | | | 100 | | | 167 | | | | | | |
| Haloperidol | | | | | | | | | 100 | | | 17 |
| Chlorprothixene | | 100 | 165 | 271 | | | 494 | | | | | |
| Thiothixene | | | | | | | 100 | | 151 | | | |

## Chlorpromazine Blood Levels

As mentioned previously, different patients respond to widely different dosage levels, as illustrated in Table 22-5 which condenses studies of the effectiveness of chlorpromazine at different dose levels. In practice, one sees patients who do not respond to a low or moderate dose but who do respond

to a high dosage and, conversely, one sees patients who respond quite well to very low doses but who do poorly on moderate doses. Some degree of understanding of this phenomenon may be derived from studies relating blood chlorpromazine to therapeutic improvement and side effects (Berman, 1971; Curry, 1970; Curry, 1970; Curry, 1971; Curry, 1972; Curry, 1972; Curry, 1970; Curry, 1971; Curry, 1972; Curry, 1968; Curry, 1970; Gram, 1972; Gram, 1972; Hollister, 1971; Kupfer, 1971; Lewis, 1971). Patients exhibit wide differences in blood chlorpromazine levels with comparable doses of the drug (Curry, 1971). Some patients receiving a moderate dose are found to have an extremely high level of blood chlorpromazine and to be excessively sedated; with reduction of the dosage the patient improves remarkably (Curry, 1971; Curry, 1972; Curry, 1970; Curry, 1968). Such a patient may have a metabolic deficit and consequently built up a psycho-toxically high level of blood chlorpromazine. Quite in contrast to this are the patients who exhibit extremely low blood levels, even on very high doses (Curry, 1968; Curry, 1972; Curry, 1970). Such patients may metabolize chlorpromazine so rapidly that even with very high doses, adequate amounts of chlorpromazine do not reach the brain. Preliminary evidence suggests that antiparkinsonian administration may lower blood CPZ levels.

*Table 22-5. The Effectiveness of Different Dose Levels of Chlorpromazine*

| | PERCENT OF STUDIES IN WHICH CHLORPROMAZINE WAS | | |
|---|---|---|---|
| DOSE MG./DAY | MORE EFFECTIVE THAN PLACEBO | SLIGHTLY MORE EFFECTIVE THAN PLACEBO | EQUAL TO PLACEBO |

| | | | |
|---|---|---|---|
| 300 or less | 42 | 23 | 35 |
| 301-400 | 50 | 38 | 13 |
| 401-500 | 80 | 0 | 20 |
| 501-800 | 100 | 0 | 0 |
| 800 | 100 | 0 | 0 |

There are wide individual differences in the metabolism of other phenothiazines. Patients on the same dose may have a thirtyfold variation in serum butaperazine levels or a twentyfold variation in serum thioridazine levels. Curry and his co-workers found that chlorpromazine is metabolized to a significant extent in the gut. If an individual is a rapid metabolizer, he may metabolize CPZ too completely in the gut, with the result that the CPZ which reaches the blood is already an inactive metabolite and is excreted without effect (Curry, 1970). The patient who is a nonresponder and has low blood levels is shunting the active drug out through excessive metabolism in the gut. It would follow that these patients may respond to intramuscular medication such as depo fluphenazine.

Curry and Adamson (1972) screened chronic schizophrenic patients and found a number whose blood chlorpromazine levels were lower on oral dosage than on parenteral dosage. A significant number of these patients responded differentially and more favorably to fluphenazine enanthate (a

long-acting, parenterally administered phenothiazine), a finding which would be consistent with the above hypothesis (Curry, 1972; Curry, 1970). It may be that some patients never build up adequate blood levels of the drug due to excessive metabolism in the gut.

Curry has also shown that the property of chlorpromazine to produce central behavioral toxicity in hepatic coma is due to an enhanced response of the brain to the drug's sedative properties, rather than to an impairment of metabolism as reflected in chlorpromazine blood levels (Maxwell, 1972). For optimal results, empirical variation of dosage, routes of administration, and different types of antipsychotic agents should be tried. Unfortunately, however, methods for measuring blood levels of antipsychotic drugs remain technically complex, and it may be several years before it will be possible for psychiatrists to routinely check unresponsive patients to make sure that appropriate antipsychotic drug levels have been achieved.

## High-Dosage Phenothiazine Treatment

Some patients do not benefit significantly from any antipsychotic drug medication and therefore the question naturally arises as to whether abnormally high doses would have brought about a remission (Goldman, 1958; Schiele, 1959).

Two collaborative studies were performed by the NIMH in order to test

the efficacy of "mega" dose strategy (Prien, 1968; Prien, 1969). In both studies chronically hospitalized patients were used. In one study the drug administered was chlorpromazine (2000 mg./day), in the other study the drug of choice was trifluoperazine (70 mg./day). Both studies compared the drug to normal dose and to placebo. Results showed that while the younger, more acute patients seemed to improve with the higher dose, the older, chronic "burned-out" schizophrenics exhibited no benefit from the "mega" dose. Led by these results, Clark et al. (Clark, 1972; Clark, 1972) reexamined data from dose-response studies of maintenance treatment in chronic schizophrenics. Subsequent to a drug free washout period chlorpromazine was administered to patients in doses of 150, 300, or 600 mg./day. The result of this study was that while younger subacute patients responded best to 600 mg./day the older chronic patients (more than forty years old, hospitalized more than ten years) exhibited no improvement beyond that achieved with a 300 mg./day dose. Of course, one must note that in these, as in any statistical study, one is looking at a mean or average effect. Therefore, it is quite possible that some individual patients in the older, more chronic group may have responded to massive doses of the drug and, conversely, that some of the semi acute patients would have been better off with lower doses. Controlled studies give a good indication of how the majority of the patients respond. However, in treating individual patients one must adjust the dosage within these general guidelines, to achieve optimal effect (Itil, 1966; Rifkin, 1971).

Several groups (Itil, 1966) have performed exploratory studies using massive doses of fluphenazine, 300-1200 mg./day. These groups found that chronic as well as acute schizophrenics resistant to treatment exhibited a good to excellent response. Moreover, they found that while the predominant side effects at low doses were extrapyramidal, the predominant side effect at the higher doses was sedation. The Hillside group performed a double-blind study comparing fluphenazine at 30 mg./day to fluphenazine at 1200 mg./day (personal communication). They found little difference in therapeutic outcome between the two groups. Of course, one must differentiate between the use of moderately high doses, such as double the normal dose used by Prien and Cole (Prien, 1968), and the "mega" dose strategy used by Rifkin and his co-workers (Rifkin, 1971), which was sixty times the normal dose. Nevertheless, the controlled study noted above would tend to caution against undue optimism that mega dose antipsychotic drug treatment will cure many drug-resistant schizophrenic patients. However, since patients can receive mega doses of drugs such as fluphenazine without undue toxicity, it would seem that there need be little worry about administering doses which are moderately higher than recommended. In our view, treatment-resistant patients deserve a trial on moderately high-dose treatment. Perhaps, in selective cases mega dose treatment might be indicated on an experimental basis. However, because of the larger clinical literature on the use of mega dose fluphenazine therapy, it seems reasonable

