

Important Issues in the Drug Treatment of Schizophrenia

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Abstract

The large body of research demonstrating the effectiveness of antipsychotic drugs in the treatment of acute schizophrenia is selectively reviewed. Research evidence relevant to the following issues is assessed; indications for selective treatment; characteristics of drug responders and nonresponders; indications for high dosage phenothiazine treatment; indications for maintenance therapy; benefits and risks of antipsychotic drugs. Recommendations are made concerning areas of psychopharmacologic research that require further development.

Antipsychotic drugs are almost universally used in the treatment of schizophrenia, yet there are many unresolved issues. Should all schizophrenics receive drugs? In what dose should they be given? Do the advantages of maintenance therapy outweigh the risks? This review will focus on such issues.

General Efficacy

The effectiveness of antipsychotic medication in the treatment of acute schizophrenia has now been established by the results of many well-controlled, double-blind studies comparing chlorpromazine and other antipsychotic drugs to placebo. Not only are antipsychotic drugs one of the more effective forms of therapy used in psychiatry, but they also rival the effectiveness of accepted medications used in other specialties for the treatment of medical disorders. (For comparison, see figures 1 and 2.)

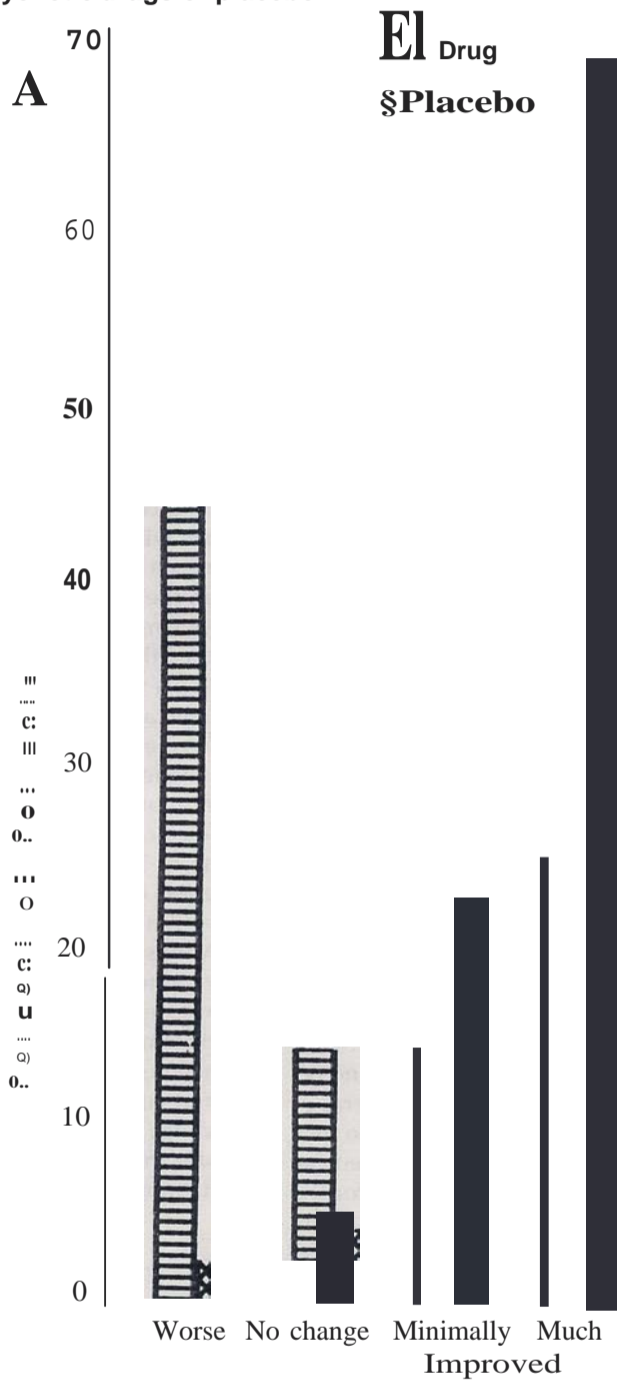
The effectiveness of antipsychotic drugs is illustrated in a collaborative study carried out by the National Institute of Mental Health (Cole,

Goldberg, and Davis 1966; Cole, Goldberg, and Klerman 1964; Goldberg, Klerman, and Cole 1965). This effort is perhaps the best single study comparing the effectiveness of antipsychotic medication vs. placebo in the treatment of acute schizophrenics. Data for patients who deteriorated or improved, as reflected by global evaluation measures, are graphically presented in figure 1. The magnitude of the drug effect is readily apparent: Three-fourths of the patients on antipsychotic medication showed substantial improvement during the 6-week trial, while virtually no patients deteriorated. In contrast, almost 50 percent of the placebo group showed clinical deterioration. Included in these results were a considerable number of patients whose conditions deteriorated so much that they had to be removed from the study for emergency treatment, or who improved to such a degree that they were discharged. Patients who completed the trial, were evaluated in terms of much improvement, minimal improvement, no change, or worse. The results are typical of those of scores of similar studies carried out by other investigators. The findings of clinical effectiveness of antipsychotic medications are striking in their uniformity.

Antipsychotic medications seem to have a normalizing effect. They improve typical schizophrenic symptoms such as hallucinations and delusions, as well as other types of abnormal behavior. The antipsychotic drugs are not uniformly sedating. Under their influence, retarded schizophrenics appear to "speed

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Figure 1. Results of the treatment of schizophrenic patients with antipsychotic drugs or placebo



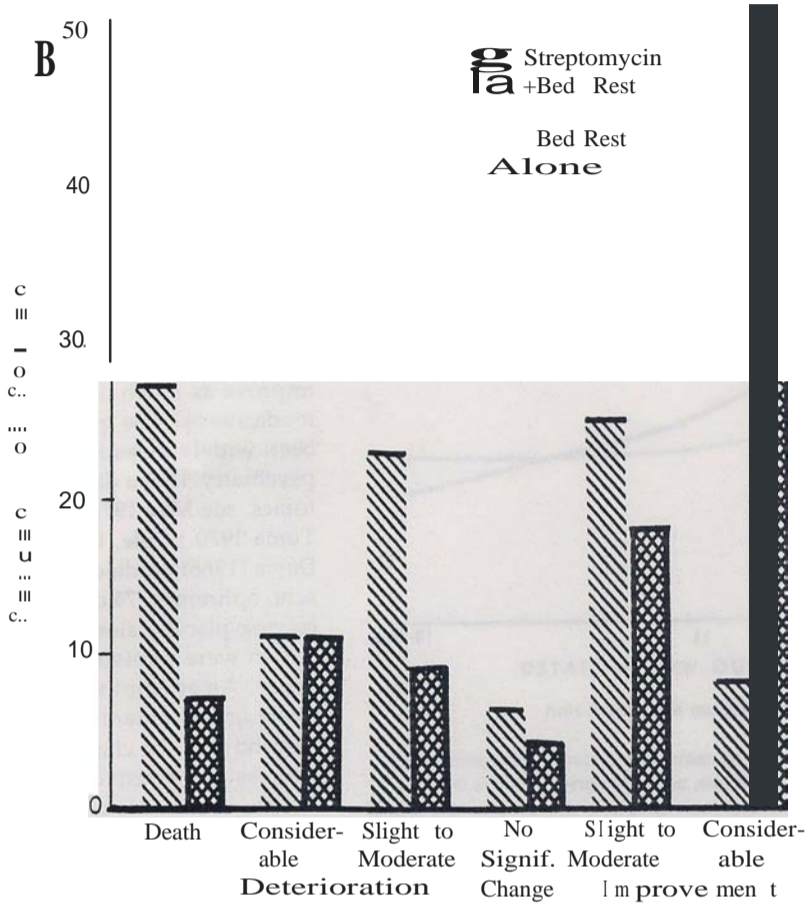
From Cole, Goldberg, and Davis (1966) and Cole, Goldberg, and Klarman (1964).

up," and excited schizophrenics seem to "slow down." These medications are not selectively antischizophrenic, for they also decrease the symptoms of psychotic depression, mania, and organic psychosis.

