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Clinical Strategies for Antipsychotic Drug Treatment, Tardive Dyskinesia, and the Training of Research Psychiatrists

John M. Davis, Philip G. Janicak, and Grant A. Killian

Illinois State Psychiatric Institute, Chicago, Illinois 60612

LAYPERSON'S SUMMARY

This chapter looks at the issue of neuroleptic treatment and tardive dyskinesia from the viewpoint of developing clinical research strategies to improve our treatment and minimize side effects. This review serves as an introduction to the problem of training psychiatrists in clinical research. Several suggestions including rare patient protocols, registries, and record keeping are discussed in the context of "mini" collaborative projects which are deemed feasible in both the state and federal systems of psychiatric care. Such a model could alleviate the critical shortage of psychiatrists trained in good clinical research.

INTRODUCTION

Tardive dyskinesia is the most important problem facing long-term psychiatric care in state and federal treatment centers. Tardive dyskinesia can develop in patients of all ages treated with antipsychotics for prolonged periods of time (3 months or longer). It is reported most often in hospitalized patients, but it has occurred also with outpatients on maintenance therapy. Because there is no effective treatment for tardive dyskinesia, prevention becomes particularly important, and since tardive dyskinesia is caused by prolonged exposure to antipsychotic drugs, the question is: Can these patients be effectively treated without antipsychotics? Clearly, methods for treatment without antipsychotics should be developed for long-term, partially remitted patients in sustaining care clinics and on the wards of state and federal hospitals.

This chapter outlines research to prevent tardive dyskinesia by utilizing strategies that reduce the intake of antipsychotic drugs. Since tardive dyskinesia is caused by drugs, we must first re-examine the evidence supporting our belief that prolonged treatment with drugs is effective in treating schizophrenia. Second, it is our contention that conventional methods for statistical analysis of such drug trials is conceptually insensitive and that a survival distribution analysis, rather than a fourfold chi square test, be used to analyze maintenance studies. Correct basic mathematics underlying relapse studies is necessary for an under-

standing of how maintenance drug studies should be designed and analyzed. Third, we will suggest some protocols to develop alternate treatment strategies for long-term patients at risk for tardive dyskinesia. Ideally, these strategies can be carried out by psychiatric researchers in one of many institutional settings.

NECESSITY FOR SURVIVAL ANALYSIS OF ANTIPSYCHOTIC RELAPSE STUDIES

The principal concern with maintenance medication in schizophrenia is the prevention of relapse. At present 29 maintenance studies have compared the efficacy of antipsychotic drugs versus placebo (Table 1). These studies report that schizophrenics on medication have fewer relapses than those maintained on placebo. Because these studies address the identical hypothesis, their separate results can be statistically combined. The probability of similarity in the results occurring by chance is substantially less than 10^{-100}. A common belief is that since 50% of these patients do not relapse on placebo, then 50% of the patients do not need drugs. We find this proposition dubious, and challenge the view that 50% of patients do not relapse. We maintain that this latter conclusion is based on an insensitive conceptual appraisal of the data. We were the first to consider the exponential nature of a relapse rate (9), and this chapter will develop our argument in greater detail.

As an example, Hogarty and Goldberg (20) compared maintenance medication with placebo in outpatient schizophrenics. Cumulative relapse rates are recorded in their paper and are expressed in Fig. 1 as the percentage of patients unrelapsed after 24 months. The percentage of patients unrelapsed plotted against time yields a curve (Fig. 1) which flattens out at 18 months, leaving about 20% of the patients unrelapsed. On first analysis, this curve might suggest a first-order function with the percentage of patients who relapsed per unit time as a constant. However, this analysis is not satisfactory. As patients relapsed, they were dropped from the study so that the number of patients left with the potential to relapse decreased with time, leaving at 18 months a group of patients (about 20% of the original group) with an exceedingly low relapse rate. Data from all three studies (5,20,26) on the number of patients relapsing per unit of time are plotted as a logarithm of the percentage of patients unrelapsed over time (see Figs. 2–4). Prien and Cole (26) presented data only for the effect of placebo with time and did not present what happens to patients maintained on drugs, whereas Hogarty and Goldberg (20) and Caffey et al. (5) did present the number of patients relapsing on drug and on placebo. Thus, it is easy to see that far more patients relapsed on placebo than on drug. To calculate the rate of relapse, the fraction of the patient population relapsing per unit time was divided by the number of patients in that study within that period of time (see bottom panels of Figs. 2–4). The number of patients unrelapsed was corrected for the decreasing sample size by calculating the natural logarithm of that percentage