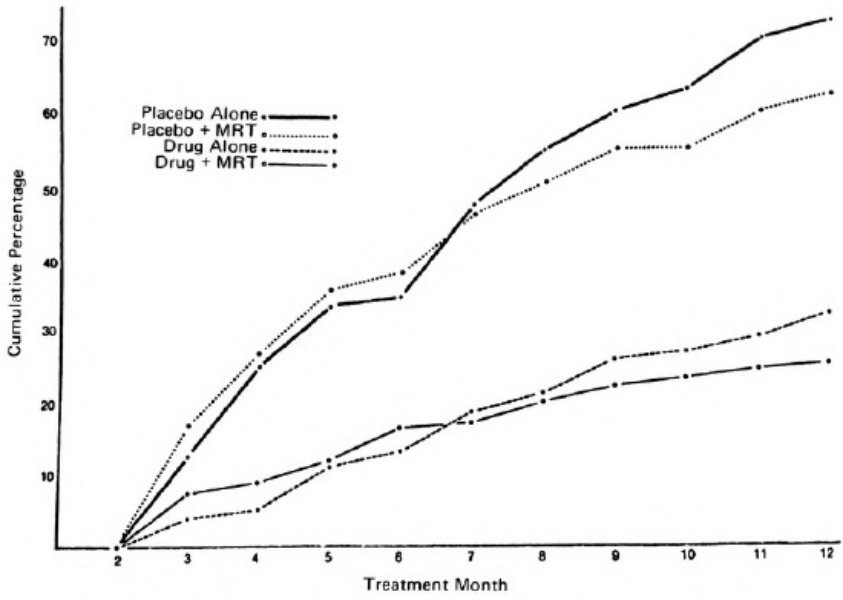
to consider this drug when high-dosage treatment is to be attempted (Ayd, 1959; Ayd, 1972).

## Maintenance Treatment with Antipsychotic Medication

Once the patient has exhibited substantial improvement with pharmacotherapy the question arises as to how long he should be maintained on antipsychotic drugs (Caffey, 1964; Caffey, 1962, Diamond, 1960; Engelhardt, 1960; Engelhardt, 1960; Engelhardt, 1963; Engelhardt, 1964; Engelhardt, 1963; Engelhardt, 1967; Gross, 1960; Gwynne, 1962; Hogarty, 1973; Leff, 1971; Marjerrison, 1964; Mitchell, 1956; Rothstein, 1960; Rothstein, 1962; Whittaker, 1963). To the best of our knowledge, every properly controlled double-blind study (with twenty-four countries reporting such studies) has shown that significantly more patients relapsed on placebo than on continued pharmacotherapy (Leff, 1971). This is a consistent finding in double-blind studies on a variety of populations, in the United States, Canada, and Great Britain. For example, Leff and Wing (Leff, 1971) studied patients who recovered from an acute schizophrenic illness and found that of those randomly placed on placebo 83 percent relapsed, while only 33 percent relapsed who were maintained on drugs. Recently Hogarty and Goldberg (Hogarty, 1973) performed a particularly important study dealing with the problem of maintenance treatment. A group of 374 schizophrenics was discharged from state hospitals upon recovery and, after a stabilization

period on maintenance outpatient phenothiazine, half of these patients were assigned to maintenance chlorpromazine and half to placebo. Half of each group received psychotherapeutic sessions consisting of individual case work and vocational rehabilitation counseling. The results (see Figure 22-4) showed that 73 percent of the patients on placebo without psychotherapy and 63 percent on placebo plus psychotherapy had relapsed. In contrast, only 33 percent of the drug maintenance group relapsed and a "mere" 26 percent of the group on drug maintenance plus psychotherapy relapsed. Thus, this study exhibits a substantial drug-placebo difference, i.e., 31 percent of the drug treated group relapsed in comparison to 68 percent of the placebo group (Hogarty, 1973). Furthermore, if we eliminate from the drug-maintenance group those patients who had spontaneously stopped taking their drugs, the relapse rate for drug patients over twelvemonths drops to approximately 16 percent. In contrast, patients maintained on placebo generally relapse at an approximately linear rate. However, because individual patients showed few signs of schizophrenic symptomatology until their relapse occurred, at which time they abruptly became markedly more psychotic, the necessity of maintenance of phenothiazine for the prevention of otherwise rather unpredictable relapses is dramatically demonstrated.

*Figure 22-4.*




*Cumulative relapse rates. MRT indicates major role therapy.*

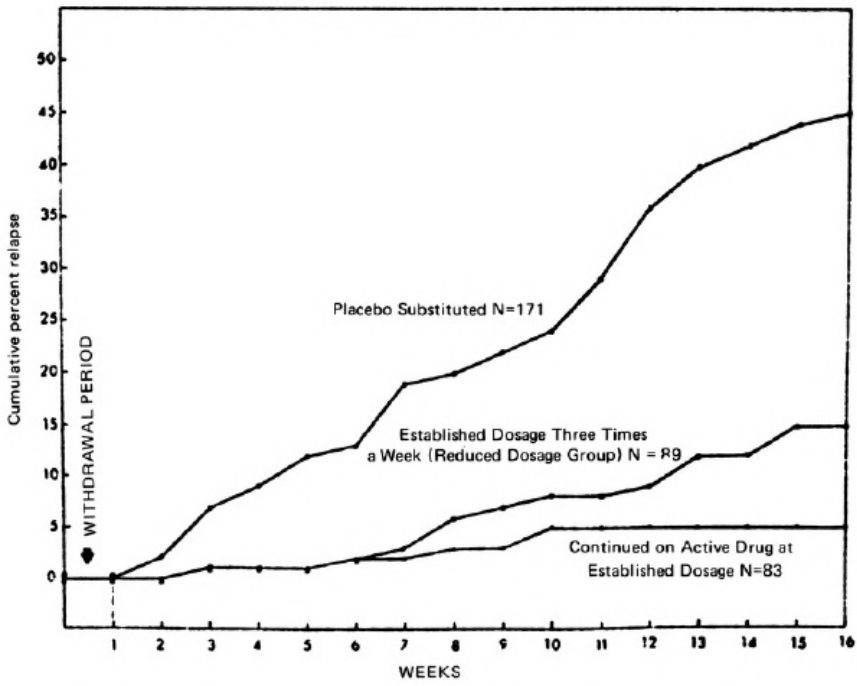
The Veterans Administration (VA) performed a major study on maintenance therapy. After sixteen weeks, 5 percent of the patients relapsed who were on drugs, and about 45 percent of the patients relapsed who were on placebo (see Figure 22-5 [Caffey, 1964; Caffey, 1962]).

Engelhardt and his collaborators (Engelhardt, 1965; Engelhardt, 1960; Engelhardt, 1960; Engelhardt, 1963; Engelhardt, 1964; Engelhardt, 1963; Engelhardt, 1967) performed an earlier major study of maintenance phenothiazine treatment of ambulatory schizophrenic outpatients. They

found that phenothiazines produced better adjustment in the community, lessened the number of relapses, and decreased the time spent in the hospital. Thus, although phenothiazines do not in any sense cure the patients, they do alter the course of the disease in a quantitative way. The result is a shortened hospitalization together with an improvement of behavior outside the hospital.

In all of the studies we have evaluated, treatment with phenothiazines did prevent some relapses. Of course, the number of relapses within a given time period varies with the sickness of the patient population studied, the sicker patients having a greater number of relapses within a time span than the less seriously ill. Thus, about 50 percent of a moderately ill population of chronic, hospitalized schizophrenics will relapse within six months after discontinuance of drug therapy. These data produce a rather ambiguous situation in the argument for phenothiazine maintenance. For, although 50 percent of these moderately ill patients do relapse, the corollary is equally true, namely, 50 percent do not relapse. Thus, half of this patient population are taking a drug they do not need. On the other hand, in regard to the 50 percent who do relapse, a relapse can often have a very serious impact on a patient and his family.

