Phenothiazine Treatment in Acute Schizophrenia

Effectiveness

THE NATIONAL INSTITUTE OF MENTAL HEALTH PSYCHOPHARMACOLOGY SERVICE CENTER COLLABORATIVE STUDY GROUP*

Chlorpromazine has now been used in the treatment of schizophrenia for 11 years. At least ten other phenothiazines have been developed and are in medical use in the treatment of schizophrenia. There are still important questions concerning the extent of the clinical effects of chlorpromazine; moreover, there are a much larger number of questions concerning the real clinical differences between chlorpromazine and the newer phenothiazines.

The nine-hospital collaborative study of phenothiazine drugs in acute schizophrenic reactions reported here was designed principally to answer these questions in as thorough a manner as current scientific methodology would permit. The present report will present detailed findings relevant to the following clinical questions:

1. What proportion of acute schizophrenic patients show *clinically* significant improvement on phenothiazine treatment? Even after improvement, to what extent are patients still mentally ill?

2. Do the active drugs differ in their effects on specific schizophrenic symptoms? For example, is chlorpromazine more effective in reducing hostility, and fluphenazine more effective in reducing withdrawal? Do these phenothiazines have a greater effect on some schizophrenic symptoms than on others? For example, is there a greater reduction in social withdrawal than in auditory hallucinations?

3. Are two newer phenothiazines, thioridazine (Mellaril) and fluphenazine (Prolixin), more effective than placebo, and are they as effective as the older standard phenothiazine, chlorpromazine (Thorazine), in the treatment of acute schizophrenic patients?

4. Are there differences between the drugs in the nature and/or frequency of the side-effects produced?

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* See Appendix.

Background of the Study

Although collaborative studies involving several hospitals following a common research design have been utilized in many other areas of medicine, eg, malaria, tuberculosis, cancer, and rheumatic fever, these have not been attempted often in psychiatry. The recent Veterans Administration collaborative drug studies in schizophrenia and the much earlier studies of the arsphenamines and penicillin in paresis are the only other large-scale attempts at treatment evaluation in the area of mental illness.

When this study was begun in April of 1961, there was little doubt that chlorpromazine was more effective than placebo in treating chronic schizophrenic patients in state mental hospitals. However, the number of controlled double-blind studies of the effect of chlorpromazine on newly admitted schizophrenics was small, and the only large-scale multihospital study of newly admitted

patients had been conducted within the Veterans Administration utilizing male veterans, most of whom had had three or more previous hospitalizations.[8]

Further, although ten other phenothiazines were then in prescription use for the treatment of schizophrenic patients, only two, promazine and mepazine, had been shown to be significantly different from chlorpromazine both having been shown to be less effective.[7] Of the other phenothiazines, the piperazine derivatives (prochlorperazine, perphenazine, trifluoperazine and fluphenazine) appeared to share a greater potency, eg, a substantially lower clinically effective dose, and a higher incidence of neurological side-effects than chlorpromazine. Fluphenazine, as the most potent of this group of drugs, was chosen for study. At the other extreme of the spectrum of available phenothiazines, thioridazine was also reported to be clinically effective but to produce a very low incidence of neurological side-effects. Thioridazine and fluphenazine were therefore chosen for comparison with chlorpromazine because they appeared to be the most different of the clinically effective phenothiazines available for study.

To obtain results with broad generalizability, nine institutions representing an appropriately varied range of psychiatric treatment settings participated in the study. The inclusion of data from nine hospitals also permitted the evaluation of a large number of patients within a reasonably short time period, 15 months.

The selection of acute schizophrenia as the condition to be studied was based on two considerations. First, the greater logistic difficulty in conducting controlled clinical studies of acutely ill patients had made that patient group less studied in the past. Second, while drug treatment has been shown to cause significant improvement in chronically ill hospitalized schizophrenic patients, the potential public health impact of drug treatments on the course of schizophrenic illnesses was judged to be much greater in acutely ill newly hospitalized patients, in whom the possibility of full rehabilitation is greater.

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Procedure

Research Design.—Within each of the nine hospitals, all newly admitted schizophrenic patients meeting the study criteria were randomly assigned to one of the four treatments on a double-blind basis. The patients were also stratified by sex with randomized assignment to drug treatment within each sex group.

The design, presented in Table 1, called for at least three patients of each sex completing six weeks on each treatment at each hospital. This condition was met in almost every instance, with a few hospitals studying five or more patients in some of the treatment-by-sex groups. The total numbers of patients in each treatment group were chlorpromazine 88, fluphenazine 91, thioridazine 91, and placebo 74. Six of the hospitals studied only white patients. In the other three hospitals, which ordinarily admitted approximately equal numbers of white and Negro patients, patients were also stratified by race. For the analyses reported here, data on all study patients have been analyzed without regard to race. The 344 patients completing the study includes 79 Negroes.†

Criteria for Selection of Patients.—To be admitted to the research sample, patients must have met the following criteria:

1. Newly admitted to the hospital
2. Age—between 16 and 45
3. No significant hospitalization during the 12 months prior to the current admission.

† Studies of possible racial differences in drug response, along with the other factors such as social class, duration of illness, etc. which might confound such a comparison, will be carried out and reported at a later date.

TABLE 1.—*Study Design for Each of Nine Hospitals: Number of Patients Per Treatment*

	Treatment				
Sex	Chlorpromazine	Fluphenazine	Thioridazine	Placebo	Total
Male	3	3	3	3	12
Female	3	3	3	3	12
Total	6	6	6	6	24

TABLE 2.—*Reasons That Patients Were Removed Prior to Completion of Study Period*

	CPZ	FPZ	TDZ	PBO	Total
No. entering study	112	115	111	125	463
Administrative removals					
Incorrect diagnosis	4	1	3	1	9
Intercurrent medical illness	1	0	1	0	2
Other, court cases, transfer, elopement, etc	9	12	11	13	45
Treatment related removals					
Marked early remission	3	2	4	1	10
Serious complication of treatment	4	6	1	0	11
Treatment failure	3	3	1	36	43
Total removals	24	24	20	51	119
No. completing study	88	91	91	74	344

4. No evidence of any of the following clinical disorders:
   a. Childhood autism or childhood schizophrenia
   b. Chronic or acute brain syndrome
   c. Mental deficiency, with IQ below 70
   d. Alcoholism as a significant feature of their clinical history (alcohol intake alone did not disqualify the patient)
   e. Epilepsy
   f. Drug addiction
5. Presence of two or more of the following symptoms or behaviors:
   a. Thinking or speech disturbances
   b. Catatonic motor behavior
   c. Paranoid ideation
   d. Hallucinations
   e. Delusional thinking other than paranoid
   f. Blunted or inappropriate emotion
   g. Disturbance of social behavior and interpersonal relations

The proportion of study patients showing significant psychopathology in each of these symptom areas is presented in Table 4.