TABLE 1 *Prevention of relapse in schizophrenia by antipsychotic drugs*

Authors	Year	Drug	Dose (mg CPZ[a])	No. of patients		Percent relapse on placebo	Percent relapse on drug
				Placebo	Drug		
Schawver et al. (31)	1959	Chlorpromazine	200	40	40	18	5
Diamond & Marks (10)	1960	Phenothiazines	468	20	20	70	25
Blackburn & Allen (4)	1961	Phenothiazines	—	28	25	54	24
Gross & Reeves (16)	1961	Phenothiazines	—	73	36	58	14
Schiele et al. (32)	1961	Phenothiazines	1,044	20	60	60	3
Adelson & Epstein (1)	1962	Phenothiazines	max 2,900	90	191	90	49
Freeman & Alson (12)	1962	Chlorpromazine	220	42	44	31	14
Troshinsky et al. (33)	1962	Phenothiazines	150–200	19	24	63	4
Whitaker & Hoy (34)	1963	Chlorpromazine	284	26	13	65	8
Caffey et al. (5)	1964	Phenothiazines	375	171	88	45	5
Kinross-Wright & Charalampons (22)	1965	Fluphenazine	300	20	20	70	5
Garfield et al. (13)	1966	Chlorpromazine	610	16	9	31	11
Melynk et al. (24)	1966	Phenothiazines	100–600	20	20	50	0
Engelhardt et al. (11)	1967	Chlorpromazine	200	142	152	30	15
Prien & Cole (26)	1968	Chlorpromazine	300 or 2,000	189	573	42	16
Morton (25)	1968	Phenothiazines	—	20	20	70	25
Prien et al. (27)	1969	Trifluperazine	540 or 2,860	107	218	56	20
Baro et al. (3)	1970	R-16341	10–40[b]	13	13	100	0
Rassidakis et al. (29)	1970	Various drugs	—	43	41	58	34
Clark et al. (8)	1971	Pimozide	—	10	9	70	44
Leff & Wing (23,35)	1971	Various drugs	418	12	18	83	33
Hershon et al. (18)	1972	Trifluperazine	575	32	30	28	7
Hirsch et al. (19)	1973	Fluphenazine	—	38	36	66	8
Hogarty & Goldberg (20)	1973	Chlorpromazine	282	174	187	67	31
Clark et al. (7)	1975	Pimozide	10–20[b]	9	26	78	27
Chien et al. (6)	1975	Fluphenazide	—	15	16	87	12
Gross (15)	1975	Chlorpromazine	625	20	41	65	34
Andrews et al. (2)	1976	Chlorpromazine	216	17	14	35	7
Ritkin et al. (30)	1977	Fluphenazine	5–30	19	43	68	7

[a] Dose was determined by transforming all drugs to CPZ equivalents; if there was more than one drug, the CPZ equivalents were averaged and these drugs were classified as phenothiazines.

[b] These drugs are not transformed to CPZ equivalents.

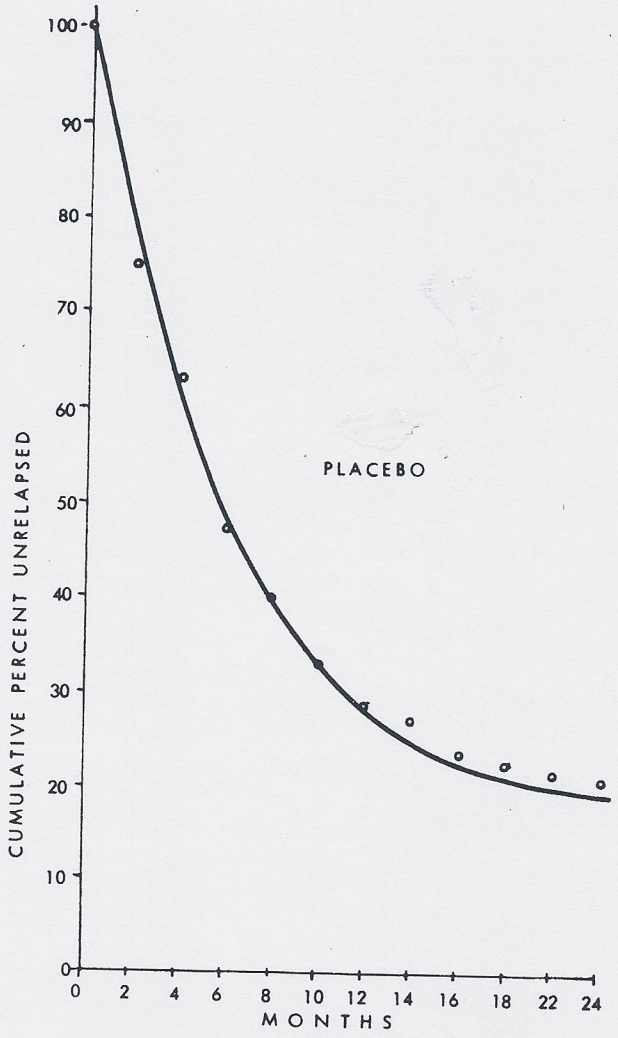

FIG. 1. Cumulative relapse over time is expressed as the percent of patients unrelapsed vs time. Data from Hogarty and Goldberg, ref. 20.

of patients unrelapsed. In Figures 2, 3, and 4, all these curves show approximate linearity.

Consider the case of determining whether a drug is more effective than a placebo. The chi-square statistic, utilizing a fourfold table with the number of patients relapsed or not relapsed with drug and placebo, is invalid for this purpose because it is excessively conservative. More appropriate ways of thinking about such data were published in 1693 by Halley (17). At present, a number of methods are available for dealing effectively with such survival curves. These