Reduction in thought disorder can also be observed. Shimkunas, Gynther, and Smith (1966) reported that overinclusive thinking, as reflected by performance on a categorization task, and bizarre and inappropriate responses were decreased by treatment with phenothiazines. In collaboration with Philip Holzman and Steven Hurt (unpublished study), we attempted to assess thought disorder before and after drug treatment. The responses of patients to standardized stimuli such as Rorschach cards and the Wechsler Adult Intelligence Scale were "blindly" categorized by a psychologist to determine the amount and change of thought disorder. Based on this evaluation, the administration of antipsychotic medication resulted in a marked reduction of both symptoms of schizophrenia and thought disorder. Particularly interesting was the observation that improvement in thought disorder occurred within the same time course and to the same degree as improvement in schizophrenic symptoms (figure 3).

Spohn et al. (1977) studied the effects of antipsychotic medications on various psychological functions of a group of chronic schizophrenic patients. In this study, patients were randomly assigned to either placebo or chlorpromazine treatment after a 6-week placebo washout period. Forty patients were studied during the washout period, and 16 of these experienced a relapse—a relapse rate of 17 percent a month. The 40 patients were evaluated on a variety of psychological tests and then were re-

Figure 2. Therapeutic effects of streptomycin with bed rest vs. bed rest alone in pulmonary tuberculosis



From British Medical Research Council Study.

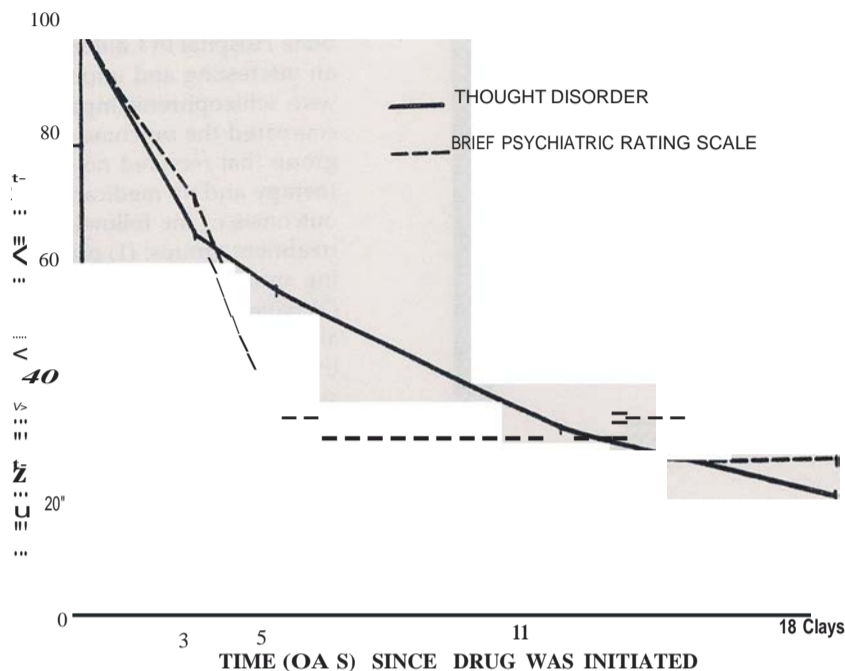
tested on weeks 1, 4, and 8. Patients who received chlorpromazine demonstrated markedly significant improvement in clinical symptomatology compared to patients on placebo. In addition, some tests measuring psychological dysfunction showed significant improvement in attention, perception, and psychophysiological parameters. Thus, chlorpromazine seems to improve the concentration-attention deficits of schizophrenia. It reduces overestimation, fixation, and time on a perceptual task, while increasing accuracy of

perceptual judgment. The basic psychological function measured by these tests may be the ability to appropriately attend to the task at hand. The attentional dysfunction, the impaired information processing, and the autonomic dysfunction noted in these chronic schizophrenic patients were normalized by the administration of antipsychotic medication. The results of Spohn et al. (1977) are consistent with the improvement in psychotic symptoms and thought disorder in the studies mentioned above.

May and his co-workers (May 1968; May, Tuma, and Dixon 1976; May et al. 1976) at the Camarillo State Hospital in California designed an interesting and important study with schizophrenic inpatients. They compared the outcome of a control group that received no psychotherapy and no medications with the outcomes of the following three treatment groups: (1) patients receiving antipsychotic medications alone, (2) patients receiving psychotherapy alone, and (3) patients receiving drug therapy plus psychotherapy. Results showed that for the group receiving drugs only, the need for sedatives or hydrotherapy was decreased, and clinical status was improved, as indicated by the Menninger Health-Sickness Rating Scale. As shown in table 1, there were some obvious differences between the drug and no-drug groups. A slight trend can be noted for psychotherapy plus drugs to be more effective than drugs, but this trend was not statistically significant. The patients receiving only psychotherapy showed no more gains than the no-treatment control group. In fact, the patients receiving only psychotherapy were slightly worse than the control group on some of the variables, but these differences did not achieve statistical significance.

May's study also included followup reassessments for 3, 4, and 5 years after completion of the 6-month treatment study. Although all patients received standard treatment after completion of the first phase of the study, there were interesting and significant outcome differences among the four patient groups. Outcome was assessed by determining the number of days patients spent in the hospital after the index admission. Patients in the no-

Figure 3. Changes in schizophrenic symptomatology and thought disorder in patients treated with haloperidol



Unpublished data collected in collaboration with PhiHp Holzman and Steven Hurt.

Note that improvement in thought disorder, as measured by responses to standardized stimuli such as Rorschach cards and the Wechsler Adult Intelligence Scale, occurred within the same time course and to the same degree as improvement in schizophrenic symptoms assessed using the Brief Psychiatric Rating Scale.

drug groups spent about twice as many days in the hospital after discharge from their index admissions as patients who were treated with drugs (figure 4). Since all patients received similar standard treatments after completing the index study, the decisive variable in creating this large outcome difference was apparently whether or not the patient initially received medication, as opposed to factors that might have influenced the patient's course subsequent to the index treatment period.

May's results suggest that an initial absence of drug treatment may result in substantially less beneficial effects

during the subsequent 3 to 5 years, relative to the beneficial effects produced following early medication. Noteworthy was the slight tendency for the group who received psychotherapy plus drugs to do better than the group receiving medications alone. Of even greater interest is the finding that outcome for patients who received only psychotherapy was significantly worse than outcome in the no-treatment control group (figure 4). May's study is also quite important for the light it sheds on whether drug treatment truly affects the natural course of schizophrenia. The obtained results sug-

gest that a lack of drug treatment during the initial phase of an acute episode may produce harmful effects that can persist for years afterward.

Indications for Selective Treatment

Figure 1 shows that approximately 25 percent of schizophrenics improve significantly on placebo alone. This finding raises an important question: Is there a subgroup of schizophrenic patients who require medications, and is there another subgroup who improve as much or more without medications? The question has not been widely investigated in psychiatry. (For a discussion of these topics, see May 1974, 1975; May and Tuma 1970.) Cole, Goldberg, and Davis (1966) studied a group of 338 schizophrenics, 74 of whom were receiving placebo alone and 264 of whom were receiving antipsychotic drugs. An attempt was made to correlate improvement on drug *vs.* placebo with the characteristics of the process and reactive distinction in schizophrenia. None of these variables predicted response when considered alone. However, it is always possible that a higher order combination might have shown evidence of predictors. Nonetheless, this is important negative evidence for research.