Early Terminations.—Not every patient who began the study finished six weeks of study treatment. Early terminations occurred for a number of reasons. At the beginning of the study we were somewhat concerned that our hospitals would experience difficulty in keeping their placebo patients on study treatment. As a result we expected a greater number of dropouts because of treatment failure in the placebo treatment than under the active drugs. Table 2 shows the number of patients who had to be dropped from the study prior to six weeks of treatment classified by reason of termination and by method of treatment. In this table, we see that our early fears were, indeed, well founded in that the vast majority of patients who were dropped because of treatment failure were on placebo. This was an indirect but important indication that the active drugs were working. Other points of interest in this table are the exceptionally few patients, 11, who had to be dropped from the study because of side-effects, attesting to the safety of the active drugs. Table 3 shows the side-effects on these 11 patients. Among these few, the fact

TABLE 3.—*Patients Removed from Study Because of Treatment Complications*

Drug	Sex	Wk on Drug	Reason for Removal
Chlorpromazine	M	1	Hypotension
Chlorpromazine	M	1	Jaundice
Chlorpromazine	F	3	Severe skin reaction and facial edema
Chlorpromazine	F	4	Severe skin reaction and facial edema
Fluphenazine	F	2	Jaundice
Fluphenazine	M	2	Seizure
Fluphenazine	F	1	Severe dystonia
Fluphenazine	F	1	Severe dystonia
Fluphenazine	F	3	Severe parkinsonian
Fluphenazine	F	3	Severe parkinsonian
Thioridazine	M	1	Hypotension

that there were six under fluphenazine and four under chlorpromazine is in accord with reports in the literature.

Social and Psychiatric History Characteristics.—Background characteristics of our patients are shown in Table 4 and generally substantiate the acuteness of the illness in the population studied. Although these characteristics are presented separately by sex, a more refined analysis of sex differences will not be given at this time. The following statements concerning these characteristics apply to the majority of our patients. The age of our patients is 28.2 years, with males almost three years younger than females. Moreover, our males are almost ten years younger than the patients in the comparable VA Study No. 6 [8] which studied newly admitted patients but with less stress of acuteness than in the present study.

Sixty per cent of our patients were first admissions, and 50% were experiencing their first psychotic episodes. The majority of the other patients had had only a single prior episode.

The age at the patient's first episode was 25.5, which was not quite three years less than the age at admission to the study. The present episode had been in progress about three months prior to hospitalization. For most patients there was a known precipitant for the current episode.

Fathers of patients have educational and occupational levels which would place them in Social Class IV according to Hollingshead's classification.[5] A class IV father, in oversimplified terms, might typically be one with an eighth grade education and a semiskilled occupational level.

About half of our patients are now, or at one time have been, married. However, a far greater number of females have been married than is true of males.

As will be recalled, one criterion for selection for the study was the manifestation of symptoms in at least two target symptom areas. Although all target symptoms were represented to some extent, they did not occur with equal severity. Table 5 presents some of the more frequently occurring target symptoms with the percentage of patients showing the symptom to a moderate or marked extent. It is interesting that "unrealistic thinking," the hallmark of schizophrenia, occurs most frequently (81%).

Fig 1 shows the distribution of clinical judgments of the severity of the patient's illness on entering the study. Although the range of severity extends from "borderline ill" to "most severely ill," the vast majority of study patients (82%) were judged to be at least "markedly ill," with the average at the "severely ill" point.

In short, the typical patient is a 28-year-old, severely and acutely ill schizophrenic patient who, if not in the first psychotic episode (50%), is experiencing his first hospitalization (60%), who has shown a rapid onset, who has florid symptomatology, who comes from a lower middle social class and who is far less likely to be married if a male than if a female.

TABLE 4.—*Background Characteristics of Patients*

Characteristic	Male	Female	Total
Present Age	26.8	29.6	28.2
% of patients first admissions	58.1	60.0	59.1
% of patients having first psychotic episode	53.4	47.7	50.4
Modal No. of previous episodes	1.0	1.0	1.0
Duration of symptoms prior to hospitalization, in mo	2.6	2.6	2.6
Percent with known precipitants	74.7	82.3	78.5
Father's social class	4.0	4.0	4.0
% married, now or ever	32.1	73.7	53.5

TABLE 5.—*Target Symptoms* *

Symptom	%
Unrealistic thinking	81
Severe anxiety	64
Excessive suspiciousness	60
Perplexity or confusion	58
Social withdrawal	55
Auditory hallucinations	47
Blunted affect	38
Overactivity	32
Impending doom	23
Generalized motor inhibition	18

* This table only includes the more frequently occurring symptoms within the seven broader target symptom areas which patients manifested to a moderate or marked degree.

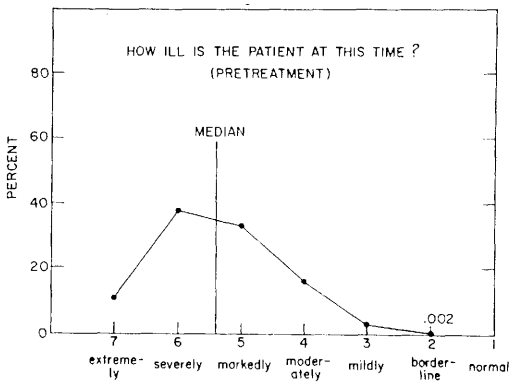

Fig 1.—Doctor's pretreatment global rating of mental illness.