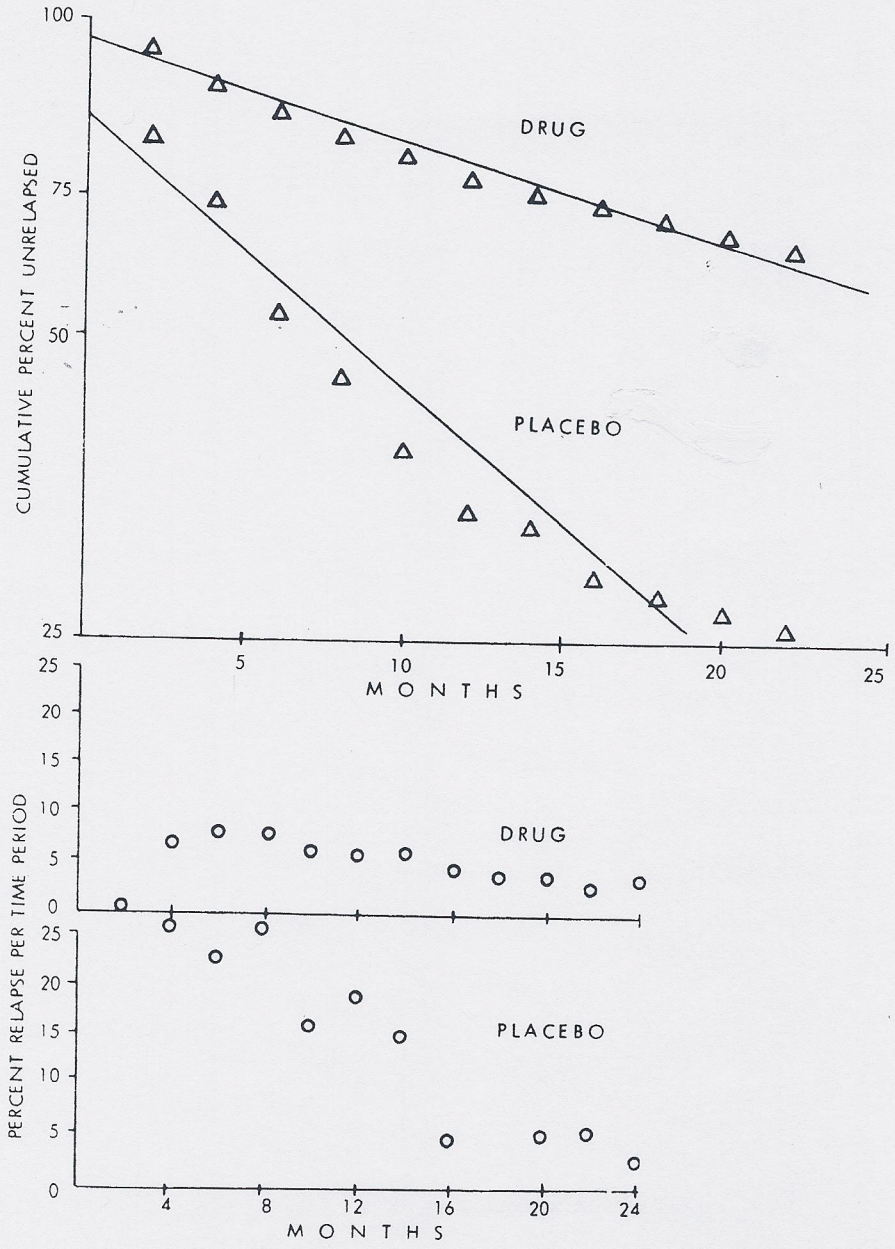

FIG. 2. Survival distribution of cumulative relapse over time is expressed as the Ln_e of the percent of patients unrelapsed vs. time. Data from Hogarty and Goldberg (20). *Bottom panel:* hazard rates, same data. Number of relapses divided by the number of patients being studied (expressed as a percent) at each time interval.