There have been only a few studies that investigated whether certain subgroups of schizophrenics are more appropriate for antipsychotic medication treatment after an acute psychotic episode. Klein and Rosen (1973) studied a group of 88 schizophrenic patients admitted to Hillside Hospital. The patients were randomly assigned to either placebo or a fixed dosage, incremental schedule of chlorpromazine (300 mg the first week, 600 mg the second, 900 mg the

Table 1. Assessment of outcome in schizophrenic patients treated with and without antipsychotic drugs¹

Outcome measures	No drugs		Drugs	
	No psychotherapy	Psychotherapy	No psychotherapy	Psychotherapy
Percent released	58.8	64.4	95.1	96.3
Nurses' rating of MACC (motility, affect, cooperation, communication)	37.7	37.7	47.8	48.1
Nurses' Menninger Health-Sickness Rating Scale	26.0	22.7	28.9	29.8
Nurses' idiosyncratic symptoms	37.3	28.8	65.7	74.2
Therapists' rating	22.1	20.9	26.4	27.3
Analysts' insight rating	3.4	3.3	3.7	4.1

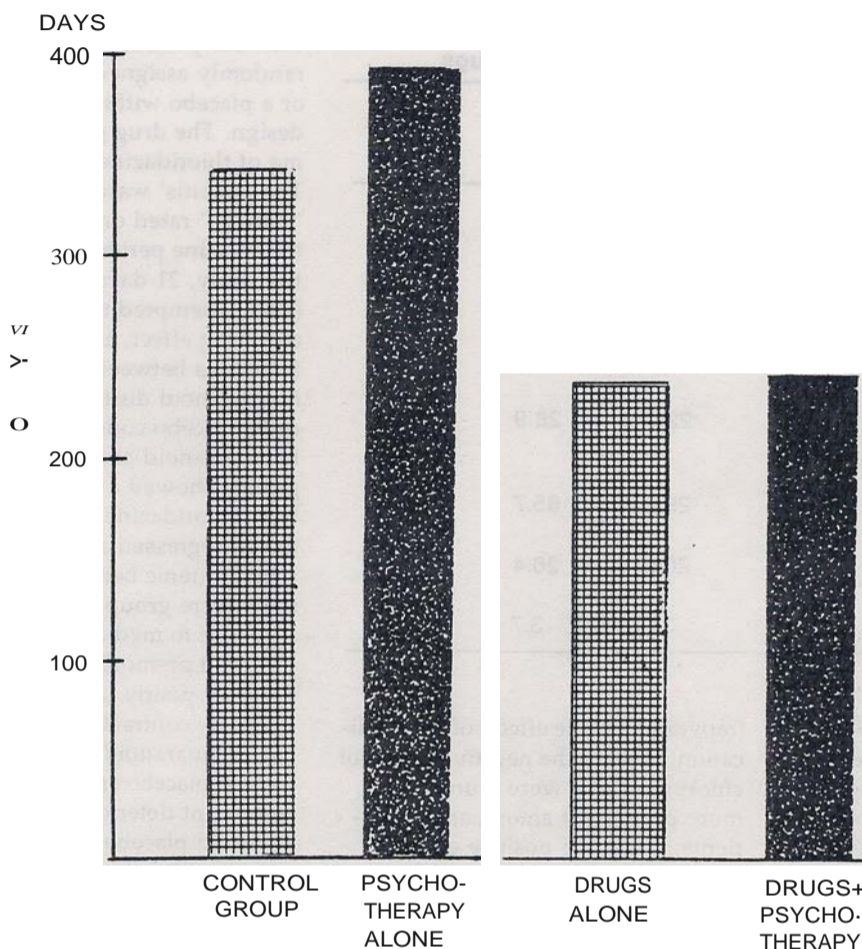
¹ From May (1968).

third, and 1,200 mg thereafter). Premorbid adjustment was assessed based on the patients' case histories, and psychological symptomatology was rated throughout the 6-week study period. The premorbid adjustment ratings were dichotomized into two major groups of premorbid adjustment: asocial (low competence) and nonasocial (high competence). Antipsychotic drug treatment was found to have a positive effect in reducing psychopathology for the nonasocial (high competence) patients, but effects on the asocial (low competence) patients were mixed. The asocial group showed positive effects from drugs on certain symptom ratings, while they did worse on some behavioral measures. Klein and Rosen speculated that some of the negative effects resulting in the reduction of such scores could have been attributed to the ex-

trapyrnidial side effects of the medication. In sum, the negative effects of chlorpromazine were found to be more prominent among asocial patients, while the positive effects of chlorpromazine were more prominent in nonasocial patients.

Judd et al. (1973) believed it would be useful to study the effects of antipsychotic medication on both paranoid and nonparanoid schizophrenics. Their hypothesis was that since paranoid patients appear to have a better prognosis than nonparanoid patients, they might also have a differential response to antipsychotic medication. In this study, 24 acute male schizophrenics with a good premorbid adjustment based on the Phillips Scale were entered into the study. Ten of these patients were placed into the paranoid group, with six receiving active medication and four receiving placebo. Of the

remaining 14 nonparanoid patients, six were given drugs and eight were placed on placebo. After a 7-day washout period, each patient was randomly assigned to either a drug or a placebo within a double-blind design. The drug group received 100 mg of thioridazine four times a day. The patients' ward behavior was "blindly" rated once a week during the baseline period and at the end of the study, 21 days later. Judd et al. (1973) attempted to determine a general drug effect, as well as the interactions between the paranoid-nonparanoid distinction and the drug-placebo conditions. In general, both paranoid and nonparanoid groups showed a positive drug effect. Thioridazine consistently reduced regressed and disorganized schizophrenic behavior. However, there were group differences in the response to medication. On placebo, the good premorbid, paranoid group did very poorly, and in fact deteriorated. By contrast, the good premorbid, nonparanoid patients did fairly well on placebo and did not show the significant deterioration seen in the paranoid placebo group. Although severe schizophrenic symptoms (regression and disorganization) improved in both groups, the good premorbid, nonparanoid group demonstrated a minimal medication response, especially when compared to the good premorbid, paranoid group. Thus, in the study of Judd et al. (1973), schizophrenics with a good premorbid history benefited from antipsychotic medication; within this group of good premorbid schizophrenics, patients with paranoid symptoms improved more substantially when medicated and exhibited more deterioration without medication when compared to good premorbid, nonparanoid patients. The results of the studies by Klein

Figure 4. Days in hospital at 3-year followup from first admission

From May et al. (1976).

and Rosen (1973) and Judd et al. (1973) are apparently contradictory. It would have been interesting if Judd et al. (1973) had tried to characterize the nonprocess and non-paranoid group, but unfortunately they made no effort to identify the types of patients in this heterogeneous group of psychotic patients.

Three studies have investigated whether particular subgroups do well with or without drugs. The large NIMH study failed to relate the process-reactive distinction to a dif-

ferential drug-placebo response. The other two studies found apparently contradictory results. Presently, we cannot state which type of schizophrenic patient does not require medication, but we also cannot rule out the possibility that such a subgroup exists. These questions remain for further research.

Our inability to predict which patients will respond to antipsychotic medication reflects a significant gap in existing knowledge. In many clinical settings, schizophrenic patients

are routinely treated with neuroleptic medication in a nondiscriminate fashion. At the other extreme, some clinicians use antipsychotic medication only as a last resort for those patients who fail to respond to psychotherapy. A more rational method of treating schizophrenics would be to use medication only as clinically indicated for those patients appropriate for medication as defined by research.