Study Treatments.—All patients selected for the study were randomly assigned to one of the four treatment groups, received individually numbered containers of medication, and were to be maintained on this medication for a six-week period. A flexible dosage schedule, which permitted the treating physician to adjust dosage to the individual patient's need, was necessitated by the great variability in the effective dose of these drugs observed in schizophrenic patients. Table 6 presents the permissible dosage ranges and actual usage. Oral medication was prepared as standard No. 2 pink capsules. These capsules contained either 100 mg of chlorpromazine, 100 mg of thioridazine, 1 mg of fluphenazine or, in the case of placebo, lactose. Intramuscular medication in the form of 1 cc glass ampules was also available, the drug dose per cubic centimeter being chlorpromazine 25 mg, thioridazine 25 mg, and fluphenazine 0.5 mg. The placebo ampules contained sterile saline. The oral dosage could be varied from 2 to 16 capsules a day. The amount of injectible medication used was left to the physician's discretion. Only 30% of the patients required intramuscular medication. The oral dosages used, roughtly 8 capsules per day being the median dosage, are presented in the same table.

Patients developing extrapyramidal side effects were allowed to receive antiparkinsonian medication in order to counteract side-effects. The number and per cent of patients receiving such medication are noted in Table 6.

During the six weeks of study treatment, patients were not permitted to receive any other drug or shock treatment but were permitted to participate in any other nonsomatic treatment that was part of the usual hospital routine, such as psychotherapy, group therapy, occupational therapy, etc.

At the end of six weeks, the investigators at the participating hospital could break the code on any patient by opening a sealed envelope which contained the name of the study medication.

Participating Hospitals.—The hospitals selected for participation in this study shared, in addition to a serious interest in the research plan, the presence of an administrative setting favorable to research and personnel capable of carrying it through to completion.

In addition, all hospitals received the vast majority of their new patients by direct ad-

TABLE 6.—*Drug Usage*

	Treatment			
	Chlorpromazine	Fluphenazine	Thioridazine	Placebo
Daily Dosage — *Oral*				
Minimum, mg	200	2	200	2 doses
Maximum, mg	1,600	16	1,600	16 doses
Daily Dosage — *Parenteral*				
Minimum, mg	50	1	50	2 inj.
Maximum, mg	400	8	400	16 inj.
Average daily usage of oral medication, mg	654.8	6.4	700.0	8.5 doses
% receiving parenteral form	35	20	26	22
Average No. of ampules per patient *	4	6	3	6
% receiving anti-parkinsonian drugs	37	44	16	6

* This includes only those patients who received parenteral form of medication.

mission; hospitals drawing patients from a receiving hospital were specifically excluded.

To achieve a reasonably representative group of treatment settings, two psychiatric units of general municipal hospitals were included: DC General Hospital in Washington, DC and Malcolm Bliss Mental Health Center in St. Louis. These hospitals ordinarily do not keep patients for longer than six weeks, patients being either discharged or transferred to other facilities after that time. The six-week period of study treatment was determined in part by the space limitations and admission rates obtaining at these hospitals which prohibited a longer treatment period.

Four state mental hospitals, three serving primarily urban areas and one a rural area, were included—Boston State Hospital in Boston; Springfield State Hospital in Sykesville, Md; Rochester State Hospital in Rochester, NY; and Kentucky State Hospital in Danville, Ky.

The three other hospitals are more difficult to classify, though all three differed from the state and city hospitals in their smaller admission rate and/or non-governmental sources of support. One, the Institute of Living in Hartford, Conn, is a medium-sized hospital with little or no government support. Another, the Payne-Whitney Clinic of the New York Hospital in New York City, is a university hospital affiliated with Cornell University Medical College. The third, Mercy-Douglass Hospital in Philadelphia, is a small state-supported psychiatric unit within a general hospital closely affiliated with the University of Pennsylvania Department of Psychiatry.

Clinical Assessments

Measures of a patient's clinical status and improvement were obtained in two ways: by means of global clinical judgments and by means of clinical judgments of the presence and intensity of specific symptoms and behaviors. In other words, it was of interest to know generally how sick a patient was, and generally how much he improved after treatment, and also more specifically, for example, the degree of hostility or social withdrawal he manifested after treatment.

Global Assessments.—Two global ratings were obtained from both the doctor and the nurse at periodic intervals:

A. Global Rating of Severity of Mental Illness
"Considering your total clinical experience, how mentally ill is this patient at this time?"
(1) normal, not ill at all; (2) borderline mentally ill; (3) mildly ill; (4) moderately ill; (5) markedly ill; (6) severely ill; or, (7) among the most extremely ill patients

B. Global Rating of Improvement
"Compared to his condition at admission to the project, how much has he changed?"
(1) very much improved; (2) much improved; (3)minimally improved; (4) no change; (5) minimally worse; (6) much worse; or, (7) very much worse

Symptom and Behavior Assessments.—The specific symptom areas were rated by the doctors on the basis of interviews and by the nurses on the basis of observing the patient on the ward. The major assessment instruments are as follows:

A. Inpatient Multidimensional Psychiatric Scale (IMPS)

This instrument developed by Lorr, et al [10] at the Veterans Administration, consists of 78 symptom descriptions with which the doctor periodically describes the condition of the patient on the basis of a one-hour diagnostic interview. Although subscales were available for this measure on the basis of the factor analyses performed by Lorr, et al, we felt it desirable to factor analyze the pretreatment data from our study patients. This factor analysis resulted in 14 independent subscales which are listed below:

1. hostility
2. disorientation
3. guilt
4. auditory hallucinations
5. agitation and tension
6. slowed speech and movements
7. delusions of grandeur
8. indifference to environment
9. incoherent speech
10. pressure of speech
11. ideas of persecution
12. hebephrenic symptoms
13. delirium
14. memory deficit, for recent events

B. The Burdock Ward Behavior Rating Scale (WBRS)

This instrument, developed by Burdock, et al, at the Psychiatric Institute, New York,[2] consists of 150 true-false items and is completed by the nurses and the ward attendants on the basis of the patient's behavior on the ward during the previous week. It does not require that the patient be interviewed, although nurses typically speak with patients for a few minutes in addition to making observations of overt behavior. The WBRS, prior to this study, did not have subcategories of items which were scored separately. Rather, a total morbidity score was obtained simply by counting the number of items on which the patient showed pathology. We subjected the pretreatment scores on this instrument to a factor analysis, and the seven independent factors that emerged are given below:

1. social participation
2. irritability
3. self-care
4. appearance of sadness
5. feelings of unreality
6. resistive
7. confusion

Results

Differences ‡ Between Global Rating of Improvement: Drugs and Placebo.—Is there more improvement on active medication than on placebo? Given improvement, to what extent are patients still mentally ill after treatment? These questions may be answered generally by analysis of the two global clinical assessments previously described under *Clinical Assessments.*

Fig 2 presents the distribution of post-treatment global improvement scores separately for active drugs and placebo. Average improvement for drug patients is beyond the point labeled "much improved." It is noteworthy that no drug patient worsened; only 5% showed no change, and consequently 95% improved to one extent or another, with 75% of them being either "much improved" or "very much improved."