*Figure 22-5.*




*Cumulative percentage of clinical relapses during discontinuation study.*

It is our view that the decision to continue a patient on the drug for a long period of time should be arrived at clinically for each individual, based upon a knowledge of his illness and his life situation. In general, it is reasonable to continue most patients on phenothiazines for six months to one year after a psychotic episode. However, for longer periods, treatment should be individualized.

In practice, the decision to maintain or discontinue phenothiazine

treatment is based upon clinical common sense (Brooks, 1959; Gross, 1960; Leff, 1971; Rothstein, 1960; Rothstein, 1962; Simpson, 1965). A history of relapse following discontinuation of phenothiazines would be an indication for a longer period of maintenance, whereas evidence that phenothiazines may not have helped the patient originally, or that their discontinuation in the past has not led to relapse, would be indications for the gradual reduction of dosage leading to termination of drug treatment. Very chronic patients, such as patients who have been hospitalized continuously for fifteen years, are less likely to relapse than more acute patients. We would like to emphasize that psychotherapeutic and social interventions during the recovery phase and in posthospital care are very important in prompting improved social adjustment.

**Drug Holidays**

There are risks of long-term toxicity with the antipsychotic drugs, although the exact factors associated with any particular risk are rather obscure. Consequently it is reasonable to seek ways of maintaining a remission while using minimal amounts of antipsychotic drugs (Freeman, 1972; Gallant, 1964; Gross, 1960; Lewis, 1971). Drug holidays, which are one way of reducing dosage, have been studied chiefly by the VA in extensive studies of chronic inpatients (Caffey, 1964). The VA group has shown that drugs can be omitted on weekends or on an every-other-day basis, either

with no increase in the frequency of relapse or a very modest one. If omitting one or several days of drugs does not lead to relapse, it would certainly follow that once-a-day schedules would not lead to relapse. In addition, drug holidays may be useful on minimally staffed maintenance wards. Furthermore, there is considerable time saved on once-a-day medication, i.e., almost forty minutes of staff time per patient.

**Depo Intramuscular Medication**

There are a number of long-acting antipsychotic agents which are being studied at present; two are currently available in the United States for general use, fluphenazine enanthate and fluphenazine decanoate. These two intramuscular depo forms provide a very useful treatment approach for patients who do not take their oral medication and, on the basis of evidence presently available from double-blind studies, depo fluphenazine is as effective as oral fluphenazine. There have been clinical reports of patients who were particularly benefited by the depo medication in open trials. Although it is presumed that this benefit is due to the fact that these patients had failed to take their oral medication it is also reasonable to suppose that improvement occurred in part due to the IM administration, which bypasses gut metabolism. Therefore, the depo IM medication should be considered for patients who do not manifest optimal responses to oral medication or who, because of frequent relapses, are suspected of failing to take the medication.

Thus, the existence of the depo phenothiazines is an important addition to our therapeutic armamentarium, specifically for outpatients but also occasionally for inpatients. Finally, despite their propensity for inducing neurological side effects, depo fluphenazines can be very useful in emergency-room and home-treatment approaches to treating acutely psychotic patients in the community without resorting to inpatient admission (Bankier, 1973; Freeman, 1972; Svestka, 1972).

A new long-acting (one week) oral agent, penfluridol (Baro, 1972; Freeman, 1972), is in use in Europe (Tanghe, 1972).

## Antipsychotic Drugs and Somatic Therapies

The paucity of evidence supporting the efficacy of insulin-shock therapy and electro-convulsive therapy (ECT) in the treatment of schizophrenics has led to the use of phenothiazine and other antipsychotic drugs (Baker, 1958; Barker, 1959; Fink, 1958; Greenblatt, 1964; King, 1960; Langsley, 1959; May, 1968). In a controlled study of treatment efficacy Ackner and Oldham (Ackner, 1962) failed to find any beneficial effect with insulin shock. Other studies have shown that the effectiveness of ECT and insulin shock is certainly no greater than that of the phenothiazines. Furthermore, although some clinicians are of the opinion that ECT is helpful in the treatment of selected schizophrenics when given concurrently with phenothiazine

therapy, there has been no extensive investigation of this point (King, 1960; Langsley, 1959). However, Smith et al. (Smith, 1967) found in a controlled study that ECT may be helpful, and that ECT plus phenothiazine led to a more rapid remission than phenothiazine alone. More precisely, they found that the number of inpatient days during the year following hospitalization for the drug group was 159 days as compared to 102 days for the drug-ECT group. Two months after admission, 84 percent of the drug group remained inpatients compared to 48 percent of the ECT-drug group which remained hospitalized (Smith, 1967). In six months 40 percent of the drug group had not been discharged compared to 14 percent of the ECT-drug group. Until cross-validated appropriate caution should be applied in interpreting these results.

**Drug Combinations**

The therapeutic value of combining one phenothiazine with another has yet to be demonstrated experimentally. Of course, for any study of combinations to be valid it is important that all treatment groups have an equal amount of antipsychotic medication. Obviously, treatment of the combination group with double the amount of antipsychotic medication used in either of the single drug groups demonstrates only a dose-response relationship.

It is necessary to have answers for the following questions: Do combinations of antidepressants and phenothiazines help the depressed schizophrenic patient or the apathetic schizophrenic patient? Does a minor tranquilizer with anticonvulsive activity help a schizophrenic with suspected psychomotor epilepsy or one with episodes of violent behavior? A large VA collaborative study (Caffey, 1961; Casey, 1961) found. that the addition of imipramine, or a monoamine oxidase inhibitor, to chlorpromazine did *not* benefit chronic schizophrenics more than chlorpromazine alone. The addition of an amphetamine to chlorpromazine may have been slightly harmful.

The Spring Grove group (Kurland, 1966; Michaux, 1966) tested several combinations. Since sedation can be a target symptom and because one is adding a sedating minor tranquilizer to an antipsychotic one might actually undertreat with the antipsychotic medication to avoid excessive sedation (Kurland, 1966). Data from the Spring Grove group and other studies relating to combinations of tricyclic antidepressants with phenothiazines suggest that this mixture may benefit some schizo-affective depressed patients, as well as patients with catatonic-like symptoms (Michaux, 1966). However, the results are not uniform and the differences exhibited are small (Buffaloe, 1961; Hanlon, 1964; Janecek, 1963; Michaux, 1966; Schiele, 1960; Schiele, 1963). Thus, we strongly emphasize that a trial-and-error approach to obtain maximum benefit from a single drug or combination of drugs is indicated for the individual patients.

When working with drug combinations it is usually best to prescribe each medicine individually, until one obtains the optimal ratio. Certainly, if there exists a proprietary preparation which contains the optimal ratio, one might use it for convenience. However, one should not assume that all patients respond best to such a preparation.

## Drug, Psychological, and Social Treatments

Drug treatments have been much more thoroughly assessed than have psychotherapeutic methods. May (May, 1968) studied a group of newly hospitalized schizophrenics who were divided into four treatment groups: control, psychotherapy alone, phenothiazines alone, and psychotherapy plus phenothiazine. His results are presented in Table 22-6. In general, maximal improvement was produced by phenothiazines alone or by phenothiazines plus psychotherapy. Psychotherapy alone was decidedly worse than drug therapy alone. In another study performed at the Massachusetts Mental Health Center (MMHC) by Grinspoon et al (1968; 1972; 1963) a small group of chronically ill schizophrenic patients were treated by senior psychoanalysts. When placebo was substituted for thioridazine the behavior of these patients deteriorated, yet there was no evidence from this study that the drug therapy made the patients unresponsive to the psychoanalytically oriented psychotherapy. Rather the opposite was the case. When receiving phenothiazines the patients seemed more involved with their psychoanalysts,

indeed, they seem more involved with the outside world in general and more aware of events such as President Kennedy's death, the absence of the psychoanalysts or the ward physician during vacations, etc.