Indications for High Dosage Phenothiazine Treatment

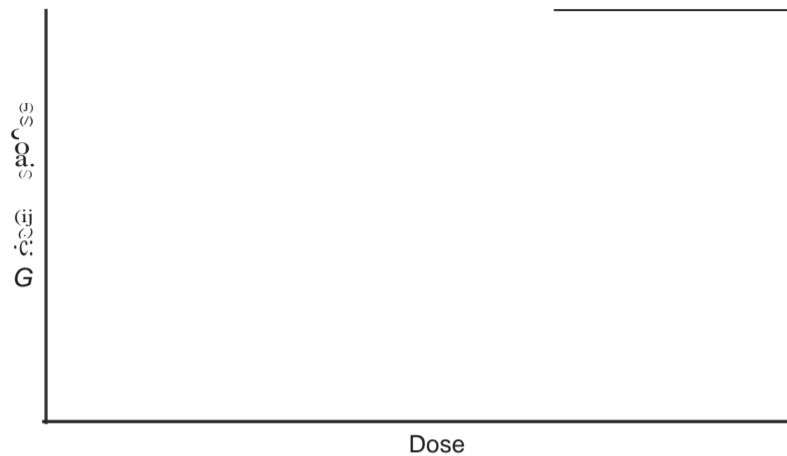
Some patients do not obtain significant benefit from standard doses of antipsychotic medication. This fact raises the question as to whether they might improve on higher than normal doses. A related question is whether high doses produce a faster response.

It has been shown that massive "mega" doses of potent antipsychotics such as trifluoperazine, haloperidol, perphenazine, and fluphenazine can be administered in daily doses as high as 700 or 1,000 mg. Can one therefore extrapolate that newly admitted schizophrenics would show a more rapid and complete recovery from massive doses? Ericksen et al. (1978) addressed this question in a double-blind study in which patients given a 5-day loading dose of 60 mg of intramuscular haloperidol were compared to patients given 15 mg of haloperidol once a day orally. The study investigated two issues: (1) Does a very high loading or "digitalization" dose result in a more rapid clinical improvement in the first day or the first few days of treatment compared to a standard dose? (2) If such a high loading dose does result in a more rapid improvement in schizophrenic symptoms, then is this improvement

maintained when the patient is on lower doses at the end of 3 weeks; i.e., is the final result after 3 weeks significantly better than the clinical effect seen with a normal dose? Fifteen mg of haloperidol would be considered on the high range of a normal dosage since it is about equal to 940 mg of chlorpromazine. Sixty mg of intramuscular haloperidol would be considered a high loading dose, because it would be equivalent to about 3,600 mg or more of chlorpromazine, and because intramuscular haloperidol probably has a greater bioavailability than the oral form. After the first 5 days of treatment, the high dose group was lowered to a normal dose of 15 mg of haloperidol, and the group of patients who received 15 mg initially were maintained on this dosage throughout the entire 3 weeks of the study. Patients chosen for the study were acutely psychotic schizophrenics who were randomly assigned to the high or normal dosage groups. Rating instruments included the Brief Psychiatric Rating Scale (BPRS), the New Haven Schizophrenia Index, and the Holzman-Johnston Thought Disorder Scale. Ratings were done on a double-blind basis. The therapeutic outcomes for both groups were identical at both 5 days and 3 weeks. The main difference was that the high loading dose group had more side effects, especially dystonias. Thought disorder symptoms showed equal improvement in both groups.

A good way to conceptualize the relationship between dose and therapeutic efficacy is to consider the dose-response curve as illustrated in figure 5. A better response is attained as the dose increases on the linear portion of the dose-response curve. When the top of the linear portion of the dose-response curve is reached,

Figure 5. Dose-response curve



an inflection point is approached and clinical results begin to diminish. Beyond this point, the increase in dose results in only a minimal increase in clinical response, and ultimately as the dose goes even further, there is no increase in clinical response. The inflection point at which the linear part of the curve shows a "diminished return" is often referred to as the optimal portion of the dose-response curve. This essentially means that all of the clinical response that is going to occur is attained at this point. The data then suggest that the equivalent of 900 mg of chlorpromazine is at or slightly above the "optimal point."

In a similar study, Donlon et al. (1978) compared the effects of a loading dose of 80 mg of fluphenazine per day with a standard dose of 20 mg per day in 32 recently hospitalized acute schizophrenics who were studied for a period of a few days to a week. The high dose group received an average of 40 to 74 mg during days 2 to 7 of the study. Like Ericksen et al. (1978), Donlon et al. (1978) found that both dose regimes produced similar clinical results. It should be noted that 20 mg of fluphenazine used in the standard

dose group is the equivalent of 3,000 to 5,000 mg of chlorpromazine.

Goldberg et al. (1972) compared the efficacy of 60 mg vs. 600 mg of trifluoperazine in a double-blind study of a group of newly admitted schizophrenic patients. Sixty mg of trifluoperazine is equivalent to about 2,000 mg of chlorpromazine a day, and since the normal dose of chlorpromazine is about 700 mg a day, this is about three times the normal dose. Six hundred mg a day is the equivalent of 20,000 mg of chlorpromazine, or 30 times the normal dose of this antipsychotic. In this study, both treatments proved to be equally efficacious.

Similarly, Quitkin, Rifkin, and Klein (1975) demonstrated that 1,200 mg a day of fluphenazine was no more clinically effective than 30 mg per day. The chlorpromazine equivalent of these two doses would be 100,000 mg and 2,500 mg, respectively.

Goldstein et al. (1978) studied 196 acute first admission schizophrenics and randomly assigned them to four groups: low dose (6.25 g q/2 weeks) or high dose (25 g q/2 weeks) fluphenazine, with or without family therapy, for an 8-week trial period

consisting of 2 weeks of inpatient care and 6 weeks of outpatient care. The results indicated a clear dose-response relationship. Those receiving high dose fluphenazine experienced significantly fewer relapses ($p = .002$, Fisher's Exact Test). Furthermore, the family therapy significantly prevented relapse independent of drug group ($p = .05$). In sum, the number of relapses for the four groups were as follows: high dose fluphenazine plus family therapy-0 relapses out of 23; high dose fluphenazine without family therapy-3 relapses out of 26; low dose fluphenazine plus family therapy-2 relapses out of 21; low dose fluphenazine without family therapy-5 relapses out of 16. At the end of a 6-month followup period, the dose-response drug effect in the family therapy group persisted and even became larger, as seen in the outcome data for the same four groups: with the high dose and family therapy, there were 0 relapses out of 23, and without family therapy, there were 5 relapses out of 29; with the low dose and family therapy, there were 5 relapses out of 23, and without family therapy, there were 10 relapses out of 21. Note that the equivalent of 73 mg a day of chlorpromazine is less effective than the equivalent of 293 mg per day of chlorpromazine. This evidence suggests that the dose range of 50 to 300 mg is on the linear portion of the dose-response curve.

In 1968, Prien and Cole contrasted the effectiveness of 2,000 mg of chlorpromazine versus 300 mg of chlorpromazine in a group of chronic schizophrenic patients. They found that the higher dose was more effective than the lower dose, so it appears that 300 mg is probably on the linear part of the dose-response curve. In essence, when a lower dose

is less effective than a higher dose, the lower dose is probably below the optimal point on the dose-response curve. One assumes that the optimal point is somewhere between the two doses and that one can bracket in the optimal point by studying multiple doses or by comparing several studies. Each study attempts to use a pair of doses to determine where the optimal break point might be bracketed.

Gardos et al. (1974) treated a group of schizophrenics with either 400 mg or 1,760 mg of chlorpromazine equivalence, and the results showed that both doses were essentially equal in clinical efficacy. In a study by Prien, Levine, and Cole (1969), a dose of 15 mg of trifluoperazine, equivalent to 535 mg of chlorpromazine, was found to be equally effective to 80 mg of trifluoperazine, equivalent to 2.8 mg of chlorpromazine. These results suggest that 535 mg of chlorpromazine or its equivalent is near enough to the optimal effective dose, since an extra high dose did not cause additional improvement in this chronic population. However, Clark et al. (1970, 1972) showed that doses of 300 mg or less of chlorpromazine are probably below the effective treatment dose for chronic patients: A dose of 600 mg is better than 300 mg, which is more effective than 150 mg.