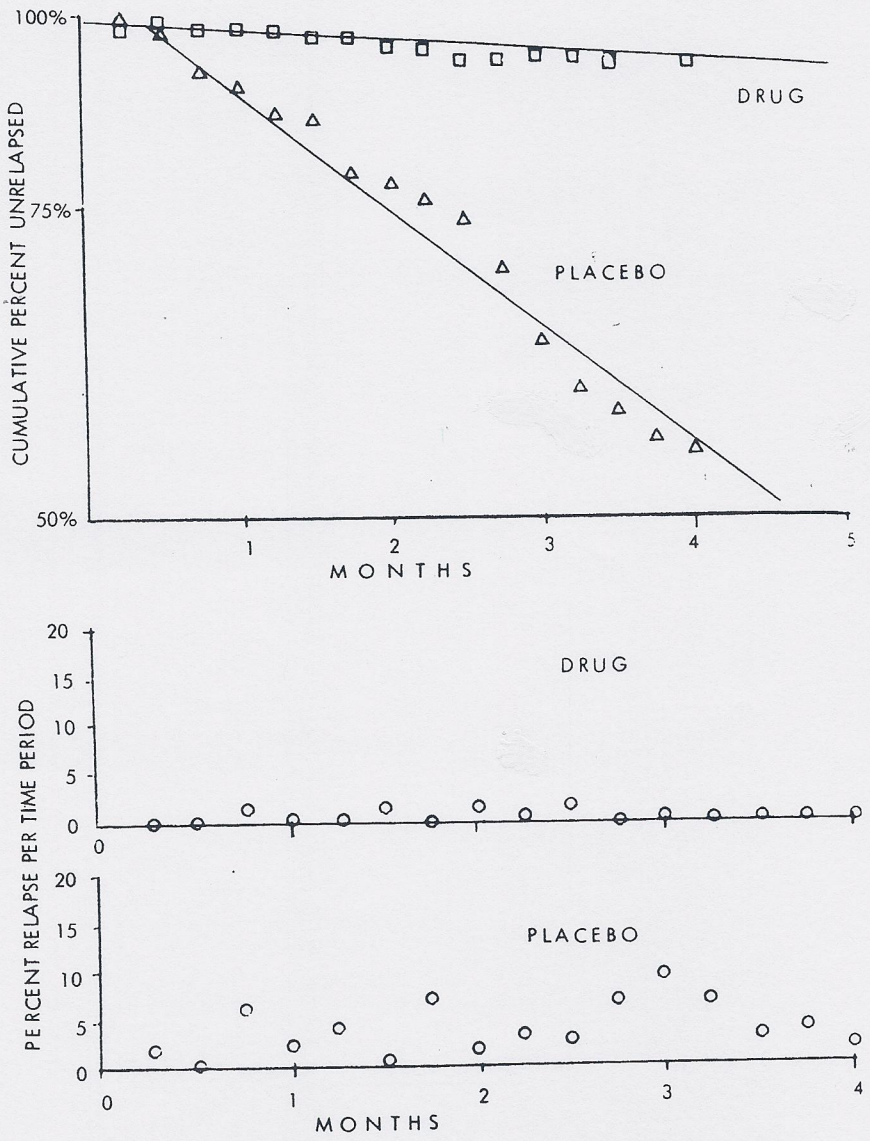

FIG. 3. Survival distribution of cumulative relapses over time is expressed as the Ln_e of the percent of patients unrelapsed vs. time. Data from Caffey et al., ref. 5. *Bottom panel:* hazard function, same data.

have been developed in a wide variety of areas concerned with survivor distribution, e.g., insurance policies, reliability of manufacturing goods over time, radioactive decay, or other measures based on concepts of half-life. Both parametric and nonparametric methods have been used by Kaplan and Meier (in 1958;

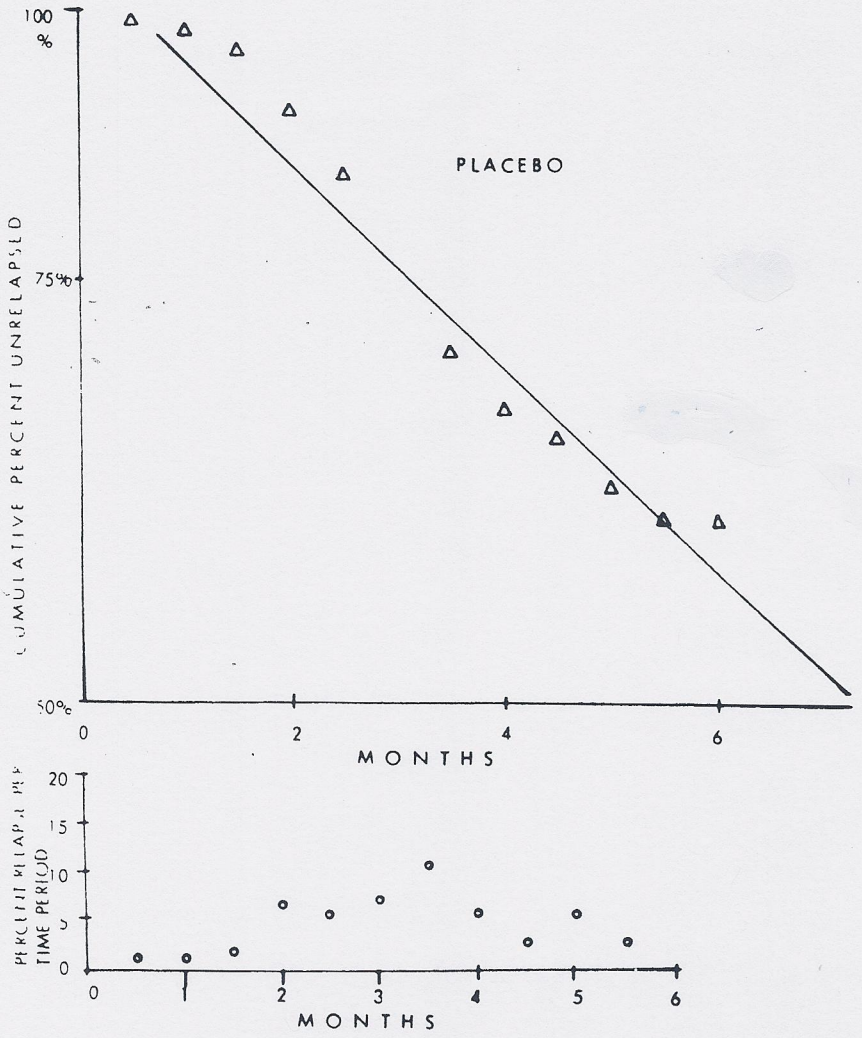

FIG. 4. Survival distribution of cumulative relapses over time expressed as the Ln_e of patients unrelapsed vs. time. *Bottom panel:* hazard function. Data from Prien and Cole, ref. 26.

21) and Gehan (in 1965; 14). Nonparametric methods are useful in situations when a distribution is not assumed, whereas survival analysis is appropriate in parametric methods for a variety of statistical models and is not limited to exponential functions. Note that normal distributions are not typically observed in survivor-type data, so the appropriate parametric survival technique provides a better statistical fit of the data.