Placebo patients, while not improving as much as drug patients, do show, on the average, some improvement, but with a wider distribution of response than drug patients. Since these placebo patients are those who could be maintained for six weeks (almost

‡ Details on statistical analyses are not reported here. Any differences or relationships reported in this paper, unless otherwise stated, were found to be statistically significant.

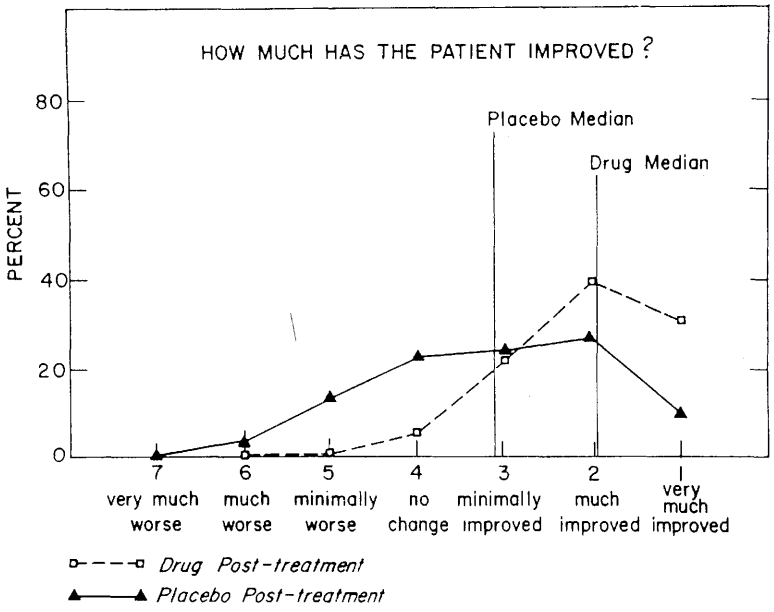

Fig 2.—Doctor's post-treatment global rating of improvement.

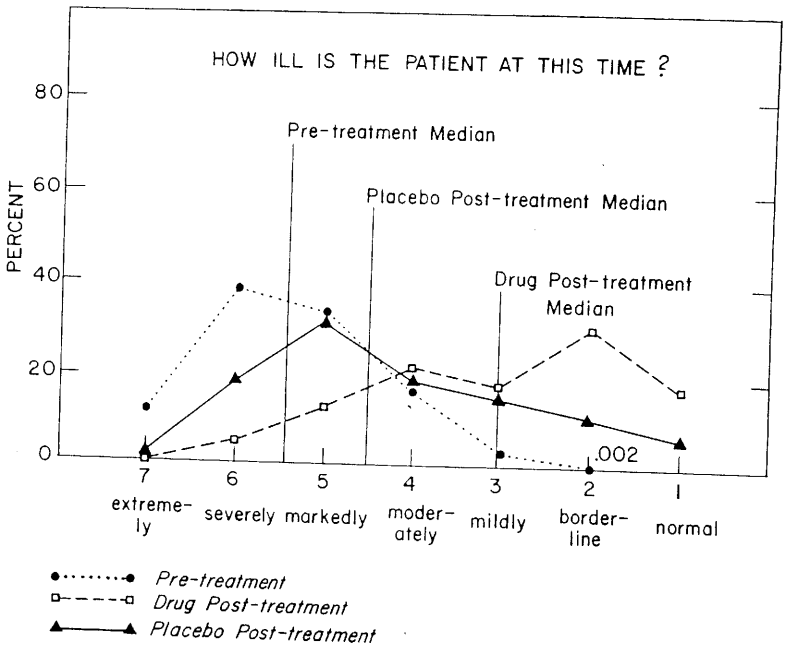

Fig 3.—Doctor's pre- and post-treatment global ratings of mental illness.

one third of the placebo patients who started the study were dropped as treatment failures), the placebo curve is biased in the direction of improvement. This would mean that the highly statistically significant difference we obtained between drug and placebo patients is itself conservative.

Despite marked improvement effected in drug-treated patients, one might ask to what extent drug patients show residual illness even after improving. Fig 3 shows the distribution of post-treatment scores on the global mental illness scale. Of these drug patients, 30% are judged to be only "borderline mentally ill" after six weeks of treatment, while 16% are described as being "normal, not ill at all." Thus, almost half these patients do not show enough residual symptoms to be judged even "mildly ill" after this short period of treatment. Status on entering the study is shown in the pre-treatment distribution also shown in Fig 3.

Preliminary trend analysis of the trends of clinical changes over the six-week treatment period indicates that we probably did not reach a plateau by six weeks, although we would need another study with a longer study period to establish this point.