Brotman, Muzekari, and Shaken (1969) attempted a double-blind, noncrossover, random trial of 80 schizophrenic patients who received placebo or 15, 30, or 60 mg a day of butaperazine (equivalent to 167, 333, and 667 mg of chlorpromazine). The group that received the equivalent of 667 mg of chlorpromazine responded significantly better on the uncooperative subscale of the BPRS. On the five other subscales of the BPRS, there was a nonsignificant trend favoring

the high dose group. These results constitute limited evidence that a dose of 667 mg is better than 333 mg or less. The effective dose level here is quite similar to the effective dose used by Clark et al. (1970)-the equivalent of 600 mg of chlorpromazine.

Simpson et al. (1968) attempted to study the dose-response profile of butaperazine by investigating 24 chronically regressed schizophrenic patients who were randomly assigned to four groups under nonblind conditions. One group was started on 5 mg of butaperazine a day (55.5 mg chlorpromazine equivalence) and the dose was increased rapidly to 40 mg (444 mg chlorpromazine equivalence) during the third and fourth weeks of the study. The other groups started at 40, 80, or 120 mg and were increased to a final dose of 80, 120, or 160 mg, respectively. During the last 2 months of the study, the four groups of patients were stabilized on 40, 80, 120, or 160 mg of butaperazine (equivalent to 444, 888, 1,333, and 1,778 mg of chlorpromazine). The four groups showed no significant difference in therapeutic efficacy, which suggests that 444 is near the optimal portion of the dose-response curve (not statistically significant). However, there was a tendency during the initial part of the study for the patients who received 5 mg of butaperazine (55.5 mg chlorpromazine equivalence) to do less well than patients who received higher doses.

The statistical analysis used by Simpson et al. was inappropriate for this problem. It would be useful to reanalyze the results with a more appropriate test such as a nested two-way analysis of variance. The small size of the sample (six in each group) precludes firm conclusions, but the results suggest that doses substantially higher than the equivalent of

440 mg of chlorpromazine show no advantage over lower doses. It should be noted that these maintenance doses were used on chronic patients, and the findings should not be uncritically generalized to acute schizophrenics.

In another study, conducted by Carscallen et al. (1960), chronic patients were again given 10 to 100 mg of trifluoperazine (357 to 3,570 mg chlorpromazine equivalence) yet there was no significant difference obtained between these two doses. Since these patients were all diagnosed as chronic, this was essentially a maintenance study, and 357 mg of chlorpromazine equivalence was sufficient for a maintenance dose.

It is important to note that in these various studies, some investigators treated acute patients, while others treated chronic patients. Moreover, there were many differences in methodological variables. However, the compiled data enable one to approximate a dose-response curve. Huge doses show no advantage over doses in the range of 900 mg of chlorpromazine or its equivalent. Attempting to fit these numbers to a dose-response curve, we find that doses of 150 to 300 mg of chlorpromazine equivalence are approximately on the linear portion of the dose-response curve. Massive doses are beyond the optimal part of the dose-response curve, i.e., past the inflection point that designates the theoretically optimal response (see figure 5). However, it is important that patients be treated individually, as different patients may require variable doses; very high doses may be indicated for certain individuals. The above discussion of dose-response relationships is intended to approximate the location of the average dose along a dose-response curve. In the case of patients who require higher

than normal doses, the dose-response curve would shift to the right, whereas those patients more sensitive to the medication would produce a dose-response curve that would be shifted to the left. This discussion of the few studies available on dose levels is intended to call attention to a neglected area and to review the available (albeit limited) evidence concerning dose-response curves for the antipsychotic medications. An optimal dose for the average patient is the equivalent of approximately 500 to 1,000 mg of chlorpromazine per day.

Indications for Maintenance Therapy

The material presented in table 2 includes all of the 29 controlled studies evaluating the maintenance treatment of schizophrenia by antipsychotic drugs for longer than 1 month. The large number of studies using random assignment designs, several of which contain a significant number of patients, enables one to estimate the prophylactic effect of antipsychotic drugs compared to placebo for maintenance therapy. The clinical settings in which these studies were performed were quite heterogeneous: e.g., private, state, and VA hospitals, and both inpatient and outpatient settings in the United States, United Kingdom, and Europe. The consistent findings that have been reported make the argument for maintenance therapy particularly robust, especially when one considers that the studies were carried out by a variety of different investigators from different countries, using different designs in different clinical settings.

Nevertheless, one must consider the possibility of systematic errors that might have produced the consis-

tent findings that drugs are more efficacious. One such source of bias could be that side effects prevented raters from being double blind for some patients. This methodological consideration has been carefully studied by several investigators. Parades et al. (1966) attempted to evaluate whether side effects could bias a double-blind study. The correlation coefficient between presence or absence of side effects in clinical improvement was negligible ($r = .01$). These results indicate that raters were not biased by the observation of side effects. A similar analysis was done by Prien and Cole (1968), and they likewise found no relationship between the occurrence of side effects and clinical improvements in patients who were treated with high doses of chlorpromazine. Hirsch et al. (1973) in an English study sponsored by the Medical Research Council also attempted to check for rater bias. The evidence and questionnaires completed at the end of the trial indicated that community nurses, physicians, and patients themselves were not aware of which patients were receiving active medication. In sum, none of these studies found evidence indicating that raters were significantly biased by the observation of side effects. Interestingly, Adelson and Epstein (1962) attempted to overcome this source of bias by using "active placebos" that contained both sedative and anticholinergic properties. Patients receiving this type of placebo experienced the same relapse rate as those receiving inactive traditional placebo.

In sum, the above studies produce convincing evidence that the appearance of side effects does not significantly influence the results. Since all of the studies except two (Good, Sterling, and Holtzman 1958; Marjerson et al. 1964) revealed how many