The next step after plotting the data for description as survival functions

and significance testing is to view the curve in a quantitative sense. A logical point of departure is to inquire as to the consistency of the rate of relapse per unit of time. The rate of relapse in most of these curves does appear to be constant per unit of time. If this is fitted to Ln_e percent of relapse per unit time, as we did by the least-squares method, the fit is really quite good. In the Prien placebo data (26), for example, the correlation coefficient is 0.98 ($r^2 = 0.96$, with a relapse rate of 10% per month), in Caffey's placebo data (4), the correlation coefficient is 0.99 ($r^2 = 0.97$, with a relapse rate of 14% per month), and in Hogarty's placebo group (20), the correlation coefficient is 0.96 ($r^2 = 0.93$, with a relapse rate of 7.1% per month). It is obviously important for the clinician to know whether a patient should be on prophylactic medication for periods longer than this. Since most of the research on relapse rates has studied patients for only the first 4 to 6 months, the empirical data showing relapse rates over 2 years collected by Hogarty are particularly important and his data are consistent with a constant relapse rate for the first 18 months. In the Hogarty and Goldberg study there is a curvature apparent in the line at 16 to 22 months (the end of the study), which suggests that the relapse may be decreasing slightly with time. It may be that the constant relapse rate applies only to the initial phases. Since the exponential function neatly fits, it provides a reasonable approximation for describing the relapse survival function for the first 18 months. Another plausible interpretation of the data suggests that there are two types of schizophrenic patients: one type that relapses at the rate of approximately 15% a month, and a small population of good prognosis schizophrenics who never relapse. In other words, this relapse-rate curve is composed of two components: one component with a relatively rapid rate and a second component that has either a very slight relapse rate or a relapse rate of zero.

DRUG-FREE MAINTENANCE FOR THE PREVENTION OF TARDIVE DYSKINESIA

To prevent tardive dyskinesia, a logical goal is to develop alternate treatment strategies for long-term schizophrenics. The appropriate treatment for chronically relapsing but partially remitted schizophrenics is maintenance antipsychotic therapy to sustain the gains that have been made and prevent further deterioration. There is an important conceptual distinction between continued therapy and prophylactic therapy to prevent relapse in a symptomatic, partially remitted patient or in an asymptomatic remitted patient. These two types of patients to some degree tend to overlap each other. In general, the therapeutic efficacy of drugs is comparable in both situations. However, a relapse for an outpatient can have a more serious impact than for an inpatient who is under continuous medical supervision in an environment where treatment can be reinstituted rapidly. Continuing therapy in the hospital can be a model for what happens in

the outpatient situation, and work in both settings must be done because of the necessity of proving that generalizations from one to the other are valid.

In view of the adverse side effects of permanent drug therapy and the exponential nature of relapse, we suggest alternate treatment modes. If a patient is under careful supervision to detect signs of relapse, it should be possible to discontinue medication entirely during periods of quiescence and move in vigorously with drug treatment only when a relapse occurs. The research question is: Can such relapses be detected early and can vigorous treatment check the relapse so that it is relatively minor?

If the process involved in the decompensation of schizophrenia is difficult to reverse once it starts, then this method of treatment would be impractical. On the other hand, if early drug intervention can abort a schizophrenic episode, then the strategy outlined above might provide a method of management with a much lower incidence of tardive dyskinesia.

Research shows that relapse rates are much lower among inpatients who are maintained on relatively low antipsychotic doses, whereas relapse rates are greater among inpatients treated with higher antipsychotic doses (28). If techniques to treat patients who are on low levels of antipsychotics without medication could be developed, they might be extended to sicker patients who usually need high levels of medication. Designing a protocol for this research would involve identifying by the Research Diagnostic Criteria those patients with a diagnosis of schizophrenia or schizoaffective illness who require relatively low doses of a drug (under 600 mg, CPZ equivalent) for maintenance. Extremely violent patients or "brittle" patients requiring higher doses of medication for stabilization would be excluded.

A selected patient would enter four treatment groups in a double-blind random assignment study. Two groups would receive maintenance antipsychotic medication and the other two groups would receive placebo. These two groups would be crossed with two treatment procedures: one with an early identification of relapse with rapid treatment, and the other procedure would be a conventional psychiatric ward without early identification and rapid treatment (Table 2). In the early identification, rapid intervention groups, patients would be followed by a special team that would carefully monitor their status and watch for early signs of relapse. In the case of early signs of relapse, non-blind emergency medications would be added to abort the relapse. Such vigorous treatment would continue until the relapse was clearly prevented, a period which could be as long as several weeks. In the study, it would be necessary to specify the maximum period that such an extra treatment procedure could be administered. Under all conditions, the psychiatric status would be assessed at periodic intervals. In evaluating the outcome of all groups, if a patient relapsed to a clinically significant degree (as defined by certain criteria) there would be two different factors which would be assessed: First, the number of patients who deteriorated to such a degree that they were considered to have relapsed and had to be dropped

TABLE 2. *Drug-free vs. maintenance design*

	Special monitoring and early vigorous drug treatment	No special monitoring or extra medication
Maintenance drug	A	B
Placebo	C	D

Selected inpatients who require under 600 mg CPZ equivalents for maintenance and who do not pose a significant risk of violence or suicide, or other management problem.
Random assignment to treatment group according to design above.

from the study; and second, the degree of psychiatric illness would be calculated over time and the area under the curve summated. Consequently, an index could be calculated which would quantitate how unrelapsed patients remaining in the study were doing. Of course, both measures could be combined in the final global score.