*Table 22-6. Comparison of Four Methods of Therapy of Acute Schizophrenia*

| TREATMENT | PERCENTAGE OF PATIENTS RELEASED IN STUDY PERIOD |
|---|---|
| Control | 65 |
| Psychotherapy alone | 70 |
| Drug alone | 90 |
| Drug and psychotherapy | 95 |

At Massachusetts Mental Health Center (MMHC) Greenblatt, et al. (Greenblatt, 1965) compared four variations in drug and social therapies. High social therapies were administered at the MMHC and consisted of a variety of psychotherapies, social work, occupational therapies, psychodrama, etc. The low social therapies were administered at a state hospital. Some of these chronic schizophrenic patients were transferred from a state hospital to the MMHC and were divided into two groups, one group receiving high social therapy with drugs and the other group receiving high social therapy without drugs. Those remaining at the state hospital were also divided into two groups and once again, one group received low social therapy with drugs and the other group received low social therapy without drugs. The results showed that both groups of patients who received drugs exhibited greater

improvement (drug plus high social therapy group 33 percent) (drug plus low social therapy 23 percent) than that observed in the nondrug groups in the state hospital milieu (10 percent) or at the MMHC (0 percent). Finally, regarding the ultimate fate of these patients, Table 22-7 shows that those who were able to leave the hospital because of symptomatic improvement were those who had received both drug and the social therapies. Moreover, high social therapies without drugs seem to mitigate against improvement since this group, when placed back on drugs after having been off them for six months never did catch up with the group continuously treated with drugs plus social therapies.

In a large double-blind study comparing group therapy alone, group therapy with phenothiazine therapy, and phenothiazine therapy alone performed by the VA, it was found that in most symptom areas typical of psychosis phenothiazine therapy with or without group therapy produced maximum improvement. There were, however, several interactions of phenothiazine with group therapy and several effects which were due to group therapy alone (Gorham, 1964).

*Table 22-7. Drug Versus Social Therapies in Chronic Schizophrenia. Results of Four Treatment Regimes (Greenblatt, 1965)*

| REGIME | PERCENT HIGHLY IMPROVED AFTER 6 MOS. | PERCENT DISCHARGED AFTER 6 TO 9 MOS. | PERCENT HIGHLY IMPROVED AFTER 36 MOS. |
|---|---|---|---|
| Drug + high | 33 | 27 | 35 |

| | | | |
|---|---|---|---|
| social therapy | | | |
| Drug + low social therapy | 23 | 9 | 19 |
| No drug + high social therapy | 0 | 7 | 26 |
| No drug + low social therapy | 10 | 5 | 6 |

It is important to remember that these therapies are complimentary (Davis, 1972; Evangelakis, 1961; Gorham, 1964). The social therapies do not have the antipsychotic activities of the drugs. Conversely, phenothiazine therapies may be beneficial in reducing the patient's psychotic symptomatology, but they do not help him to get a job, adjust to his family situation, or give him the motivation and judgement to stay out of the hospital (Davis, 1972; Evangelakis, 1961; Grinspoon, 1968; Grinspoon, 1963).

## Side Effects

A physician must be familiar with possible side effects produced by the drugs that he prescribes (Cole, 1969). Moreover, since psychotropic agents are some of the most frequently prescribed, he must be acquainted with the side effects of all of these agents, since there is a reasonable likelihood that he will have to diagnose and treat side effects produced by drugs prescribed by

other doctors or taken on the patient's own initiative (Hollister, 1957; Hollister, 1958; Hollister, 1959, Hollister, 1964).

The sharing of common pharmacological modes of action by many of the psychotropic drugs has made it convenient to consider categories of related side effects (Caffey, 1961; Dewar, 1962; Hollister, 1957; Hollister, 1958; Hollister, 1959, Hollister, 1964; Lafave, 1967). For example, the antipsychotic and tricyclic antidepressant medications block biogenic amines reuptake and also cholinergic receptors. This can produce a family of autonomic side effects, such as blurred vision, dry mouth, constipation, urinary retention, etc. Also, all of the antipsychotic agents produce extrapyramidal side effects because of their central blockage of dopamine receptors. It is useful to think of side effects as belonging to categories, because it is easier to remember general patterns than it is to think of thirty to forty individual side effects. We can classify the effects of the antipsychotic drugs as: autonomic, extrapyramidal, other central-nervous-system effects, allergic, endocrine, and long-term skin and eye side effects.

**Autonomic Side Effects**

The autonomic side effects of the antipsychotic agents are a result of their anticholinergic and antiadrenergic properties. Among autonomic side effects which may present themselves are: dry mouth and throat, blurred

vision, cutaneous flushing, constipation, urinary retention, paralytic ileus, mental confusion, miosis, mydriasis, and postural hypotension.

Dry mouth is one of the most frequently occurring complaints. For relief, the patient can be advised to rinse his mouth out frequently with water. However, he should not be advised to chew gum or candy since adding sugar to the mouth provides a good culture medium for fungal infections such as moniliasis and, in addition, may increase the incidence of dental caries. Pharmacologically, pilocarpine can be administered to reduce this side effect, although the relief it provides is sometimes transitory. In any case, patients develop a tolerance to dry mouth, as well as to other autonomic side effects.

Orthostatic (postural) hypotension (Jefferson, 1972) occurs most frequently during the first few days of treatment and patients readily adapt to it. It develops more frequently when acute, high doses of IM medication are administered. It can be occasionally troublesome, the chief dangers being that the patient may faint, fall and injure himself, although such events are very rare. In susceptible patients (i.e., those taking a high dose of parenteral medication), it is sometimes prudent to take the patient's blood pressure (lying and standing) during the first few days of treatment. Such a practice will present the clinician with the need to make arbitrary judgements. A patient may show a blood pressure of 85/50 but be asymptomatic. Should one worry or change dose? The authors think not. Asymptomatic blood

pressure decreases have to be handled differently than symptomatic drops in patients who become faint, weak, or dizzy upon standing up. On a more pedestrian level, support hose may provide some relief to patients with chronic mildly symptomatic hypotension.

The patient should be warned of this side effect when appropriate, and the usual instructions should be given: rise from bed gradually, sit with legs dangling, wait for a minute, and sit or lie down if you feel faint. In general, postural hypotension is not troublesome. However, when it occurs it can usually be managed by having the patient lie down with his feet higher than his head. On very rare occasions, vasopressor agents may be indicated. Obviously, since phenothiazines are alpha-adrenergic blockers, they block the alpha-stimulating properties of epinephrine, while leaving the beta-stimulating properties untouched. Consequently, the administration of epinephrine results in a paradoxical hypotension and this is contraindicated in phenothiazine-induced hypotension. For persons with cardiovascular disease, the doses should be increased more slowly and the blood pressure carefully monitored.

A predrug ECG for baseline purposes is sometimes indicated in patients with preexisting heart conditions, and is probably desirable in all patients in the geriatric age range (over sixty-five).

An electrocardiogram abnormality, consisting of broadened, flattened, or cloven T-waves and an increased Q-R interval of uncertain clinical significance has been described in patients receiving thioridazine at doses as low as 300 mg./day (Wendkos, 1964). This abnormality does not seem to be associated with clinical electrolyte disturbances, but, nevertheless, has been reversed by potassium supplements, isosorbide-dinitrate, and ergotamine tartrate, as well as by discontinuation of the drug. In addition, ST-segment depression has been observed in patients treated with a number of other phenothiazines, as have alterations in heart rate, both bradycardia and tachycardia.

