Treatment of Schizophrenia

by John M. Kane

Abstract

Antipsychotic medication remains a mainstay of treatment in both acute and chronic schizophrenia. Emphasis in recent years has focused on maximizing benefits and minimizing risks of medication by attempting to establish minimum effective dosage requirements for all phases of treatment and to provide alternative strategies for individuals who fail to benefit from antipsychotic drug treatment. At present all approaches to the treatment-refractory patient remain experimental, and further research in this area is of critical importance. Definite advances have been made in exploring the impact of psychological and psychosocial treatments administered in conjunction with various antipsychotic drug strategies. More sophisticated and comprehensive assessment measures have been applied in long-term treatment trials, enabling us to be more specific about treatment goals and treatment evaluation. Although no major "breakthrough" has occurred in the treatment of schizophrenia, incremental advances which can reduce rates of relapse and rehospitalization, improve the quality of adaptation, and reduce the risk of significant adverse effects are of enormous importance to affected individuals, their families, and society at large.

The treatment of schizophrenia remains one of the major challenges of modern-day medicine, not only because of its prevalence, severity, and chronicity, but also because its treatment requires the true integration of biological, psychological and environmental perspectives. Other sections of this *Special Report* have reviewed data relating to phenomenologic, genetic, neuroanatomic, psychophysiologic, and psychosocial aspects of schizophrenia, documenting both the complexity of the illness and its probable heterogeneity.

The clinician is faced with the need to integrate and assimilate this information while continuing to remain alert to the potential implications of new findings in any of these areas for planning treatment strategies. The clinician must also recognize the individual variations in premorbid adjustment, nature of onset, symptomatology, and social and environmental factors that may influence treatment response and level of adaptation. In addition, there may be considerable within-subject variability in symptomatology and treatment response over time. We need not despair at the complexity of this challenge, however, for a renewed emphasis on research and treatment development in schizophrenia comes at a time when a new generation of clinicians better trained to integrate different perspectives should be available to help advance the field.

This review will attempt to summarize some aspects of current knowledge about the treatment of schizophrenia, to highlight recent developments, and to point out areas in need of further clinical observation and research.

Acute Treatment

The acute treatment phase refers to that stage of schizophrenic illness resulting in obvious signs and symptoms with substantial behavioral dysfunction as well as psychosocial and vocational disability.

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Usually an acute exacerbation is marked by an increase in so-called positive symptoms such as delusions, hallucinations, thought disorder, and agitation, but an increase in negative symptoms such as extreme withdrawal may also occur. An episode may be rapid in onset or insidious, the form and content of the symptoms may change over time, and much of the illness involves subjective experiences that the individual may or may not be able to articulate reliably or consistently.

Pharmacotherapy

Antipsychotic (neuroleptic) drugs remain the primary modality in the treatment of an acute episode or an acute exacerbation of a schizophrenic illness. The efficacy of medication in this context has been established in numerous double-blind, placebo-controlled trials. Heterogeneity of drug response, however, remains a major concern, since a substantial minority of patients derive little benefit from drug treatment. Given the presumed heterogeneity in schizophrenia, variation in drug response should be anticipated, and to some extent, it is remarkable that these drugs have a degree of therapeutic efficacy in as large a proportion of patients as they do. It is also important to point out that although improvements in the validity and reliability of diagnostic criteria have been in part directed toward identifying relatively homogeneous populations for biological research and clinical trials, we should not lose sight of the fact that many individuals currently excluded from a schizophrenic diagnosis according to *DSM-III* (American Psychiatric Association 1980) may also benefit to some extent from antipsychotic drug treatment (e.g., schizotypal or borderline personality, paranoid disorders, schizophreniform disorder, and schizoaffective disorder).

It is possible that variation in drug response is influenced by biological (e.g., genetic, neurochemical, neuroanatomical) factors as well as psychological, psychosocial, and environmental influences. Substantive advances in any of those areas may ultimately lead to improvements in treatment efficacy or specificity.

There are several pharmacological factors which should be considered in planning the treatment of an acute episode.

Drug Type

Despite the introduction of a variety of different antipsychotics and chemical classes of antipsychotics over the past 30 years, there are at present no convincing data that among medications currently marketed in the United States any one is more effective either in schizophrenia in general or in specific subtypes of the disorder. It remains conceivable that differences do exist, but appropriately designed studies have not been carried out to identify them. Very few studies provide generalizable data on differential treatment response to specific agents. Almost all of our available information is based on comparisons of overall response rate in group data contrasting one drug versus another. Although a sample of patients randomly assigned to drug A or drug B may experience a 70–80 percent proportion of at least moderate therapeutic response to either drug, this does not necessarily mean that a given individual would respond equally well to either drug. There are remarkably few studies (Gardos 1978) looking at this issue despite its obvious clinical importance for the patients who fail to respond to an initial course of an antipsychotic drug. Despite anecdotal experience that a patient who shows poor response to one drug might occasionally benefit from another drug, it is difficult to establish a cause and effect relationship in a single case, since other factors besides the change in medication (e.g., additional time on medication) could contribute to improvement.