Since the research program would require spotting relapses early, it would be necessary to develop a methodology for their detection to make rapid intervention possible. Built into this study would be a natural history component. Whenever a relapse occurred, there would be a staffing in order to determine if there were any signs which indicated that the patient was relapsing. The problem would be to identify the prodrome of a schizophrenic relapse and its early warning signals, such as perhaps a slight increase in bizarre behavior and bizarre nightmares. Patients would have to be rated at frequent intervals on a behavioral evaluation form. The data then could be analyzed to determine if such prodromal signs did, in fact, herald any major relapse. The development of such predictive measures is an important part of the study, and provisions should be made to permit changes in the behavioral evaluation form (if needed) as the study progresses.

If the drug-free strategy is ineffective, one might consider using extremely low doses of antipsychotic drugs, supplemented by occasional moderate-dose treatment during exacerbations, or electroconvulsive therapy (ECT) which could be valuable in controlling an acute exacerbation of schizophrenia. A pilot study could compare conventional maintenance treatment for continuously ill inpatients versus a low-dose treatment which is supplemented by a high-dose treatment during exacerbations with the judicious use of small amounts of ECT given unilaterally to the nondominant hemisphere. Since one must be concerned about memory loss as a side effect of ECT, this mode of treatment is suggested only as a pilot trial to test its efficacy.

If mildly to moderately ill patients can be managed by a drug-free model

of early detection, then the same strategy might be applied first to sicker inpatients and then second to outpatients. Since many chronic schizophrenics are no longer maintained exclusively in an acute treatment hospital, but rather in halfway houses or sheltered care facilities, such a study could be done in a wide variety of inpatient and after care settings.

If the early detection of relapse is possible and such relapse is containable and reversible by vigorous drug treatment, then the drug-free maintenance of schizophrenics may become feasible and the risk of tardive dyskinesia decreased accordingly.

RARE PATIENT PROTOCOLS

In order to compare the effectiveness of one treatment against a placebo and/or another treatment, it is necessary to have a population of at least 10 to 15 patients in each experimental group. Although this minimal sample size does not yield results which are "written in stone," it is clear that one cannot do a treatment evaluation study with only one or two patients in each group. In psychiatry, there are some rare conditions that occur with insufficient frequency so that no single medical center will have a sufficient number of patients to conduct a valid study. However, several centers collaborating may generate enough patients for a valid study. Thus, there is a need for a mechanism by which investigators in several hospitals can get together to conduct low-budget minicollaborative studies on rare patients. For example, some patients have an acute onset of a highly "reactive" psychosis with a good premorbid personality. These episodes are now called either "brief reactive psychosis" or "schizophreniform psychosis." Is antipsychotic drug treatment necessary or will these patients remit spontaneously? In the latter case, drugs may not be necessary for this type of psychosis.

Tourette's disease provides another example. It is a rare but serious disorder, and one medical center seldom sees enough cases to make a treatment study feasible. Another example would be acute psychotic emergencies. Many of these emergencies, involving highly disturbed or violent patients, constitute crises which seem to preclude even minimal research interventions. Nevertheless, there are infrequent occasions when highly disturbed patients could undergo alternate but effective treatment programs for the purpose of comparison. Comparing sedative antipsychotics to nonsedative antipsychotics is one example. Other examples would be treatment of temporal lobe epilepsy, or use of lithium alone for prophylactic purposes in schizoaffective disorders, strictly defined so as not to include manics and atypical manics. Another possible project would be to find out if methadone is an effective antipsychotic agent (methadone may be a dopamine blocker). Occasionally, narcotic addicts are also psychotic, and with a collaborative study it would be possible to compare methadone versus placebo in treating their psychosis.

RARE PATIENT REGISTRY

An idea related to the rare patient protocol is the rare patient registry. A system could be established so that psychiatric services would be notified of rare diagnostic entities: When patients with rare clinical problems or side effects are identified, this central registry could be informed. Any researcher could then contact the facility concerning treatment, clinical care, and/or research.

RARE PATIENT RECORD KEEPING

Many other types of studies can be conducted in a large hospital system that has high-quality medical, computer and clerical facilities. A computerized mechanism for systematically recording rare side effects could be instituted. Side effects might include agranulocytosis, fatal hyperpyrexia, sudden death during treatment with tricyclics and/or phenothiazines, or renal failure with chronic lithium treatment. At present, a medical event could occur in a schizophrenic patient and be falsely attributed to a drug. On the other hand, rare, but true, side effects could occur which are true side effects of a drug, but go unnoticed. For example, fatal hyperpyrexia has been falsely attributed to drugs received by schizophrenics. Records have been found that show that some reactions attributed to the drugs occurred before neuroleptic drugs were in use. A systematic way of recording rare side effects will require the construction of a list that would be circulated with a comment-reporting format attached. This would allow for the first time an accurate evaluation and computation of the incidence of side effects, together with background data, the descriptions and the course of rare effects, as well as clinical data, laboratory data, and outcome. These compilations should result in new and useful knowledge.

LOW-BUDGET COLLABORATIVE STUDIES

In the VA medical center system, collaborative studies have been used successfully both in general medicine and in psychiatry. Additional collaborative studies with schizophrenic patients may prove important to the resolution of other important clinical questions. It may be possible to conduct some of these studies with a low budget and minimal risk. For example, it is not known whether some antipsychotics have a greater propensity for causing tardive dyskinesia than other antipsychotics. A prospective investigation of tardive dyskinesia would require a long-term study. In state and federal care facilities (chronic hospitals, nursing homes, and halfway houses where chronic schizophrenics in a quasi-inpatient setting are receiving drugs), it would be possible to randomly assign patients to several different neuroleptics to see if certain neuroleptics have a higher propensity for causing tardive dyskinesia. We know that some drugs cause more sedation, whereas others cause greater extrapyramidal side effects; however, the overall risks are approximately equal. If a given neuroleptic causes

less tardive dyskinesia, it would clearly be the preferred drug for maintenance therapy. Patients could be randomly assigned for maintenance purposes to thioridazine, fluphenazine in tablet form, or fluphenazine decanoate. They could be evaluated once annually with the AIMS Scale and the BPRS. Over the course of several years, it could be determined whether there was more tardive dyskinesia associated with one or the other drug. A low-budget, multihospital study focusing just on the essential measurements could accomplish this purpose. The problem in such a long-term prospective study is to maintain sufficient enthusiasm to obtain valid data over such a long period of time.