Table 2. Antipsychotic prevention of relapse

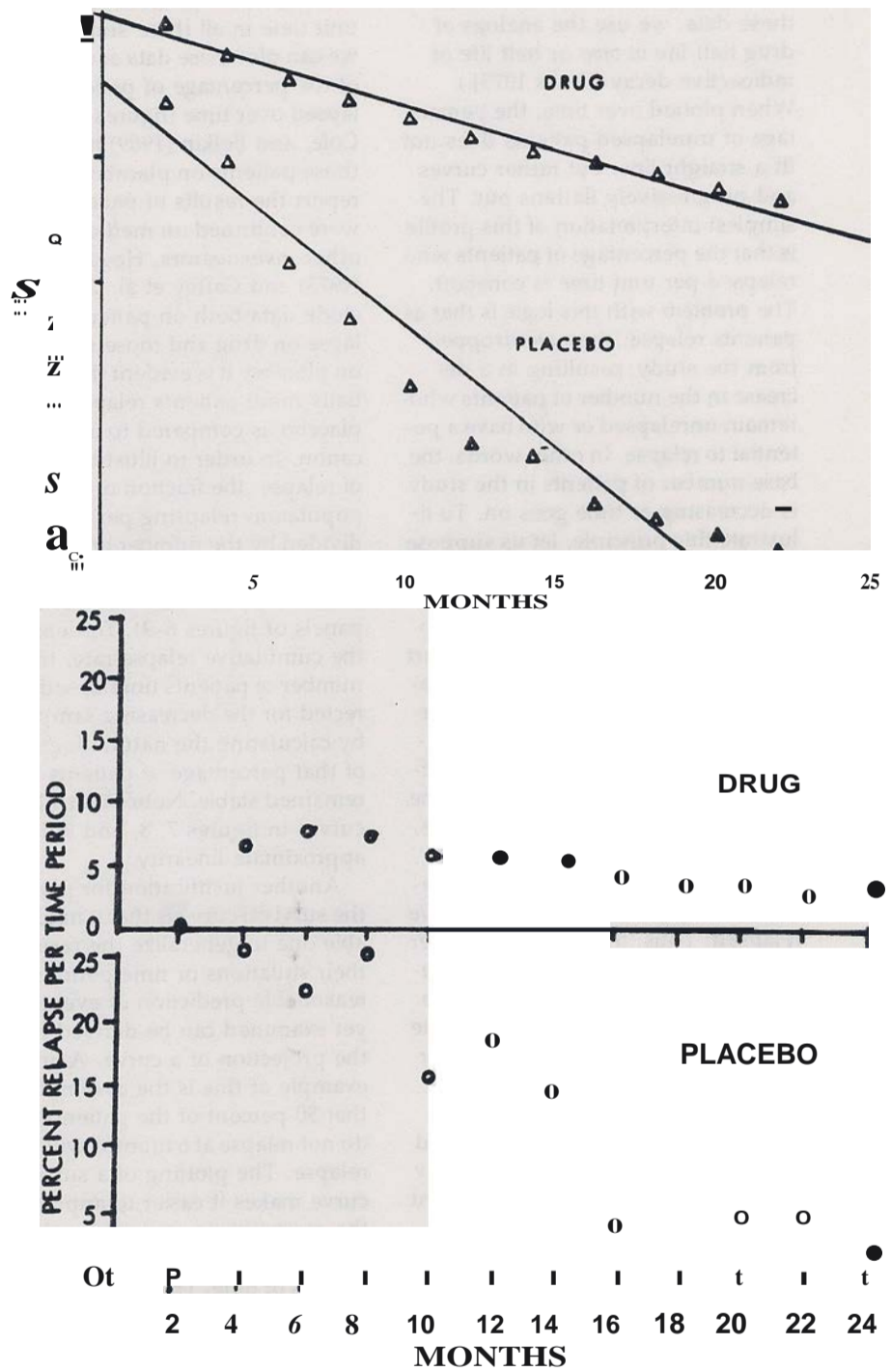
Study	Number of patients	Percent relapse on placebo	Percent relapse on drug	Percent difference in relapse rate (placebo drug)
Adelson and Epstein (1962)	281	90	49	41
Andrews, Hall, and Snaith (1976)	31	35	7	28
Baro et al. (1970)	26	100	0	100
Blackburn and Allen (1961)	53	54	24	30
Caffey et al. (1964)	259	45	5	40
Chien and Cole (1975)	31	87	12	74
Clark et al. (1971)	19	70	44	26
Clark et al. (1975)	35	78	27	51
Diamond and Marks (1960)	40	70	25	45
Engelhardt et al. (1967)	294	30	15	15
Freeman and Alsen (1966)	86	31	14	17
Garfield et al. (1966)	27	31	11	20
Gross (1975)	61	65	34	31
Gross and Reeves (1961)	109	58	14	44
Hershon, Kennedy, and McGuire (1972)	62	28	7	21
Hirsch et al. (1973)	74	66	8	58
Hogarty et al. (1973)	361	67	31	36
Left and Wing (1971)	30	83	33	50
Kinross-Wright and Charalampous (1965)	40	70	5	65
Melynk, Worthington, and Lavery (1966)	40	50	0	50
Morton (1968)	40	70	25	45
Prien and Cole (1978)	762	42	16	26
Prien et al. (1969)	325	56	20	36
Rassidakis et al. (1970)	84	58	34	24
Rifkin et al. (1977a, 1977b)	62	68	7	61
Schawver et al. (1959)	80	18	5	13
Schiele, Vestre, and Stein (1961)	80	60	3	57
Troshinsky, Aaronson, and Stone (1962)	43	63	4	59
Whitaker and Hoy (1963)	39	65	8	57
Summary	3,519	55	19	36

Summary statistics: $p < 10^{-100}$

patients relapsed or sustained improvement, the data can be presented in a 2 x 2 contingency table. The results can be combined using the method of Fleiss (1973), a modification of the method of Cochran (1954), which is appropriate for situations in which the percent of relapse varies from study to study. In a further modification of this method, the combined data for the various studies can be partitioned into two statistical components. The first component indicates to what degree the association found in the various studies is similar, and the second component identifies the magnitude of this association. The first analysis showed that the degree of association (prophylactic effect of the drug) was quite similar. The second component indicated that the magnitude of the association demonstrated a highly statistically significant result; the probability that these results would have been achieved by chance alone is less than 10 to the minus 100th power (10^{-100}). Using the method of Winer (1971), the combination of the probabilities obtained for the 31 studies also produces a *p* value of less than 10^{-100} . These statistical tests indicate overwhelming evidence that antipsychotic drugs prevent relapse in schizophrenia when compared to placebo. In other words, all of the studies are in approximate agreement in finding that medication prevents relapse.

We shall begin the discussion of this issue by examining the data descriptively. The most complete study was conducted by Hogarty and his associates (Hogarty et al. 1973, 1974a, 1974b; Hogarty and Ulrich 1977) who compared the effectiveness of maintenance antipsychotic medication to placebo in outpatient schizophrenics. Cumulative relapse rates are shown in figure 6 as the

Figure 6. Cumulative relapse rates from Hogarty et al. (1973)



percentage of patients who remained unrelapsed. (In the discussion of these data, we use the analogs of drug half life *in vivo* or half life of radioactive decay [Davis 1975].) When plotted over time, the percentage of unrelapsed patients does not fit a straight line, but rather curves and progressively flattens out. The simplest interpretation of this profile is that the percentage of patients who relapsed per unit time is constant. The problem with this logic is that as patients relapse, they are dropped from the study, resulting in a decrease in the number of patients who remain unrelapsed or who have a potential to relapse. In other words, the base number of patients in the study is decreasing as time goes on. To illustrate this principle, let us suppose that the percentage of patients who relapse over time is constant, for example, 15 percent per month. To facilitate calculations, we might start out with an initial number of 100 patients. At the end of 1 month, 15 percent will relapse (15 patients), leaving 85 remaining patients. In the second month, another 15 percent of the 85 patients (13 patients) will relapse, leaving 72 patients. Likewise, after the third month, 61 patients will remain if 15 percent (11 patients) have relapsed. Thus, the absolute number of relapsing patients continues to decrease. In this example, the relapse rate is compounded at a monthly rate for purposes of illustration—similar to the calculation that is used in computing compound interest.

If the relapse rate is compounded continuously as opposed to monthly or daily, the relapse rate of 15 percent per month would yield 86 patients remaining unrelapsed at the end of the first month, 74 at the end of the second month, and 63, 54, 47, 41, 35, 30, 25, 22, 19, and 17, respectively, for each of the 12 months. In the first