The preclinical observations that antipsychotic drugs differ considerably in their relative affinities for specific brain receptors (Hyttel et al. 1985; Richelson 1985), including the dopamine receptors suggested to mediate therapeutic response, also support the possibility that all drugs do not have the same spectrum of therapeutic activity. On the other hand, it has been suggested that the milligram potency of various antipsychotic drugs does correlate with receptor affinity in theoretically relevant binding assays (Creese, Burt, and Snyder 1976). Antipsychotics do differ in their profiles of adverse effects, and these differences may be important in choosing a medication for patients with known sensitivity to specific adverse effects. In addition, knowledge of a patient's previous therapeutic response to specific antipsychotic drugs should be weighted heavily in choosing a particular medication.

One notion that continues to be prevalent in some clinical settings is that sedating drugs (e.g., chlorpromazine) are more effective in controlling highly excited or agitated patients, and nonsedating drugs (e.g., haloperiodol, trifluoperazine) are more appropriate for withdrawn or psychomotorically retarded patients. This relationship has never been established, and numerous studies suggest that high- and low-

potency drugs are equally effective for both types of patients.

Dosage

We still have insufficient information about dose-response curves for antipsychotic drugs (the related issue of blood levels will be discussed subsequently). Many studies of drug efficacy have not used fixed doses. When flexible dose strategies are used, the clinician adjusts the dose based on clinical response. This can be misleading, however, in establishing a dose-response relationship. As an example, if a patient receiving a given dose of an antipsychotic shows little improvement after 10 days, the clinician may decide to increase the dose; subsequent improvement might then be attributed to the higher dose when, in fact, improvement may have occurred merely by allowing more time on the original dose. In those studies comparing high dose (defined as in excess of 2,000 mg chlorpromazine equivalents) to standard dose treatment, there is no evidence of a statistically significant advantage for high dose (Wijsenbek et al. 1974; Quitkin, Rifkin, and Klein 1975; Donlon et al. 1978; Ericksen et al. 1978; Donlon et al. 1980; Neborsky et al. 1981). This does not preclude the possibility that some patients may benefit from higher doses, but it would suggest that such individuals represent a small subgroup, and better means of identifying appropriate candidates for high-dose treatment should be established. In general, the literature suggests that doses of 400–600 mg/day of chlorpromazine or equivalents should be sufficient for the average patient.

There has been a tendency in recent years to use particularly large doses of the "high-potency" antipsychotics, because apart from parkinsonian side effects, high doses are generally well-tolerated, but this practice should be discouraged unless it is clearly established that such doses are necessary for a specific patient.

Dose Equivalents

Given an appropriate increase in emphasis on establishing minimum effective dosage requirements for both acute and long-term treatment, a clear understanding of dose equivalence among antipsychotics is important. Chlorpromazine has frequently been the standard against which equivalent doses are established. Unfortunately, the customary methods of determining dose equivalencies are somewhat crude and unsystematic. The usual method has involved a double-blind clinical trial comparing two antipsychotics, with the clinician adjusting dosage as seen fit. When the trial is completed, comparisons are made of the doses used and a conversion ratio is suggested. In addition, results from drug-placebo comparisons may be pooled to identify the clinically "effective" dosage range of a particular drug. The potential problems in assuming the validity of these results are numerous. It is also important to consider the possibility that conversion ratios that may be appropriate at the lower end of the dosage spectrum may not apply at higher dosage levels.

It does appear that clinicians are using dissimilar dosing practices with high-potency as compared to low-potency antipsychotics. Baldessarini, Katz, and Cotton (1984) compared the findings of a survey of 110 private hospital inpatients with the dosing practice as reported in surveys of nearly 16,000 Veterans Administration patients. Doses of high-potency drugs above the daily equivalent of 1 gram of chlorpromazine accounted for more than 40 percent of all prescriptions. The mean chlorpromazine equivalent dose of the two most potent antipsychotic agents (haloperidol and fluphenazine) was 3.54 times as high as the mean doses prescribed of chlorpromazine or thioridazine. As these authors suggested, the sedative and autonomic effects of low-potency drugs may limit their use in the higher dose range, whereas it is feasible for clinicians to increase doses of high-potency antipsychotics without substantial increase in immediate adverse effects.