Very rarely, sudden death has been reported in patients receiving phenothiazine treatment (Hollister, 1965). However, one cannot make an accurate assessment as to whether or not these drugs were the causal agent involved in such a death, since sudden death, in the absence of drugs, can occur even in young, apparently healthy, adolescents. Sudden deaths were reported in healthy hospitalized young schizophrenics long before antipsychotic drugs were ever invented (Peels, 1972). Mechanisms proposed for such sudden deaths are: ventricular fibrillation, asphyxia caused by regurgitated food, and endobronchial mucus plug in an asthmatic schizophrenic, shock in patients with acquired megacolon, and convulsive seizures or their complications.

## Extrapyramidal Side Effects

Extrapyramidal effects fall into three arbitrary categories: (1) parkinsonian syndrome, (2) dyskinesias, and (3) akathisia. The parkinsonian syndrome involves tremor of resting muscles, masklike face, a slowing of voluntary movements, a festinating gait, and rigidity. In symptomatology, it bears much resemblance to idiopathic parkinsonism. Dyskinesia is characterized by a variety of peculiar movements of the neck, face, and tongue, such as torticollis, oculogyric crisis, opisthotonus, and bucco-facial movements with salivation. Akathisias are marked by the fear of sitting down and by the inability to stay still, a semi-involuntary motor restlessness most marked in the lower extremities.

Diagnosis of this family of side effects can occasionally present problems. The parkinsonian syndrome can sometimes be mistaken for schizophrenic apathy, especially when motor retardation is prominent, the dyskinesias can appear to be the bizarre mannerisms of psychotic patients, and akathisia strongly resembles agitation.

It is important to diagnose these symptoms correctly so that proper treatment can be administered (Klein, 1969). A therapeutic trial of antiparkinsonian agents, such as benztropine (Cogentin), procyclidine (Kemadrin), or diphenhydramine (Benadryl), is especially useful in making an accurate diagnosis (Klein, 1969). Dramatic dyskinesias, in particular, respond

readily to intravenous or intramuscular treatment with antiparkinsonian medication. Comparative quantitative data on these side effects is imprecise (Klein, 1969). The greatest incidence of extrapyramidal effects if produced by butaperazine, fluphenazine, haloperidol, thiothixene, and trifluoperazine. Acetophenazine, chlorpromazine, and chlorprothixene produce a moderate number of such effects, and thioridazine produces the fewest neurological side effects.

Even patients receiving small amounts of phenothiazine can experience the acute dyskinetic reaction which normally occurs during the first several days or weeks of treatment. The same reaction often occurs in children who have been treated for nausea with a single dose of prochlorperazine (Compazine). The reaction causes the patient to be brought hastily to the emergency room. Patient and family often fail to recognize the relationship between the symptoms and the previously administered antiemetic drug. Consequently, they usually fail to inform the examining physician that the patient has been using a phenothiazine-type medication. Dyskinesias can disappear of their own accord after minutes or hours but since they are frequently painful and psychologically distressing to the patient, it is best to administer antiparkinsonian medication.

Occasionally one encounters an acute dyskinetic reaction which is resistant to treatment with typical antiparkinsonian medication. In these

cases, caffeine, diazepam, or methylphenidate (Ritalin) may be effective. Dystonic reactions are more likely to occur in patients suffering from hypoparathyroidism.

Akathisia and the parkinsonian syndrome can also occur early in treatment and continue for a few weeks until tolerance develops. Sometimes patients can exhibit a very subtle form of parkinsonian disease. This presents itself as zombielike appearance or emotional blunting. One must be cautious not to confuse these symptoms with emotional withdrawal or retardation. Antiparkinsonian medications readily alleviate such symptoms.

The akathisias, the third branch of parkinsonian side effects, can be confused with psychotic agitation. An akathisia patient is driven by motor restlessness. Antiparkinsonian drug treatments often bring dramatic results in akathisia patients. However, those who are resistant to such treatment can be aided by reducing dosage or changing to a different phenothiazine.

There has been debate among psychiatrists as to whether antiparkinsonian medication should be administered (1) prophylactically to all patients under antipsychotic treatment, or (2) to only those patients exhibiting a given side effect. Physicians opposing the routine method of treatment argue that (1) extrapyramidal symptoms do not occur in most patients; (2) high doses of parkinsonian medication cause side effects such as

blurring of vision, dry mouth and *very rarely* paralytic ileus and/or urinary retention; (3) cost of treatment rises; (4) there is no conclusive evidence that routine use of antiparkinsonian medication prevents parkinsonian symptoms; and (5) patients can develop albeit rarely what is essentially an atropine-type psychosis. In the most severe form, this could be the central anticholinergic syndrome characterized by loss of immediate memory, disorientation, vivid hallucinations, etc., (Davis, 1972).

Those in favor of routine or prophylactic administration of antiparkinsonian medication point out that the extrapyramidal effects are often distressing to the patient, especially when he is not in the hospital. For example, a case of dramatic dystonia is frequently interpreted as a medical emergency and the patient is rushed to the hospital, a disturbing incident for the patient and his family. The proponents go on to note the existence of some clinical manifestations of parkinsonian extrapyramidal effects, such as apathy, drowsiness, lack of spontaneity, relative inability to participate in social activity, and lifelessness, which are sufficiently indistinct to make diagnosis difficult. Avoidance of the dramatic and unpleasant side effects which tend to alarm the patient and alleviation of the more subtle manifestations of extrapyramidal syndromes are, thus, the arguments used by those in favor of routine administration of antiparkinsonian medication.

For every 400 mg. of chlorpromazine or its equivalent, approximately 5

mg. of procyclidine or an equivalent antiparkinsonian medication can be prescribed. Initially, procyclidine is given on a three-times-a-day schedule, because it has a short-term effect. Later on in treatment, however, it can be administered twice daily or at the hour of sleep. Dosage need not be increased beyond a 15 mg. daily total.

Despite the fact that there is a lack of quantitative data on this point, it is the opinion of the authors that patients develop a degree of tolerance to extrapyramidal side effects. We would not recommend routine administration of antiparkinsonian drugs in a hospital situation. For some outpatients, we would favor judicious use of preventive antiparkinsonian medication in the minimum dosage. Adjustment of the dose is often required. After several weeks or months of phenothiazine treatment, the patient may no longer require antiparkinsonian medication (Klett, 1972; Pecknold, 1971). In two studies in which antiparkinsonian medication was systematically withdrawn from chronic patients, it was found that approximately only 20 percent of the patients showed any neurological side effects after withdrawal. The other 80 percent had apparently received the medication without needing it. We therefore suggest that antiparkinsonian medication be gradually reduced after phenothiazine treatment has continued for a few months.

Given that extrapyramidal effects are produced by all antipsychotic

drugs, the hypothesis is raised that the qualitative presence of the effects may bear a relationship to the antipsychotic properties of the drugs. One author has gone on to suggest that the optimal therapeutic dose of phenothiazine is reached when a certain minimal type of extrapyramidal effect begins. This so-called "neuroleptic threshold" is manifested by certain subtle changes in handwriting. No solid evidence has been found to support this hypothesis. That extrapyramidal side effects and therapeutic effects should be related is not surprising, however, for the two are dose related. There is no correlation between therapeutic improvement and the presence of extrapyramidal effects. Thioridazine (Mellaril), which produces only minimal extrapyramidal side effects, has as much therapeutic effect as butyrophenones such as haloperidol, and phenothiazines such as fluphenazine and trifluoperazine, which produce far more extrapyramidal effects (Cole, 1964).