DEVELOPMENT OF RESEARCH PSYCHIATRISTS

The types of research we have discussed require the enthusiasm and motivation of young researchers. Both state and federal hospital systems have some difficulty recruiting psychiatrists into their facilities. The field of psychiatry, in general, has experienced a great deal of difficulty developing research psychiatrists. Only 2% of the National Institute of Mental Health's training dollars goes toward the development of training research psychiatrists, and a good proportion of these trainees are physicians doing work in basic science, so that there is virtually no support for psychiatrists doing clinically oriented research.

Most university medical schools do not have psychiatrists whose primary orientation is research and they lack specific research units for psychiatric studies. In contrast, every university medical school has research endeavors in almost all the other specialties of medicine, surgery, and pediatrics. In addition, there is substantial support for research in the basic sciences (e.g., physiology, biology, biochemistry, psychology, and sociology).

From an educational point of view, the basic science graduate student is in a peer group with other students, and as a postdoctoral fellow he is in a laboratory working in a peer group with other postdoctoral trainees and other members of the department. At every level, there are individuals who can teach the student substantive knowledge and with whom he can identify. Thus there is a social infrastructure where an individual can "master his trade." A similar type of infrastructure has also been developed for the training of researchers in the areas of medicine and surgery, but not in psychiatry. By and large, no research hierarchy exists in psychiatry. There is clearly a need to develop such an infrastructure for training research psychiatrists. This should be one of the highest priorities for all state and federal hospital systems.

Psychiatric research has never been fully established as a specialty. Yet, it is necessary to promote research in psychiatry so that new knowledge can become available for better clinical practice.

We particularly advocate the need for small starter grants for young researchers in psychiatry. There is often a "catch 22," that keeps psychiatrists out of psychiatric research: an investigator is not really eligible for a psychiatric research grant unless he is a proven researcher with a given productive "track

record," yet, there is no social infrastructure for psychiatrists to develop such a record. At the present time, a high priority should be assigned to funding earmarked for the career development of young psychiatrists and their initial research work.

A psychiatrist in training should be salaried as a research psychiatrist. Funds for a research assistant and some supplemental equipment should be available so that he may work as an apprentice on an existing research ward. In short, what is needed is the development of a research training infrastructure for the clinical psychiatrist, similar to that which exists in basic science, medicine, surgery, and pediatrics.

SUMMARY

Tardive dyskinesia must be a high research priority in both state and federal hospital systems. We have suggested the development of treatment strategies for schizophrenics that would include drug-free intervals, viz-à-viz, understanding the exponential process of research. This may not work, but it has to be tried as it may lead to a much safer method of treating patients. In a system of hospitals, it is easier to work out collaborations between several units, and we have suggested a number of ways. The existence of a system of hospitals under a common management allows an organizational solution to some of the difficult problems of collaboration, and we have outlined several ways in which such cooperation among facilities could be useful. Stimulation of research in schizophrenia should be seen in the context of a necessity for developing research wards for clinical investigations and the development of suitable research psychiatrists who actually participate in the work.

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Discussion

Perez-Polo: Obtaining informed consent is a practical problem, as most patients come in at a time of crisis, but it's also a problem in ethics and the protection of patients. How would you go about getting informed consent for the violence protocol you suggest?

J. Davis: To do a violence protocol study in the outpatient situation is almost impossible, but in the inpatient situation you have a patient whose history you know. You can get your informed consent from the patient when he or she is in a good period, or from family members, or, if necessary to do research that's clearly in the patient's benefit, you could get a court order. When an episode occurs, you can go right into the protocol. No one hospital has enough patients to do the overall study, but it could be done in a set of hospitals cooperatively.

Cole: Where populations are large, most places will have a proportion able to give informed consent that will be large enough to study.

Schooler: We (2) did a withdrawal study that compared patients who had been treated with fluphenazine decanoate or fluphenazine hydrochloride for a year and then had been withdrawn from medication, double-blind, for 15 weeks. Using the survival-curve technique that you recommended, what we considered as the "death" in terms of lifetable analysis was the development of a global Abnormal Involuntary Movement Scale (AIMS) rating above a threshold of 2, which is "mild." In the patients discontinued from oral fluphenazine a higher percentage of cases reached this threshold than among patients discontinued from the decanoate. Most cases who developed movements did so within 3 weeks of discontinuation. This represents prospective evidence *against* the claim that fluphenazine decanoate leads to tardive dyskinesia. This drug is particularly likely to be present in the histories of chronic patients. Similarly, chlorpromazine, the prototypic phenothiazine, is likely to be present in most patients' histories, which may account for the observed association in nonprospective studies. In this study, where treatment was experimentally manipulated, the decanoate was not associated with greater development of movements. A final point that this study makes is that the placebo was the experimental condition and continuation of drug treatment was the control. In the consent form provided to patients, we assured them that if they fell into the continued medication group they would have an opportunity to have medication withdrawn after the study was over.