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Differences Between Drugs and Placebo in Improvement on Specific Symptoms.—We have shown so far that active drug treatment results in a high degree of improvement, but improvement has been characterized in a very general sense. Since schizophrenia manifests itself in many different symptoms and behaviors, it was necessary to determine whether the drugs affected all of these and whether some behaviors were more affected than others. To answer these questions, comparisons between drug and placebo patients were made on all 21 of the specific subscales previously described in the section on clinical assessments. Table 7 presents the 13 measures on which there was a significant difference between drug and placebo patients. We find that almost all symptoms or behaviors which can be characterized as schizophrenic in nature were affected by active drug treatment. The exceptions are "Guilt," "Delusions of Grandeur," "Pressure of Speech," "Delirium," and "Memory Deficit." Moreover, since in the refinement of our assessment instruments these subscales had been shown to be relatively independent, the present evidence would argue that the active drugs have a rather varied action; that is, not only did

TABLE 7.—*Relative Improvement of Patients on Drugs and Placebo: Selected Assessment Measures With Significant Drug-Placebo Differences* *

Symptom or Behavior	Placebo	Drug	Difference
Social participation, WBRS	0.49	1.51	1.02
Confusion, WBRS	0.33	1.11	0.78
Self-care, WBRS	0.13	0.88	0.75
Hebephrenic symptoms, IMPS	—0.13	0.58	0.71
Agitation and tension, IMPS	0.27	0.95	0.68
Slowed speech, IMPS	—0.07	0.57	0.64
Incoherent speech, IMPS	—0.17	0.43	0.60
Irritability, WBRS	—0.20	0.40	0.60
Indifference to environment, IMPS	—0.05	0.45	0.50
Hostility, IMPS	0.09	0.54	0.45
Auditory hallucinations, IMPS	0.18	0.62	0.44
Ideas of persecution IMPS	0.36	0.78	0.42
Disorientation, IMPS	0.16	0.37	0.21

* Improvement scores are given here in standard score units in order to permit comparisons between different symptom measures. The standard improvement score on any given measure is the difference between the pre-treatment score and the post-treatment score, divided by the standard deviation of the pre-treatment score. In short, it is the raw amount of change in the measure, divided by the amount of natural variation on that measure that patients exhibit at the baseline time. Without standardizing, one could erroneously conclude there was change in a measure due to treatment, which in reality could be accounted for by its natural variation at a pre-treatment baseline point in time.

the drugs reduce hostility, they also reduced apathy, made movements less retarded, reduced hebephrenic symptoms, etc. From these results it is clear that the characterization of these phenothiazines as agents which calm and tranquilize excited or boisterous patients is a greatly oversimplified one. It is apparent that they have many actions.

Relative Improvement in Different Schizophrenic Symptoms: From the drug effects that we have first cited, one should not draw the implication that placebo patients showed no improvement. The lack of a significant drug-placebo difference on any single measure could mean equally little or equally great improvement under both conditions. Table 7 also presents the average improvement for placebo patients on the specific measures § where the drug-placebo difference was statistically significant. It is clear that placebo patients improve differentially depending on the symptom area in question. Reference to Table 7 shows that placebo patients have the greatest improvement in Social Participation, Confusion, Agitation and Tension, and Ideas of Persecution. On the other hand, they show the least improvement, or even deterioration, on Irritability, Hostility, Hebephrenic Symptoms, Incoherent Speech, Indifference to Environment, and Slowed Speech and Movements. In other words, in the latter group are those symptoms and behaviors in which there is essentially no improvement at all except by means of drug treatment.

Table 7 shows the relative improvement of drug patients in the same group of specific measures. Here, we may see that there is the greatest improvement in Social Participation, Confusion, Self-Care, and Agitation and Tension. On these symptoms one would expect to observe the greatest improvement in patients on drug even though the drug is not exclusively responsible for the improvement.

The final column in Table 7 indicates the difference in improvement between drug and placebo patients and should show relative improvement on each symptom that was due to drug treatment. From the rank order of these differences, it would be incorrect to conclude that improvement due to drug is simply more extreme in degree than improvement on whatever other hospital therapies the placebo patients were on. Rather, the relative improvement due to drug on different symptoms appears to be different from the pattern of improvement on placebo.

Differences Among the Three Phenothiazines: Despite the highly significant differences observed between the drugs as a group and placebo, an analysis of variance

§ Improvement scores are given here in standard score units in order to permit comparisons between different symptom measures. The standard improvement score on any given measure is the difference between the pre-treatment score and the post-treatment score, divided by the standard deviation of the pre-treatment score. In short, it is the raw amount of change in the measure, divided by the amount of natural variation on that measure that patients exhibit at the baseline time. Without standardizing, one could erroneously conclude there was change in a measure due to treatment, which in reality could be accounted for by its natural variation at a pre-treatment baseline point in time.

showed no significant differences between any of the three drugs on any of the 25 measures of clinical state described previously. Since these drugs were selected to represent the available spectrum of active phenothiazines, the absence of significant differences on any measure of clinical state is particularly striking. Since, as noted subsequently, these drugs do differ in the incidence of a number of side-effects, the present evidence strongly suggests that the therapeutic properties of these drugs may be quite independent of their tendency to produce specific side-effects. The conventional hypotheses about these drugs in the clinical literature indicate that fluphenazine might be expected to be more stimulating than the other two drugs and, therefore, more effective in the treatment of Slowed Speech and Movements or of Indifference to Environment or Social Participation, while the other drugs might be expected to be more effective in controlling Hostility or Agitation and Tension. These hypotheses are certainly not supported by the evidence at hand.‖

This result also strongly supports the hypothesis that the two newer drugs are generally *as* effective clinically as chlorpromazine. In the case of fluphenazine, at the start of the study, the presumption was that such a result would occur. In the case of thioridazine, there was some suspicion that its low incidence of neurological side-effects might carry with it a lower clinical efficacy, a fear which appears to be quite unfounded.

Although it is possible that other approaches to the analysis of clinical change or an approach which compares drugs in specific patient types rather than on individual symptoms may show drug differences not evident at present, the current analysis clearly shows that the differences in clinical efficacy between these three drugs, if present at all, are neither striking nor obvious.

‖ The single case in which we obtained a significant difference among the active drugs was on Hostility at the end of the *first* treatment week. Even in this single case, fluphenazine, opposite to general expectations, was most effective in reducing hostility.

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Side-Effects: The side-effects observed in the course of this study were generally mild or infrequent, thus attesting to the general safety of the drugs used. As might be recalled from the earlier table on dropouts, only 11 patients out of those who began the study had to be dropped because of serious side-effects. The administration of antiparkinsonian medication at the discretion of the treating physician probably contributed to this.