**Tardive Dyskinesia**

Tardive dyskinesia, or terminal extrapyramidal insufficiency, is an extrapyramidal syndrome which emerges late in the course of treatment with antipsychotic drugs (Crane, 1968; Crane, 1972; Crane, 1967; Kazamatsuri, 1972; Kazamatsuri, 1972).32-34,124,125 It occurs particularly in cases in which high doses of the medication have been used for years. The syndrome is present only when the patient is awake (Crane, 1968; Crane, 1972; Crane, 1967). It consists of bucco-facial mandibular or buccolingual movements such

as "smacking" of the lips, sucking, lateral or "fly catching" movements of the tongue, grimacing, lateral jaw movements, tonic contractions of the neck and back, and choreic movements of the upper extremities of fingers, ankles, and toes (Crane, 1968). The symptoms may appear during antipsychotic treatment. They may also recur or become intensified several days or weeks after the drug treatment has been reduced or ceased. When this happens, the symptom may be unmasked, since dystonic movements can be suppressed by phenothiazine induced rigidity. Paradoxically, then, if the patient is given high doses of butyrophenones and phenothiazines, the syndrome may be undetectable. In some patients, symptoms disappear soon after treatment ceases, while in others they persist at length. Antiparkinsonian medication is not beneficial. Reserpine like medications (Gilligan, 1972; Kazamatsuri, 1972; Kazamatsuri, 1972) may prove helpful. Attention is called to an FDA-ACNP Task Force Statement in the *AMA Archives of General Psychiatry* [28 (1-973), 463-467], and to a series of systematic studies by Crane (1967; 1968; 1972; 1967) and Cole (Kazamatsuri, 1972; Kazamatsuri, 1972). In populations who have not had long-term, high-dose treatment with phenothiazine, tardive dyskinesia appears less frequently; for example, incidence among chronic schizophrenic patients in Turkey is low.

## Other Central Nervous System Effects

The threshold of seizures in animals is decreased by most antipsychotic

compounds. When humans are given antipsychotic medication in high doses, seizures can occur but do so only rarely. It is usually clinically observed that psychotic epileptic patients who are given antipsychotic drugs show improvement of both their seizure disorder and their behavioral disorder. If seizures do occur, they are generally single and isolated and occur with high doses of the medication. Obviously the patient should receive the appropriate medical workup. Dosage can often be decreased slightly without fear of seizures. Occasionally, when a seizure occurs on phenothiazine medication, an anticonvulsant such as diphenylhydantoin (Dilantin) can be added to the treatment program and antipsychotic medication can be continued without further seizures, even at high doses.

**Behavioral Toxicity**

The term "behavioral toxicity" refers to adverse behavioral changes, including performance decrements, produced by the ingestion of an antipsychotic drug. It is exceedingly difficult to evaluate behavioral toxicity severely in schizophrenic patients since to do so accurately would require the separation of the symptoms of drug-induced toxicity from nondrug-related increase in schizophrenic symptoms. Patients treated with psychotropic drugs can display such symptoms as somnambulism, insomnia, toxic confusional states, bizarre dreams, hindered psychomotor activity, and aggravation of schizophrenic symptoms. Since some of these effects may be

dose-related, they can be treated by changing dosage, switching drugs, adding or deleting drugs, etc. Within minutes, IM antiparkinsonian drugs can reverse akathisia or an organic psychosis which is thought to be an ideational concomitant of extrapyramidal disorder. The anticholinergic properties of the drugs may be related to some of the confusional states (Davis, 1969). Also, the rates of metabolism of a specific drug vary from patient to patient; consequently, slow metabolizers may build up psychotoxic amounts of drug or metabolites and manifest excessive sedation.

## Allergic Reactions

When chlorpromazine treatment was first being used, jaundice occurred about once in every 200 cases. For some unknown reason, the occurrence of this side effect has lessened considerably (Hollister, 1959). Today the incidence is approximately one per 1000 chlorpromazine-treated patients, although no precise data on incidence is available; only one case was observed in an active public mental hospital over a five-year period where about 400 new patients a year probably received the drug. Jaundice usually follows one to seven days of flulike symptoms, including nausea, vomiting, fever, malaise, abdominal pains, and diarrhea (Barancik, 1967; Denber, 1972; Hollister, 1958; Hollister, 1959). It occurs during the first five weeks of phenothiazine treatment. Indicators of phenothiazine-induced jaundice are the timing of the jaundice in relation to phenothiazine treatment, lack of a

tender, enlarged liver, and chemical indications of cholestasis, including increase in alkaline phosphatase, decrease in esterified cholesterol, greater increase in direct relative to indirect bilirubin, a modest increase in the liver enzymes SGPT (Serum Glutamate Pyruvic Transaminase) and SGOT (Serum Glutamate Oxaloacetic Transaminase). Eosinophilia can be observed on peripheral blood smears. Liver biopsy can reveal bile plugs in the canaliculi with eosinophilic infiltration in the periportal spaces. Chlorpromazine jaundice usually disappears in a few days to several weeks. The majority of such cases are benign and normal liver function returns entirely. Plasma bilirubins do not generally exceed 15 mg./100 mg. Very rarely, the more prolonged exanthematous biliary cirrhosis can occur. If this does happen, it clears, but sometimes with a chronic course of six to twelve months. Indications that chlorpromazine jaundice may be an allergic reaction (in a broad sense) are its temporal association with treatment, its relationship with eosinophilic infiltrations in the liver and with peripheral eosinophilia, its not infrequent relationship with other allergic reactions, and its long-lasting retention of sensitivity on the challenge test. On occasion, patients have contracted chlorpromazine jaundice five to ten years after their first jaundice has developed. Although most cases of phenothiazine induced jaundice are reported to have occurred with chlorpromazine, the condition is also associated with thioridazine (Barancik, 1967), mepazine, promazine, fluphenazine, and prochlorperazine. It has not been proven that

chlorpromazine jaundice can be produced by haloperidol. Since infectious hepatitis is not uncommon in psychiatric patients, not all of these reported associations between psychoactive drugs and jaundice can be assumed to be clearly drug caused.

Routine weekly or biweekly liver-function tests are neither useful nor indicated. When a patient contracts chlorpromazine jaundice, the chlorpromazine treatment should be discontinued.

**Agranulocytosis**

The most serious, but very rare, side effect of phenothiazines is agranulocytosis. When it occurs, the mortality rate is often 30 percent or higher. Agranulocytosis usually appears suddenly during the first two months of treatment. It is characterized by the abrupt appearance of fever, sore throat, and sometimes mouth ulceration. When it occurs, the patient should enter a medical facility for reverse isolation procedure and phenothiazine treatment should be immediately halted. The infection should be treated rigorously (Council, on Pharmacy and Chemistry, 1956; Hughley, 1964; Pisciotta, 1958; Pretty, 1965). Adrenal corticosteroids are said to contribute nothing to speeding recovery from agranulocytosis. Although accurate data are lacking, some patients may show cross-sensitivity to other phenothiazines. Again, concrete data are not available, but agranulocytosis

occurs probably once in every 500,000 cases. It also has been reported to occur very rarely with mepazine, prochlorperazine, promazine, and thioridazine.

Phenothiazine-related agranulocytosis tends to strike older women. It is certain that routine blood counts are not of value in spotting agranulocytosis. Hence these are not indicated. The condition develops at such a pace that only daily blood counts could detect an unusually uncommon complication.