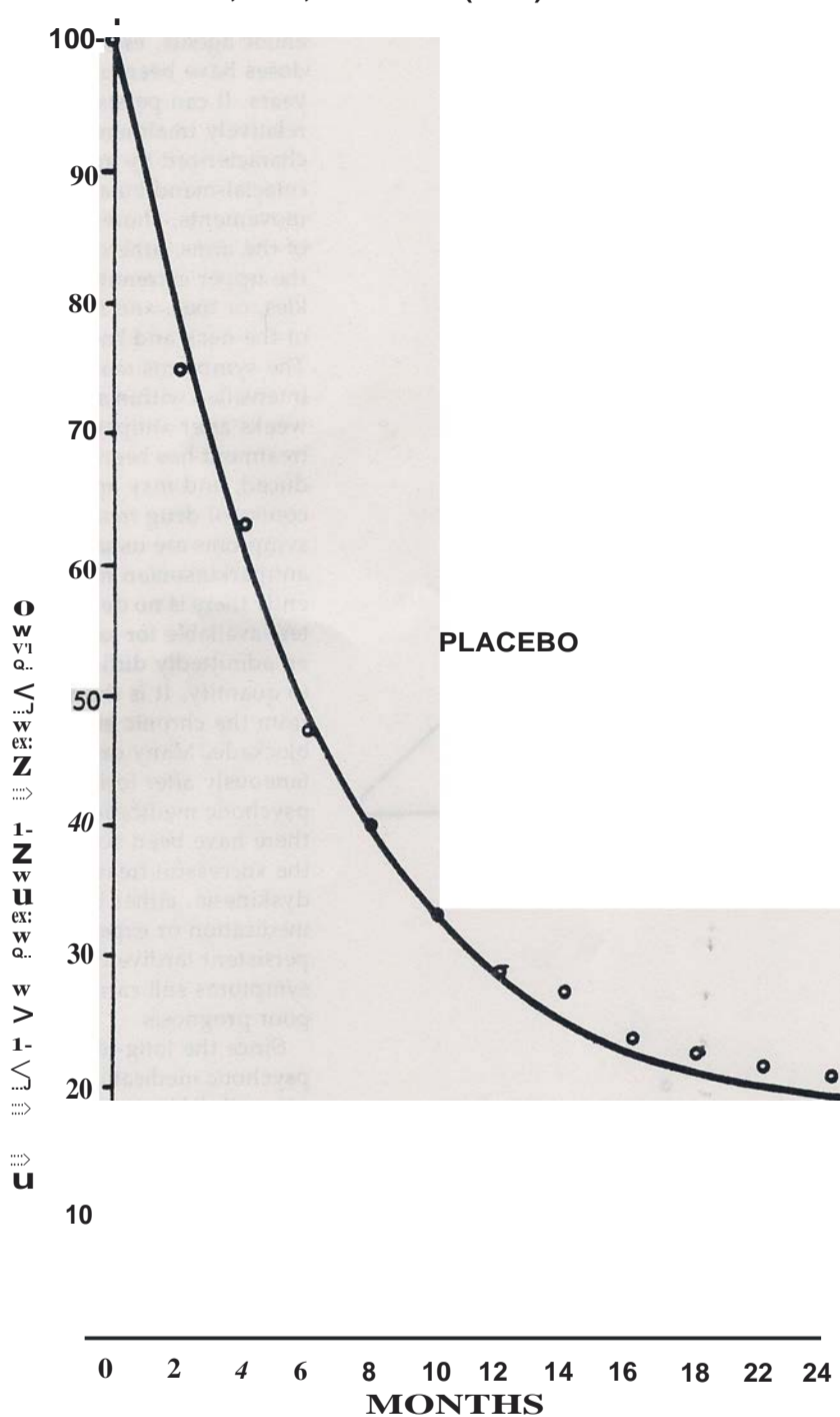
year, using the data available from the number of patients relapsing per unit time in all three studies below, we can plot these data as a logarithm of the percentage of patients unrelapsed over time (figures 6-9). Prien, Cole, and Belkin (1969) include only those patients on placebo and do not report the results of patients who were continued on medications. The other investigators, Hogarty et al. (1973) and Caffey et al. (1964), include data both on patients who relapse on drug and those who relapse on placebo. It is evident that substantially more patients relapsed on placebo as compared to active medication. In order to illustrate the rate of relapse, the fraction of the patient population relapsing per unit time divided by the number of patients in that study within that period of time, should be presented (see bottom panels of figures 6-9). To determine the cumulative relapse rate, the number of patients unrelapsed is corrected for the decreasing sample size by calculating the natural logarithm of that percentage of patients who remained stable. Notice that all of the curves in figures 7, 8, and 9 display approximate linearity.

Another justification for plotting the survival curve is that it might enable one to generalize the results to their situation^s or time periods. A reasonable prediction of events not yet examined can be derived from the projection of a curve. A good example of this is the assumption that 50 percent of the patients who do not relapse at 6 months will never relapse. The plotting of a survival curve makes it easier to appreciate the assumptions underlying the projection of this curve for longer periods of time. The plot of the curve is important for two reasons: First of all, it makes the representation of the data more digestible because it can be

visualized more readily; secondly, and equally important, it enables one to present the underlying assumptions of the data in a more explicable fashion.

At this point, we would like to underline the important misconceptions that can result from the use of the X^2 2×2 table method. This statistical manipulation can be misleading, for it promotes the unintended projection of an implicit survival curve and results in false conclusions, such as that 50 percent do not relapse on placebo and, therefore, will never relapse. We feel that this projection is not appropriate and that survival curves can explicate the assumptions involved in this and other projections. The long-term data from the study by Hogarty and Goldberg (1973) confirm that patients continue to relapse beyond the 50 percent point. After the first 18 months the curve may flatten out. It is possible that the relapse is constant only during the initial phases of the study. The graph of the relapse rate over the first 18 months fits nicely into an exponential function (r^2 is in the high 90's). Thus, it may provide an accurate approximation of the relapse survival function over this initial period of time. A more complex explanation of the relapse rate may be necessary for periods greater than 18 months. The relapse rate may decrease or go to zero after 18 months. There may be two types of schizophrenic patients: one group who relapse at a steady rate of 15 percent a month and a smaller group of good prognosis patients who never relapse. Thus, the possibility arises that one may be able to separate this relapse rate curve into two parts: one component with a relatively rapid relapse rate of about 15 percent a month and a second component that is characterized by a negligible or

Figure 7. Cumulative percent of unrelapsed placebo-treated patients from Prien, Cole, and Belkin (1969)



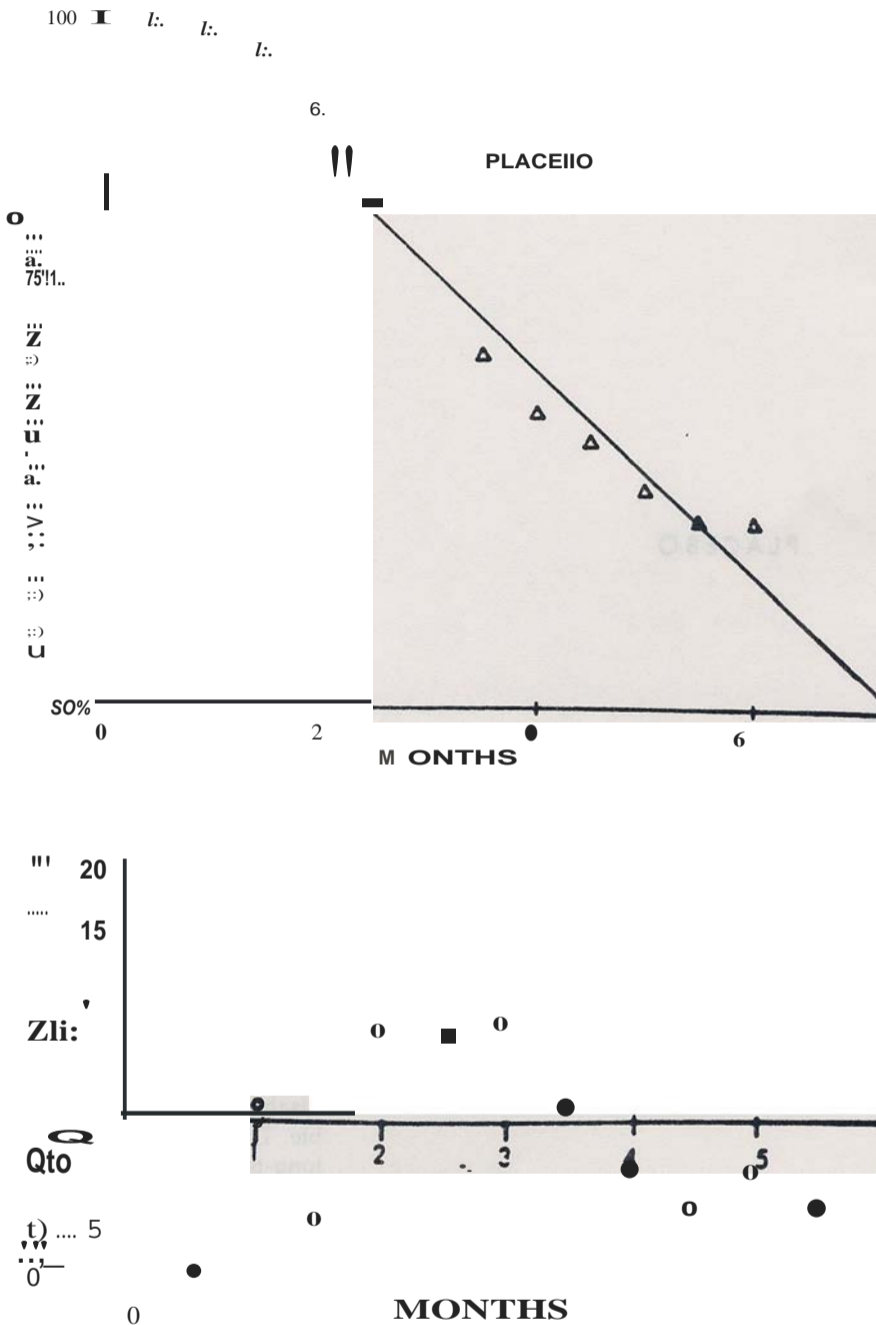
zero relapse rate. The rate constant does appear to be significantly decreasing.