Because of the low intensity of the side-effects experienced by patients who completed the six weeks of study treatment, their relative occurrence among the active drugs or placebo is more a matter of patient comfort than of medical safety. Table 8 presents the incidence of side effects judged to be moderate or marked in each study treatment. In the case of eight side-effects there was a significant difference among the four treatments.

Chlorpromazine and thioridazine show equally the highest incidence on "Drowsiness" and "Dizziness, Faintness and Weakness"; fluphenazine results in less "Drowsiness" and "Dizziness, Faintness and Weakness," but more than on placebo.

In the case of the neurological side-effects, "Muscle Rigidity" and "Loss of Associated Movements," the greatest incidence occurs with fluphenazine, as expected. In both cases the evidence of side effects with chlorpromazine hardly seems greater than with placebo. Thioridazine as expected seems to be no different from placebo.

There is a group of side-effects in which thioridazine has the highest and fluphenazine the lowest incidence. These are "Dryness of Mouth or Throat," "Vomiting," and "Nausea or Upper Gastrointestinal Distress."

Finally, the incidence of "Constipation" appears greatest with chlorpromazine and the least with thioridazine, although all drugs have a higher incidence than placebo.

It appears that the three phenothiazines do produce different side-effects, although they do not seem to differ on measures of clinical improvement.

TABLE 8.—*Side-Effects of at Least Moderate Severity: Incidence by Treatments*

Side-Effects	Treatments			
	Chlorpromazine, $N = 88$ %	Fluphenazine, $N = 91$ %	Thioridazine $N = 91$ %	Placebo; $N = 74$ %
Drowsiness	53.4	36.3	51.6	9.5
Restlessness	46.6	38.5	39.6	39.2
Constipation	33.0	27.5	20.9	12.2
Nausea or upper gastrointestinal distress	25.0	5.5	33.0	4.1
Dryness of mouth or throat	25.0	18.7	30.8	5.4
Dizziness, faintness, weakness	23.9	12.1	24.2	5.4
Muscle rigidity	12.5	24.2	4.4	8.1
Nasal congestion	11.4	12.1	17.6	5.4
Facial rigidity	12.5	14.3	8.8	5.4
Tremor of hands, arms, face	5.7	12.1	13.2	5.4
Headache	10.2	12.1	8.8	10.8
Loss of associated movements	3.4	19.8	0.0	2.7
Akathisia—restlessness of feet	5.7	12.1	5.5	4.1
Vomiting	3.4	2.2	12.1	0.0
Increased salivation	5.7	8.8	3.3	0.0
Urinary disturbance	4.5	3.3	8.8	1.4
Dystonia	4.5	6.6	1.1	0.0
Amenorrhea	3.4	4.4	3.3	4.1
Intercurrent infection	1.1	3.3	4.4	2.7
Skin rash	3.4	1.1	1.1	2.7
Lactation	3.4	3.3	0.0	0.0
Diarrhea	1.1	2.2	1.1	0.0
Peripheral edema	2.3	0.0	1.1	0.0
Swelling of breasts	1.1	2.2	0.0	0.0
Convulsion or seizure	0.0	0.0	1.1	1.4
Oculogyric crisis	1.1	0.0	0.0	0.0
Syncope or loss of consciousness	1.1	0.0	1.1	0.0

Comment

Clinical Implications.—Although it has been clear for many decades that acute schizophrenic patients had reasonable chances of improving with available treatments, there generally has been a cautious and skeptical, if not nihilistic, attitude toward the prognosis of schizophrenia. However, in the past two decades, the situation has greatly improved, and considerable optimism now attends the treatment of acute schizophrenia. Since the mid-1950's, almost coincident with the introduction of chlorpromazine and reserpine—the first "tranquilizers"—there has been a marked increase in the discharge rate of patients newly admitted to psychiatric hospitals, and a decrease in the population resident in public mental hospitals, both trends occurring in the face of increased admissions. Associated with these statistical trends, the public has shown greater tolerance and understanding of the mentally ill, and mental health professionals have become more confident and energetic in their treatment of major psychiatric illnesses.

Although these events occurred coincident with the introduction of modern drug therapy, considerable doubt has been expressed whether the advent of "tranquilizing" drugs could be considered the cause of these improvements, or whether they were due to increased staffing and the gradual impact of existing psychiatric therapies, essentially milieu therapy and psychotherapy. Retrospective studies of patient movement in the California state mental hospital system [4] and at St. Elizabeths Hospital in Washington, DC,[9] indicated that release rates, and by implication improvement rates, for drug-treated patients were not different than those for non-drug treated patients, although release rates for both groups improved markedly after 1952-1955, the years the drugs were first introduced into American psychiatric practice. The defects in these studies based upon hospital statistics lie in the fact that the patients were not randomly assigned to drug treatments. In the early years of the modern drug era, sicker patients were more likely to be receiving the newer drug treatments.

Although numerous clinical trials have confirmed the early reports of the clinical value of phenothiazine drugs in the treatment of schizophrenics, the clinical trial reported upon here is the first to study a number of phenothiazine drugs in a large sample of acutely ill patients treated in diverse psychiatric treatment settings.

The findings of this study lend strong support to the rising optimism about and confidence in the effectiveness of treatment of acute schizophrenic psychoses. Even among the placebo-treated group, almost half the patients were rated as having improved to some extent. Almost 95% of the patients treated with one of the three phenothiazines improved. More significantly, the effects of phenothiazine therapy are not only quantitative, in that a large percentage of patients improved; but they are also qualitative, in that a wide range of schizophrenic symptoms and behavior are favorably altered.

The quality of drug-induced changes was impressive. The phenothiazines are most often regarded as prototypes of the "tranquilizers," and their effects understood in terms of alleviation of anxiety, diminution of overactivity, and reduction of disturbed behavior. However, the evidence from this study confirms the diverse and generalized effect of phenothiazines on the schizophrenic process. Almost all symptoms and manifestations characteristic of schizophrenic psychoses improved with drug therapy, suggesting that the phenothiazines should be regarded as "antischizophrenic" in the broad sense. In fact, it is questionable whether the term "tranquilizer" should be retained.