J. Davis: If, for a naturalistic study, all patients are nonrandomly assigned to different groups, the most severely ill patients would get the decanoate, and maybe the most severely ill were on it the longest.

Schooler: Relapse curves look similar to those for development of movements, but we do not find a correlation between development of abnormal movements and subsequent relapse in individuals.

Carpenter: Drug withdrawal from decanoate is gradual and from oral is abrupt. Could this factor account for both the abnormal movements and the psychiatric relapse?

Schooler: If that were the case, then the decanoate-discontinued group should simply shadow the oral discontinued group, only being 3 or 4 weeks later in development of movements and relapse; but that is not the pattern we saw.

Janowsky: Blood levels are probably different in the two groups, since only the fluphenazine was given orally. Thus, there may have been a lower decanoate level to start with, and therefore less of the movements when you stop, than in your oral medication group.

Schooler: To support that, the baseline levels of the abnormal movements were slightly although not significantly higher in the decanoate group. A larger number of cases in the decanoate group had movements we considered above threshold, which would be consistent with lower blood levels.

Kleinman: Both Dr. Cole and Dr. Davis mentioned sudden deaths on neuroleptics. Working with the local medical examiner's office I've come across many such cases. The VA might not be an appropriate place to study this.

Ewalt: With VA outpatients, that would be true; but with VA inpatients, these cases come to my desk and they are very rare. Every one is examined. Usually the hospital tries to give the case to the local medical examiner but doesn't always succeed.

J. Davis: If you had ready a common protocol for the cardiologists at all your VA hospitals, who would be notified of a sudden death, whatever data the experts wanted to study could be collected over the course of several years.

Kleinman: The medical examiner draws from a population different from VA inpatients and we see many unexplained sudden deaths.

Cole: I wonder if they are associated with any particular drug?

Yuwiler: Earlier, Dr. Zubin mentioned the episodic nature of schizophrenia and questioned whether a steady state existed in which the size of the schizophrenic population remained constant but its composition was ever changing. This implies an equivalence between rates of schizophrenic breakdown and recovery. Your first order falls in the population remaining asymptomatic after drug withdrawal would fit that model, since the decrement in the asymptomatic is matched by the increase in those with recurrence of disease. However, the abrupt break in that curve to yield a small permanently asymptomatic population should, if the steady-state model were correct, match the incidence of fresh cases. Further, if the experiment were repeated using only those who had a recurrence of symptoms on drug withdrawal, it would be interesting to see if the slope of the decline remained the same and, additionally, if that slope was maintained down to zero or if it, too, abruptly broke to leave a residual of essentially "cured" subjects.

Ethnic populations reportedly differ in sensitivity to psychotherapeutic drugs. For example, we have mentioned being told that the acceptable clinical dosage of phenothiazine in Japan is much lower than routinely used here. This difference could be due to cultural differences in defining improvement, or it could be due to real biological differences between groups. Among such differences may be environmental and genetic alterations in concentrations of blood constituents binding drugs, and drug binding could affect the transport of the drug from blood to brain. That is, most psychotherapeutic drugs are relatively nonpolar and would freely permeate into brain if they were not bound to blood constituents. If bound, however, entry into brain is some function of the binding equilibrium of the various binding materials in blood. Given this, studies attempting to relate clinical response to blood levels of drugs might usefully include some measures of drug binding to blood constituents. Gross static measures could be obtained from ultrafiltration or equilibrium dialysis measurements of free and bound drugs. Perhaps even better estimates of dynamic processes could be obtained using Oldendorf's (3) technique for assessing penetrance of substances from blood into brain. Essentially this consists of injecting a mixture of differently labeled test and reference substances into the carotid artery of a rat and comparing the ratio of isotopes in brain with that in the mix 5 sec after injection. By substituting blood from a patient for the usual carrier in these studies, Oldendorf's procedure could provide a bioassay of the relationship between total blood drug levels and that fraction available for entry into brain.

J. Davis: By using such a technique we (1,4) have shown that lithium transport abnormalities associated with affective disorders may be in the lithium-sodium exchange system.

Mosher: I'm surprised at the presentations on tardive dyskinesia. We know how to prevent it. The method is very simple and straightforward, but it was never suggested: you just don't treat people with neuroleptics. I'm surprised that it was never suggested, because the first rule of Hippocrates is to do no harm.

J. Davis: I did suggest that.

Mosher: You suggested treating them only when they're symptomatic.

J. Davis: And I also suggested that acute reactive patients, one of the small special populations, be studied without drugs.

Mosher: We ought to return to what Dr. Zubin said, and what Dr. Gordon Paul has done, and remember that in fact people get better without drugs. We have, or can establish and use, techniques for dealing with people without neuroleptic drugs. It's a viable alternative.

Schooler: You cannot compare the population in your study with the population Gordon Paul looked at. They were different, different things were probably happening there, and the treatment was not the same. The difficulty with nondrug treatment is in specifying what about a particular manipulation is having the direct effect. Psychopharmacology is so much easier to do, since it's substantially easier to specify the independent variable.

Mosher: Remember that 85% of Dr. Paul's patients were obtained from the 3% return rate over 2 years, all off medication. You can do it even in chronics without medication.

Perez-Polo: Dr. Davis, you mention checking psychological tests done 20 years ago. Will you also study the effects of being institutionalized for such a long time?

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