One factor potentially contributing to the use of higher doses is the increasing pressure on clinicians to reduce length of hospital stay. The problem, however, is that the use of "rapid neurolepticization" and/or high-dose treatment has not been shown to shorten the time required for these drugs to exert their therapeutic effect or to improve clinical outcome in general (Neborsky et al. 1981). Though the time course of response is unpredictable, with a degree of clinical improvement occurring rapidly in some patients and more slowly in others, our experience and reading of the literature suggests that 4–6 weeks is usually necessary to begin to see full therapeutic benefit, but in many cases even longer intervals are needed.

Drug Blood Levels

Since the first recognition of enormous individual variability in absorption and metabolism of antipsychotic drugs and the availability of assays to measure levels of neuroleptics in blood (Currey and Marshall 1968), there has been considerable interest in attempting to determine the relationship between blood levels and clinical response. It

was hoped that this strategy would go a long way toward explaining the enormous variability in drug response seen in schizophrenia. To a large extent these efforts have not fulfilled the original expectations, but blood levels may have some utility in specific clinical studies. In the last decade we have seen enormous advances in the laboratory techniques available for measuring minute quantities of antipsychotic drugs in clinical specimens (e.g., plasma, cerebrospinal fluid, and red blood cells). Ironically, despite sophisticated technology, flaws in design and methodology of clinical trials using blood levels have frequently limited the potential to draw meaningful conclusions.

Diagnostic and prognostic heterogeneity has been one factor complicating studies in this area. If patients with a variety of diagnoses or those who have proved nonresponsive to antipsychotic treatment are included in studies, the ability to find meaningful correlations can be limited. In addition, the development of steady-state blood levels following fixed-dose treatment is essential in relating blood levels to clinical response. If, on the other hand, dosage adjustment is based on clinical response, then those patients who are intrinsically poor responders to antipsychotic drugs (regardless of dose or blood level) may end up with the highest blood levels. This could then be interpreted as negating the value of blood levels or suggesting that high blood levels are countertherapeutic.

Sufficient length of time in a trial is also important since many patients with schizophrenia require several weeks to achieve full benefit from pharmacotherapy. Studies that have examined blood level-clinical response relationships after relatively brief periods (e.g., 14 days) may be measuring one aspect of clinical effect, such as reduction in psychomotor agitation or excitement, whereas other aspects of psychopathology may not have improved within the same time frame. It is also important to consider the influence of other psychotropic drugs that might be prescribed either in altering the absorption or metabolism of the antipsychotic or influencing the clinical state directly such as sedative hypnotics or antiparkinsonian drugs (the latter may reduce behaviorally manifest neurological side effects of antipsychotic drugs).

Table 1 summarizes 18 studies that involved some type of fixed dose design. We excluded reports focusing on treatment-resistant patients. None of these studies are "ideal" in addressing all of the methodological concerns that have been raised, but it is extremely difficult to carry out such investigations in the kind of clinical setting where appropriate patients can be found.

The most frequently studied drug is haloperidol, and several of these investigators suggest a curvilinear relationship between blood level and clinical response or a putative "therapeutic window." Although these findings are intriguing, considerable further work is necessary to establish and define a therapeutic window. Many studies suggesting this phenomenon have had few patients above the suggested upper limit and, more importantly, hardly any attempts have been made at random assignment of patients whose blood levels are out of the therapeutic range to a dosage necessary to manipulate the blood level into the putative therapeutic range or to remain at their current blood level (to control for continued time on drug). Until this is done in a systematic, replicable fashion, conclusions must remain tentative.

This issue is also relevant to the previous discussion of high-dose or megadose treatment. If patients were specifically selected because of relatively low blood levels on standard doses of antipsychotics, then a substantial dosage increase might have a greater likelihood of being helpful. On the other hand, if studies using substantial dosage increases involve a heterogeneous group of drug nonresponders, the likelihood of seeing a desired clinical effect may be reduced considerably.

Another important issue in interpreting the suggestion of a therapeutic window is the possibility that those patients showing poor or minimal clinical response at the higher blood levels are in fact experiencing behaviorally manifest adverse effects of antipsychotics that could alter or impede the therapeutic response (Bolvig-Hansen, Larsen, and Gulmann 1982). Though some investigators have suggested that an increase in side effects does not account for lack of beneficial effect at higher blood levels, this question requires further study. Behaviorally manifest adverse effects can be difficult to distinguish from psychopathology at times, and a patient in the midst of a psychotic episode may not be able to articulate subjective feelings and sensations in a way that would contribute to a differential diagnosis.