It is to be emphasized that schizophrenic patients improved with phenothiazine treatment even when they were not overactive, excited, belligerent, or deluded. The physician confronted with a patient who, though obviously psychotic, is withdrawn and underactive and superficially appears "tranquil," need not hesitate to prescribe phenothiazine therapy. The results of this study indicate that patients with these symptoms have a high probability of improving with drug treatment, even though they do not resemble the usual image of the excited and overactive patient for whom the term "tranquilizer" was originally introduced.

The incidence of side-effects experienced by patients receiving the three phenothiazines was consistent with knowledge of their pharmacologic actions. However, these differences in side-effects among subgroups within the phenothiazines were not associated with any demonstrable differences in over-all clinical effectiveness or effect on specific symptoms.

This study did not find any significant differences among chlorpromazine, fluphenazine, or thioridazine on 25 measures of symptomatology and behavior. It is possible that other approaches to the analysis of the data, such as that employed by Overall et al,[11] relating drug effects to patient subtypes, may reveal differences between the drugs which were not evident in this study. However, the results of this study and also those of the Veterans Administration, strongly indicate that the differences in clinical efficacy between these three drugs, if present at all, are far from striking or obvious.

Widely held clinical beliefs about the differential action of the phenothiazines[3] predicted that fluphenazine as a potent piperazine derivative would have more "activating" and "stimulating" actions than the other two drugs, and, therefore, would be more effective than chlorpromazine or thioridazine in patients with symptoms such as "Slowed Speech and Movements," "Indifference to Environment" or poor "Social Participation." In contrast, chlorpromazine, a phenothiazine with sedative effects, would have been expected to be more effective in controlling "Overactivity," "Hostility," and "Agitation and Tension." The findings of this study do not support these two conventional hypotheses. If anything, they indicate that the clinical similarities among the effective phenothiazines are greater than their pharmacological differences and strongly support the view that the new drugs, while generally as effective as chlorpromazine, do not offer any greater range of clinical use or specificity of action.

The findings of this study also cast doubt on any theory directly relating clinical efficacy to actions upon the extrapyramidal system. Soon after chlorpromazine and reserpine were observed to produce parkinsonian-like syndromes, the hypothesis was advanced that the efficacy of their clinical use was due to induced extrapyramidal dysfunctions and many practitioners advocated increasing the dose until these effects were apparent. This view was strengthened by the advent of piperazine phenothiazines which were clinically effective, highly potent on a milligram-to-milligram basis, and produced extrapyramidal symptoms in a significant percentage of patients.

Among the subclasses of phenothiazines developed, the piperazine derivatives, represented by fluphenazine, trifluoperazine, perphenazine, prochlorperazine, and thiopropazate, were generally regarded as clinically more efficacious and pharmacologically more potent than chlorpromazine because of their propensity to induce extrapyramidal dysfunction. Thioridazine had a low incidence of extrapyramidal side-effects, and it was predicted that, lacking this action upon the extrapyramidal system, it would have less clinical efficacy. The results of this study do not confirm this view. Considerable doubt exists of any necessary relationship between the capacity of the drug to induce extrapyramidal symptoms and its clinical efficacy.

At the end of six weeks, the patients on drug treatment were doing quite well clinically. Analyses of trends for rate of improvement indicated that a plateau had not been reached. In a number of areas, especially "Hostility," "Indifference to Environment" and "Social Participation," some acceleration of improvement is evident between the third and sixth week of treatment. The question arises whether, with more prolonged periods of treatment, patients would show even greater clinical improvement, and the proportion of patients in remission would increase. All the available clinical experience favors this view, and a large-scale clinical trial with patients receiving 26 weeks of drug treatment is currently being undertaken by this group of collaborating institutions.

The findings of this study serve to support the practicing physician's capacity to prescribe phenothiazine treatment.

The physician in practice may choose from among a large number of phenothiazines. Chlorpromazine, members of the piperazine group, and more recently of the piperidine group, as represented by thioridazine, are now demonstrated to be clinically effective agents. The available drugs offer a wide range of dosage, and accordingly, a wide range of safety. Although side effects do occur, they are for the most part trivial and more annoying and discomforting to the patient than potentially dangerous. They seldom necessitate discontinuance of treatment, at least in a hospital setting.

Not only can the physician be reasonably confident that patients with a wide range of symptoms will improve, but he need not be overly concerned about subtle differences among active phenothiazines.

Implications for Public Health Programs: Schizophrenic psychoses are the major source of psychiatric disability in the young and middle-aged adult population. Approximately one fifth of all patients admitted to psychiatric hospitals in the United States are diagnosed as having schizophrenic reactions. More significantly, because of its tendency toward chronicity, over 50% of patients resident in public mental hospitals suffer from schizophrenic psychoses. As such, schizophrenia constitutes a grave public health problem and represents a challenge, not only to clinical practice, but also to research and investigation.

The advent of pharmacologic treatments of psychiatric disorders offers a public health potential heretofore not available in the mental health field. Scientific demonstration of the efficacy of phenothiazine therapy of acute schizophrenic psychosis provides an opportunity for placing the treatment of the schizophrenic into the broader public health framework, rather

than considering him merely a problem for custodial care in public mental hospitals.

What are the requirements for a public health approach to acute schizophrenic psychoses? One major requirement would be the availability of treatments which would not only be effective in a large number of patients, but would also be inexpensive and relatively safe. Also, such treatments should be capable of being administered in a wide variety of treatment facilities, ones which would not require highly specialized equipment or staff. The previously available treatments, such as insulin coma therapy and electric convulsive treatment, required highly trained personnel and special anesthesia facilities. Similar considerations apply to the individual and group psychotherapies, which also require highly trained personnel.

As long as the available treatments required specialized settings and highly trained personnel, a fully public health approach to acute schizophrenia could never be developed. However, with the introduction of the drugs, it is now more feasible to treat acute psychoses in a variety of clinical settings. The results of this and other studies suggest that the wide range of acute schizophrenic psychoses, with its diverse symptoms and manifestations, can be treated in many settings, including psychiatric services in general hospitals, and by extrapolation, probably also on an ambulatory basis or in day-care centers.[6]

Two related approaches merit special attention: (1) the role of intensive phenothiazine treatment in programs designed to prevent hospitalization; and (2) the potential value of maintenance phenothiazine treatment for discharged patients to prevent relapse and rehospitalization. Although the findings of this study do not bear directly on these two problems, they are consistent with reports of the efficacy of both these approaches.