Benefits vs. Risks With Antipsychotic Drugs

Like most medications, the antipsychotic drugs possess inherent long- and short-term risks that must be weighed against the benefits of the resolution of psychotic symptoms. The short-term hazards are now well known. Although uncomfortable and difficult to treat, they nonetheless are not life threatening and usually can be dealt with by dosage manipulation, medication change, or the use of other drugs that counteract side effects. These short-term risks include extrapyramidal symptoms, anticholinergic symptoms, and allergic reactions, as well as such less common effects as blood dyscrasias (agranulocytosis) and liver toxicity. The above symptoms usually appear shortly after treatment has begun. Although the short-term side effects are relatively benign, they do make it mandatory that the antipsychotic drugs be administered only for appropriate psychiatric disorders. These medications should not be initiated in a cavalier manner, and their use should be justified by a rational and serious assessment of the patient.

The long-term use of antipsychotic medications involves risks that are decidedly more serious than the short-term effects, occasionally more disabling, and sometimes irreversible. The hazards associated with long-term therapy include tardive dyskinesia, discoloration of the skin, corneal depositis, and retinopathy (usually only seen with thioridazine). Tardive dyskinesia is the most feared and frequent of the long term risks.

Figure 8. Percent of relapsed and unrelapsed patients from Hogarty et al. (1973)

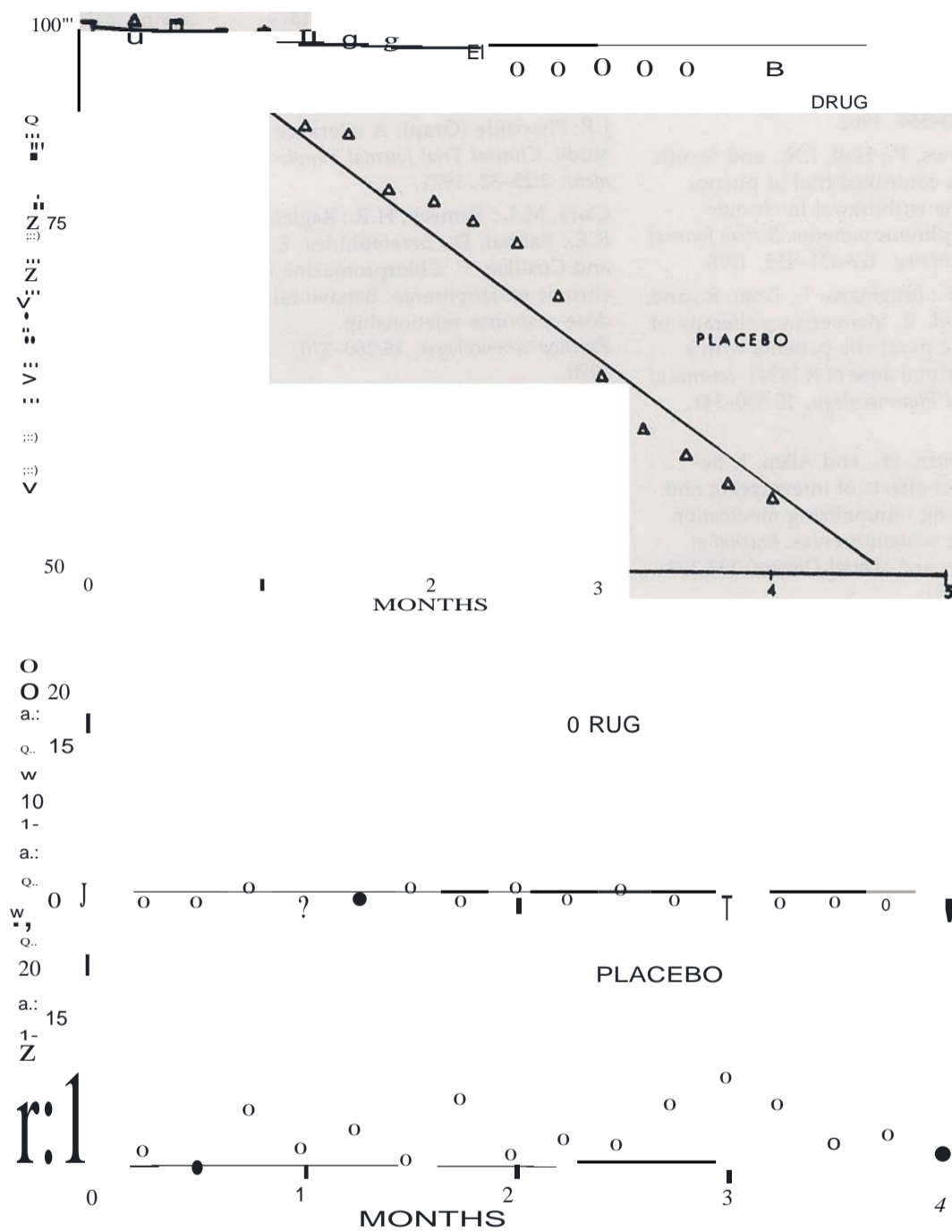


It is a variant of an extrapyramidal syndrome that can emerge late in the course of treatment with antipsychotic agents, especially when high doses have been used over several years. It can persist for years and be relatively treatment resistant. It is characterized by grimacing, buccofacial-mandibular or buccolingual movements, choreiform movements of the arms, athetoid movements of the upper extremities or fingers, ankles, or toes, and tonic contractions of the neck and back (Crane 1968). The symptoms may occur and/or be intensified within a few days to a few weeks after antipsychotic drug treatment has been terminated or reduced, and may appear during the course of drug treatment. The symptoms are usually aggravated by antiparkinsonian medication. Presently there is no definitive diagnostic test available for tardive dyskinesia, an admittedly difficult clinical entity to quantify. It is thought to result from the chronic effect of dopamine blockade. Many cases recover spontaneously after termination of antipsychotic medication. Although there have been scattered reports of the successful treatment of tardive dyskinesia, either by recognized medication or experimental drugs, persistent tardive dyskinesia symptoms still carry by definition a poor prognosis.

Since the long-term risks of antipsychotic medications are more serious and difficult to treat than the short-term side effects, the clinician

must be cautiously selective in decisions as to which schizophrenic patients are appropriate for long-term maintenance therapy. Thus, the use of long-term maintenance antipsychotic medication is a serious issue that can be justified if the benefits outweigh the above-mentioned risks.

Figure 9. Percent of relapsed and unrelapsed patients from Caffey et al. (1964)



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