The overall value of measuring blood levels of antipsychotic drugs remains far from clear, but the available data should encourage clinicians and investigators to recognize the potential problems of using dosages that are too high as well as the importance of appropriate clinical evaluation and research methodology in using or studying high-dose treatment in specific subgroups of schizophrenic patients.

There has also been renewed in-

Table 1. Neuroleptic blood levels and clinical response

Author	*n*	Dose	Duration	Method	Blood level	Results	Window
Smith et al. (1984)	26	Thioridazine, fixed-random	24 days	GLC	195–1685 ng/ml (thioridazine & mesoridazine)	No significant correlation	No
Wode-Helgodt et al. (1978)	38	Chlorpromazine, fixed-random	28 days	GC/MS	0–150 ng/ml	Significant correlation at 2 but not 4 weeks	No
Dysken et al. (1981)	29	Fluphenazine, fixed	15 days	GLC	.1–4.4 ng/ml	Significant correlation	Yes .2–2.28 ng/ml
Cohen et al. (1980*b*)	11	Thioridazine, fixed	14 days	RRA	1100–6200	Significant correlation	No
Bergling et al. (1975)	40	Thioridazine or thiothixene	56 days	Fluorometric	Thioridazine 1000–6000 ng/ml; thiothixene 0–160 ng/ml	No significant correlation	No
Neborsky et al. (1984)	20	Haloperidol, fixed-random	7 days	RIA	Low $\bar{X}$ = 8.2 High $\bar{X}$ = 34.0	Plasma: RBC correlation with response	No
Garver et al. (1977)	10	Butaperazine, flexible-fixed	12 days	Fluorometric	2.3 = 321 ng/ml	Plasma & RBC curvilinear relationship	30–80 ng/ml RBC
Garver et al. (1984)	14	Haloperidol, fixed-random	17 days	GLC	.7–87 ng/ml	Significant correlation for plasma but not RBC	Window for plasma but not RBC
Smith et al. (1985)	33	Haldoperidol, fixed-random	24 days	GLC	2–23 ng/ml	Significant correlation	Plasma: 6.5–16.5 ng/ml RBC: 2.2–6.8 ng/ml
Mavroidis et al. (1983)	14	Haloperidol, fixed-random	14 days	GLC	2–19 ng/ml	Significant correlation	Plasma: 4.2–11.0 ng/ml
Mavroidis et al. (1984)	19	Fluphenazine, fixed-random	14 days	GC	.1–2.4 ng/ml	Significant correlation	Plasma: .1–.7 ng/ml, RBC: .2–.6 ng/ml
Cohen et al. (1980a)	58	Various drugs, flexible-partial fixed	?	RRA	—	Significant correlation	No
Casper et al. (1980)	24	Butaperazine, random-fixed	14 days	Fluorometric	23–250 ng/ml	Significant correlation with RBC, but not plasma	RBC only: 30–60 ng/ml
Potkin et al. (1985)	73	Haloperidol, flexible-fixed	42 days	RIA	0–75 ng/ml	Trend	Curvilinear (trend) 4–26 ng/ml

Table 1. Neuroleptic blood levels and clinical response—*Continued*

Author	*n*	Dose	Duration	Method	Blood level	Results	Window
Van Putten et al. (1985)	47	Haloperidol, random-fixed	28 days	RIA	?	Significant at 1 but not at 2 or 4 weeks	Curvilinear at 1 week (5–16 ng) but no relationship at 2 or 4 weeks
Magliozzi et al. (1981)	17	Haloperidol, flexible-fixed	21–84 days	GLC	0–96 ng/ml	Significant correlation	8–17.7 ng/ml
Bolvig-Hansen, Larsen & Vestergard (1981)	14	Perphenazine, flexible-fixed	56 days	GC	.6–10.1 ng/ml	No significant correlation	No
May et al. (1981)	48	Chlorpromazine, fixed	28 days	GC/MS	?	No significant correlation (plasma or saliva)	No

Note.—GLC = gas liquid chromatography. GC/MS = gas chromatography/mass spectroscopy. RRA = radioreceptor assay. RIA = radioimmunoassay. RBC = red blood cell.