Evidence from studies by Kris[6] in New York would indicate that intensive treatment of psychotic patients still in the community can obviate the necessity for hospitalization in a significant proportion of acutely ill schizophrenic patients. The increasing psychiatric sophistication of practitioners and the availability of community psychiatric services should make this increasingly practical.

Although many patients will have achieved remission with six weeks of phenothiazine therapy, there is ample evidence from other studies that with discontinuance of drug therapy or the precipitous reduction of dose, a significant percentage of patients experience relapse. Findings of a number of studies attest to the value of long-term maintenance phenothiazine therapy in the prevention of chronicity, the treatment of imminent relapse, the reduction of rehospitalization rate, and the reinforcement of social adjustment and the facilitation of vocational rehabilitation.

These considerations are especially appropriate in light of the recent report of the Joint Commission of Mental Illness[12] and the recent special message of the President on mental illness and mental health, advocating development of comprehensive mental health centers in all population centers.

Summary and Conclusions

In a double-blind study involving over 400 acutely ill schizophrenic patients treated at nine collaborating hospitals, two newer phenothiazines (fluphenazine and thioridazine) were compared with a standard drug (chlorpromazine) and with a placebo.

The results demonstrated the clinical efficacy of drug therapy in acute schizophrenic psychoses. Ninety-five per cent of drug-treated patients showed some degree of improvement within six weeks—over 75% showed marked to moderate degrees of improvement.

In comparison, although over half of the schizophrenic patients treated with placebo showed some improvement, only 23% of the placebo group were rated as showing marked or moderate improvement.

Not only did phenothiazine treatment show over-all effectiveness in a large proportion of patients, but a wide range of schizophrenic symptoms and behavior, including

thought disturbance, paranoid symptoms, delusions, social withdrawal, loss of self-care, anxiety and agitation, were favorably influenced. At the end of six weeks, 46% of the patients were rated as having no symptoms or only borderline illness, indicating the potential for rapid achievement of symptom remission.

These clinical effects were achieved with a relatively low incidence of serious side-effects. Less than 3% of the patients had to be removed from the study because of side-effects. One patient developed grand mal seizures and two patients developed jaundice. No fatalities occurred.

The findings of this study support the view that phenothiazine drugs have a generalized anti-schizophrenic effect and are useful in patients suffering from acute schizophrenic psychoses, irrespective of whether or not overactivity and excitement are the major components of the clinical picture.

No significant differences in clinical efficacy were found among the three active phenothiazines. No evidence was found to support the view that chlorpromazine was more effective in patients requiring sedation or that the peperazine derivative, fluphenazine, was more effective in withdrawn patients in need of "activation or stimulation." Thioridazine, a piperadine derivative, although producing low incidence of extrapyramidal symptoms, was clinically effective, casting doubt on the view that extrapyramidal dysfunction is a necessary feature of clinical efficacy of phenothiazines.

The findings of this study support the increasing confidence in and optimism about the treatment of acute schizophrenic psychoses. Moreover, the efficacy and feasibility of drug treatment have great potential value in the development of a public health approach to the treatment of acute schizophrenic psychoses and the prevention of chronic disability.

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REFERENCES

1. Bellville, T. P.; Heistad, G. T.; and Schiele, B. C.: A Comparative Study of Thioridazine and Carphenazine Using Sequential Analysis, Paper read at American Psychiatric Association, Toronto, Canada, 1962.

2. Burdock, E. I.; Hakerem, G.; Hardesty, A. S.; and Zubin, J.: Ward Behavior Rating Scale, 1959.

3. Cole, J. O., and Clyde, D. J.: Extrapyramidal Side Effects and Clinical Response to the Phenothiazines, in Bordeleau, Jean-Marc, editor: Extra-Pyramidal System and Neuroleptics, Montreal: Editions Psychiatrique, 1961, pp 469-478.

4. Epstein, L. J.; Morgan, R. D.; and Reynolds, L.: An Approach to the Effect of Ataraxic Drugs on Hospital Release Rates, Amer J Psychiat 119: 36-47, 1962.

5. Hollingshead, A. B.: Two Factor Index of Social Position, unpublished manuscript, Yale University, New Haven, Conn.

6. Kris, E. B.: "Prevention of Rehospitalization Through Relapse Control in a Day Hospital," in Mental Patients in Transition, edited by Greenblatt, M.; Levinson, D. J.; and Klerman, G. L., Springfield, Ill: Charles C Thomas, Publisher, 1961, pp 155-162.

7. Kurland, A. A.; Hanlon, T. E.; Tatom, M. H.; Ota, Kay Y.; and Simopoulos, A. M.: The Comparative Effectiveness of Six Phenothiazine Compounds, Phenobarbital and Inert Placebo in the Treatment of Acutely Ill Patients: Global Measures of Severity of Illness, J Nerv Ment Dis 133:1-18, 1961.

8. Lasky, J. J.; Klett, C. J.; Caffey, E. M.; Bennett, J. L.; Rosenblum, M. P.; and Hollister, L. E.: A Comparison Evaluation of Chlorpromazine, Chlorprothixene, Fluphenazine, Reserpine, Thioridazine and Triflupromazine, Dis Nerv Syst 23:1-8, 1962.

9. Linn, E. L.: Drug Therapy, Milieu Change, and Release From a Mental Hospital, AMA Arch Neurol 81:785-794, 1959.

10. Lorr, M.; Klett, C. J.; McNair, D. M.; and Lasky, J. J.: Inpatient Multidimensional Psychiatric Scale (IMPS) Manual, Copyright, Maurice Lorr, 1962.

11. Overall, J. E.; Hollister, L. E.; Honigfeld, G.; Kimbell, I. H.; Meyer, F.; Bennett, J. L.; and Caffey, E. M.: Controlled Comparison of Acetophenazine With Perphenazine in Schizophrenics, Report No. 40, October, 1962, Central N. P. Research Laboratory, VA Hospital, Perry Point, Md, prepublication of personal communication to the author.

12. Action for Mental Health: Final Report of the Joint Commission on Mental Illness and Health, New York: Basic Books, Inc., 1961.