It is not uncommon for chlorpromazine and other phenothiazines to temporarily reduce a normal white count by 40-80 percent. The hematological phenomenon is not that of agranulocytosis, however. This leukopenia is a benign phenomena and requires no special treatment or deletion of the drug.

Rarely patients taking phenothiazines may develop hemolytic anemias, thrombocytopenic or nonthrombocytopenic purpura or pancytopenia. In such cases, the medication may be deleted or changed.

**Dermatologic Side Effects**

Skin eruptions of a petechial, maculopapular, urticarial, or edematous character may occur in patients receiving phenothiazine treatment. These effects generally develop in the first weeks of treatment. Those who handle

chlorpromazine may also be susceptible to contact dermatitis of the hands and face.

Chlorpromazine treatment can cause a phototoxic photosensitivity reaction similar to severe sunburn (Ban, 1965). Physicians should make sure that patients are aware of this possible side effect; patients on CPZ should avoid sunlight, using sun screens when appropriate.

### *Long-Term Eye and Skin Effects*

When chlorpromazine was first introduced, phenothiazines were assumed to be entirely safe, even on a long-term, high-dose basis. Since then, however, longitudinal studies plus even longer clinical experience have made it possible to notice long-term side effects such as long-term skin and eye effects (Cole, 1969; Barsa, 1965).

Skin discoloration of areas exposed to sunlight is one such effect. Face, nose, and other open areas may turn tan and proceed to turn slate gray, metallic blue or purple, or even a vivid purple. In such cases, histological examination of skin biopsies reveals pigmentary granules similar to, but histo-chemically not identical to, melanin.

Long-term, high-dose chlorpromazine (over 1-3 kg.) treatment has also been associated with whitish brown, granular deposits localized in the

posterior cornea and anterior lens. These deposits eventually progress to opaque white and yellow-brown, and are often star shaped. They are visible only by slit-lamp examination. The conjunctiva will occasionally become discolored by a brown pigment. These opacities are in no way related to senile cataracts.

According to statistical data, lens changes are found more often in patients with skin discoloration. Such patients do not display retinal damage and do not have impaired vision. Statistics on the incidence of skin and eye effects vary among hospitals, from under one to over 30 percent. One reason for this variance may be the amount of sun to which a hospital generally exposes its patients.

Since skin and eye effects are related to sunlight, it is suggested that patients exhibiting these effects be treated by curtailing exposure to the sun and shifting patients still requiring antipsychotic drugs to haloperidol or low-dose phenothiazines, since both eye and skin changes are probably a function of total phenothiazine dose taken over time.

### *Retinopathy*

Thioridazine is the only phenothiazine really dangerous to the eye. Retinitis pigmentosa develops when dosage exceeds 800 mg./day. Serious visual impairment or even blindness may result. Therefore, one must strictly

avoid thioridazine doses exceeding 800 mg./day.

**Endocrine Effects and Impotence**

Although there exists a large basic literature relating to the effects of antipsychotic agents, given in large doses, on the endocrine systems of a wide variety of obscure species, in practical terms the clinically important effects for the human species are lactation and male impotence. Of these, the latter is presumably autonomic, not endocrine, in origin. In addition, these drugs may result in a shift in glucose tolerance curves in a diabetic direction. Finally, false positive hormonal (not immunological) pregnancy tests have been reported among females receiving antipsychotics.

Breast engorgement and lactation in female patients is a well-known effect of these drugs and, although figures are lacking, if every patient were checked for lactation by manual pressure on the breast, an incidence of as high as 20-40 percent might be found. However, subjective complaints of overt lactation are quite rare, less than 5 percent. When such spontaneous lactation does occur, however, it is usually adequately handled by dose reduction or by shifting the patient to another drug. Finally, drug-related gynecomastia in male patients has been described.

Clinical studies of the effects of these drugs upon other sex hormones and upon adrenocortical, thyroid, or pituitary hormones have produced

negligible and/or inconsistent results. In addition, marked weight gain is sometimes associated with phenothiazine treatment.

Thioridazine, among all the antipsychotics, produces the most frequently reported incidence of sexual impotence in male patients. This impotence begins with delayed ejaculation and, ultimately, to loss of erectile ability. The reason for this special effect of thioridazine is, perhaps, that the drug has more autonomic (and fewer extrapyramidal) side effects than do the higher-potency antipsychotic agents.

The physician should be aware that drug-induced impotence is a potentially disturbing side effect which he may miss simply because the patient is too embarrassed to speak of it. He should therefore be alert for such a possibility and attempt to mitigate some of the embarrassment by providing a general statement as to the possibility of such an effect.

### Side Effects in the Elderly

For unknown reasons, elderly psychotic patients tolerate and require lower dosages of antipsychotic drugs than do younger adult schizophrenics (Honigfeld, 1964; Honigfeld, 1965; Klein, 1969; Tsuang, 1971). Lower dosages are indicated; for example, a dose of 10 or 25 mg. of thioridazine or 0.25 mg. haloperidol is a safe dose in elderly patients. Clinically effective dosages are 100 mg. or less of the former, or 1.0 mg. of the latter per day

(Honigfeld, 1964; Honigfeld, 1965). Caution is advised in establishing initial dosage levels, since hypotension or ataxia, with high risk of falls and hip fractures, can result if elderly patients are placed rapidly on high drug levels (Tsuang, 1971). Nevertheless, these drugs can prove most effective in psychotic geriatric patients. Finally, where hyperarousal clearly exists at the modest dose levels suggested above, careful and gradual raising of the dose, until symptomatic relief is obtained, is clearly indicated.

## Theoretical Implications

There is a wide variety of drugs which seem to benefit schizophrenic patients. These include the phenothiazine and the thioxanthene derivatives, the butyrophenones, and reserpine, as well as several experimental antipsychotic agents. Thus, it is reasonable to ask whether these antipsychotic agents act through a common mechanism and, furthermore, whether this mechanism would provide a clue as to the organic causes of schizophrenia. Certainly there are a great many postulated causes of schizophrenia, the more important of which are reviewed in other chapters of this *Handbook.* In this chapter we are restricting ourselves to a discussion of drug-related findings which point toward a biological theory of schizophrenia.

It is noteworthy that all antipsychotic drugs cause parkinsonian side

effects. Inasmuch as Parkinson's disease has been shown to be a dopamine deficiency disease, one would assume that these side effects are produced through dopaminergic mechanism. In addition, it is also true that all the antipsychotic agents block central dopamine receptors and, compensatorily increase dopamine synthesis. Consequently, it is reasonable to hypothesize that the common denominator which underlies all the drugs which benefit schizophrenia is their property of blocking central dopamine. Both reserpine and tetrabenazine exhibit antipsychotic properties, but neither seems to be as effective an antipsychotic agent as the phenothiazine derivatives (Abse, 1956; Ashcroft, 1961, Lingjaerde, 1963; Shawver, 1959). Both interfere with the storage of biogenic amines, thus one would assume that the beneficial effect they produce in schizophrenics is accomplished through the mechanism of decreasing the level of dopamine in the brain. Theoretically, if one reduced the dopamine level in the brain through the administration of an inhibitor of dopamine synthesis, one might potentiate the action of the antipsychotic drug. This in fact seems to be the case. If dopamine synthesis is blocked with alpha-methyl-p-tyrosine, the result is a reduction in the amount of antipsychotic agent necessary to achieve a beneficial effect in schizophrenics. This observation is evidence that the neuroleptics produce their antipsychotic action by means of an interaction with a catecholamine. Thus, we have several lines of evidence that the antipsychotic drugs may benefit schizophrenia through blocking the receptors for the catecholamines, or

interfering with catecholamine storage, the former being potentiated by catecholamine synthesis inhibitors. Alpha-methyl-p-tyrosine is itself ineffective in treating schizophrenia.

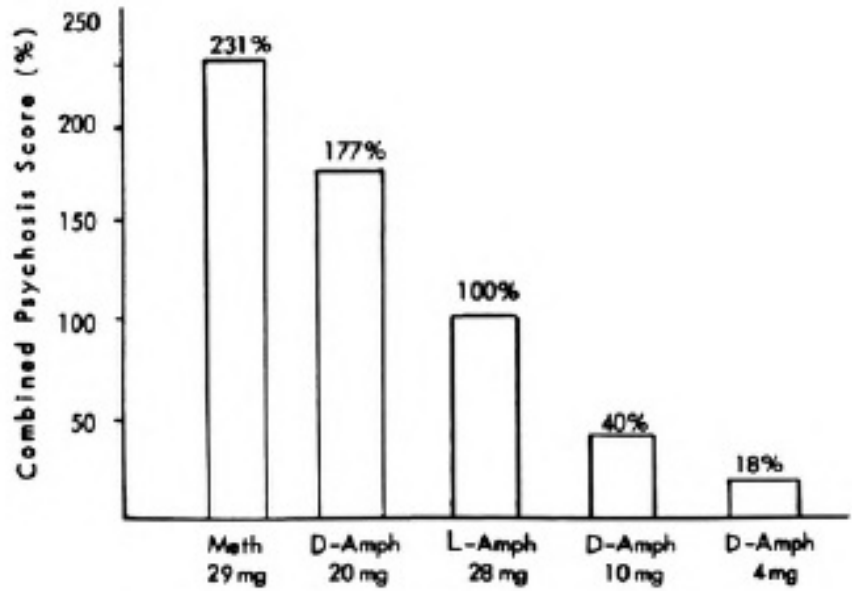
Inasmuch as decreasing dopaminergic activity benefits schizophrenics, it is reasonable to ask whether the schizophrenic process can be produced, or exacerbated where it already exists, by increasing dopamine activation. In this regard psychomotor stimulants such as amphetamine and methylphenidate are potent releasers of dopamine and it is further known that large doses of amphetamine can cause a paranoid schizophrenic episode and IV doses can exacerbate schizophrenia (Janowsky, 1973; Janowsky, 1972; Janowsky, 1972; Janowsky, 1972). The administration of a number of psychostimulant drugs, including amphetamine and methylphenidate, quickly results in stereotyped activity in rats, consisting of repetitive sniffing and gnawing behavior. This behavior is generally thought to be caused by increased dopaminergic stimulation in or near the neostriatum or tuberculum olfactorium. It is believed to be the animal model of human psychosis since many of the agents which cause it have also precipitated or intensified psychotic behavior in man, and since all existing antipsychotic drugs antagonize and prevent it in rats probably by causing receptor blockades or by the depletion of central dopamine (DA).

Janowsky and Davis (Janowsky, 1973; Janowsky, 1972; Janowsky, 1972;

Janowsky, 1972) have shown that psychomotor stimulants administered IV can markedly exacerbate schizophrenic symptomatology producing in a well-controlled schizophrenic a florid exacerbation of his illness for about one to two hours. Furthermore, methylphenidate is roughly two to three times as potent as L-amphetamine in worsening schizophrenic symptoms, and n-amphetamine is almost twice as potent as methylphenidate (see Figure 22-6). This differs from the order of potency in the rat, for n-amphetamine is two to three times more potent than l-amphetamine or methylphenidate. It is reasonable then to ask the question: Why is methylphenidate more potent in schizophrenia and less potent in causing stereotyped behavior, an animal model for schizophrenia? Methylphenidate and D-amphetamines both produce stereotyped behavior by releasing the dopamine; however, they do so through somewhat different mechanisms. It is thought that they represent two different types of psychomotor stimulants, i.e., (1) methylphenidate releasing dopamine from the stores and (2) amphetamines releasing dopamine from the newly synthesized source. In addition, alpha-methyl-p-tyrosine does not benefit schizophrenia by itself and inhibits synthesis, hence, would be more effective on a newly synthesized pool of amine. Reserpine, which depletes stores of dopamine does have some antipsychotic properties. This evidence would be consistent with stored DA being more important in schizophrenia. Janowsky and Davis have shown (Janowsky, 1973; Janowsky, 1972; Janowsky, 1972; Janowsky, 1972) that there may be an antagonism on

many types of behavior between dopaminergic (or noradrenergic) activation and cholinergic stimulation. It is of interest that the worsening in schizophrenia produced by methylphenidate can be reversed or prevented by physostigmine, a drug which increases brain acetylcholine (Janowsky, 1973; Janowsky, 1972; Janowsky, 1972; Janowsky, 1972). Thus, the worsening of schizophrenia produced by methylphenidate is under control of cholinergic and presumed dopaminergic balance.

*Figure 22-6.*




*Comparison of the ability of various intravenously administered psychostimulants to increase the psychosis score in psychiatric patients*

*expressed as percentage of the effect of L-amphetamine (28 mg.). Methylphenidate (Meth), D-amphetamine (D-Amph), and L-amphetamine (L-Amph) are equimolecular.*

Amine released from stores would be expected to be released to some extent intracellularly and thus be vulnerable to destruction by monamine oxidase, an intracellular enzyme. If methylphenidate is differentially more potent in schizophrenia, it may be that schizophrenic patients have a deficit in monamine oxidase. Empirically, schizophrenic patients have low platelet monoamine oxidase (MAO) and furthermore, the great similarity between platelets and adrenergic neurons has led to the suggestion that platelets are a model for the neuron (Murphy, 1972). The observation that platelet MAO may be under hereditary control, may provide an explanation for the hereditary predisposition to schizophrenia. If schizophrenia were simply dopaminergic overactivity, phenothiazines should turn it off as rapidly as they block amphetamine psychosis; that is in hours or a few days. In fact the improvement with antipsychotic drugs takes place more slowly than this. One can easily formulate, as the authors have, a two-factor theory of schizophrenia. It is hypothesized that dopaminergic stimulation can turn up the gain and hence worsen schizophrenia and that the antipsychotic drugs turn down the gain and thus suppress the schizophrenic process. The schizophrenic process, however, could be related to some "second" factor, as yet undefined, either biological and/or psychological. When a patient is treated with antipsychotic drugs, these agents tone down their psychosis and

give normal reparative processes a chance to work. D. X. Freedman has termed such theories to be meta-psychopharmacological theories. This term serves to emphasize that these theories are speculative. They might be considered as strategies for research more than as well substantiated theories. They are included here to give examples of the fact of the pharmacological properties shared by these antipsychotic agents and may provide clues as to the underlying cause of the disorder. It is important that such theorizing be kept in perspective, e.g., pneumococcal pneumonia is not a penicillin deficiency disease. With the increased understanding of the mechanisms by which these drugs work, it would be unreasonable not to look for common denominators in these mechanisms, as long as one does not prematurely conclude that the cause of schizophrenia has been discovered. Aside from these theoretical considerations, appreciation of the mechanism of these drugs is also useful in understanding side effects and hence, leads to more effective medical management of our patients.

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## Notes

1 In this study chlorpromazine was compared with fluphenazine and thioridazine. No differences were found between the three drugs in a wide range of clinical measures of psychopathology.