terest in attempting to use the neurological adverse effects of neuroleptics as a guide in identifying appropriate therapeutic dose. This concept was explored originally by Haase (1961; Haase and Janssen 1965), who suggested that the first appearance of hypokinesia-rigidity as reflected by handwriting changes indicated that a sufficient dosage for antipsychotic effect had been achieved. This suggestion has been either largely ignored or misinterpreted to imply that there is a linear relationship between extrapyramidal side effects and clinical response or that more clinically obvious extrapyramidal symptoms were necessary to indicate adequate dosage. McEvoy, Stiller, and Farr (1986) have pointed out the potential importance of this suggestion and have begun to test the neuroleptic threshold hypothesis in a systematic fashion. Their open pilot study found that the mean daily dose of haloperidol at which the neuroleptic threshold (the emergence of subtle extrapyramidal side effects) was crossed was 4.2 ± 2.4 mg/day. The plasma haloperidol levels obtained at these neuroleptic threshold doses average 4.9 ± 2.9 ng/ml, which is very close to the lower end of the therapeutic range reported in several studies (Mavroidis et al. 1983; Potkin et al. 1985; Van Putten et al. 1985). Sixty-seven percent of the patients in McEvoy's study had at least moderate therapeutic response at the neuroleptic threshold dose. This is an intriguing finding, and further double-blind, random-assignment studies should prove interesting.

Predictors of Response and Role of Alternative Treatments

Since there is considerable variability in antipsychotic drug response, repeated attempts have been made to identify predictors of response. Although there are suggestions in the literature involving variables ranging from premorbid social adjustment (Klein and Rosen 1973; Judd et al. 1973) to ventricle-brain ratio (Weinberger et al. 1980), there are no well-established predictors of antipsychotic drug response during an acute episode or exacerbation. At the same time there have been suggestions that some patients with schizophrenia may respond to lithium (Small et al. 1975; Hirschowitz et al. 1980; Delva and Letemendia 1982) or electroconvulsive therapy (ECT) (May 1968; Taylor and Fleminger 1980; Salzman 1980; Brandon et al. 1985), or may at times improve without somatic treatment.

These two lines of investigation may at some point produce evidence on which to base recommendations for a particular alternative somatic therapy in the acute treatment of specific patients. At our present level of knowledge, however, antipsychotic drugs are clearly the most effective treatment for the largest proportion of patients with this illness.

Strategies for Managing Antipsychotic Drug Nonresponders

Although antipsychotic drugs have a dramatic effect on the majority of patients with schizophrenia, we are faced with a substantial number of individuals who derive little if any benefit from these agents. The treatment of such individuals remains a major clinical dilemma. It is frequently in this context that clinicians consider or employ therapeutic trials of all antipsychotic drug classes, megadoses, high doses of long-acting injectable medication, concomitant lithium, propranolol, carbamazepine, high doses of benzodiazepines, ECT, and experimental compounds under development. Although there are some anecdotal reports describing patients who benefit from such strategies, few systematic, well-controlled studies have been carried out suggesting any more than occasional benefit. It is probably reasonable for the clinician to conduct a "therapeutic trial" of some alternative treatment strategy in patients who fail to respond to an adequate course (or courses) of antipsychotics, but there is also a point where we may have to recognize and accept our inability to help some patients given our current level of knowledge.

In addition, if such therapeutic trials are conducted, a clear process of identifying and documenting target symptoms as well as response over a reasonable time frame should be employed to avoid either an inadequate trial or the lack of followup and evaluation necessary to justify continuation of a specific treatment. In our experience in reviewing medical records in such patients, it is not unusual to see nonstandard or experimental treatment continued for months without any clear evidence of a beneficial effect.

Other than the potential value of identifying patients who are idiosyncratic metabolizers through assays showing unusually low or unusually high blood levels, we are not aware of any logical basis for determining the next treatment to be tried. No comparisons have been made, to our knowledge, of ECT, lithium, and other alternatives in this context. Even the determination of blood levels requires caution in interpretation. Laboratories vary in their methods. Values published by one laboratory should not be assumed to be relevant to results produced by a laboratory using a different method. Therapeutic levels

have not been well-established, and for some drugs there are hardly any data. Unless blood levels are obtained and interpreted in collaboration with experts in this area, they can only be used as a guide in identifying relative extremes in drug absorption and metabolism.

One major emphasis in evaluating an apparently nonresponsive patient should be the adequacy of the length of the initial trial before failure to respond is assumed. Four weeks may not be adequate in this context, but clinicians may find it difficult to continue a treatment beyond 4 weeks when it does not appear to be working. Abandoning a treatment before 4 weeks, however, may very well be premature.

It is informative to look at a series of studies that included treatment-resistant schizophrenic patients who were randomly assigned to a standard-dose treatment or a high-dose treatment (see table 2). None of these studies found a significant advantage for the high-dose treatment, but it is of considerable interest to note the overall improvement rate among these apparent neuroleptic nonresponders. This could suggest that additional time on medication may lead to improvement in some patients. It is also possible that nonpharmacological aspects of the research contributed to improvement, but in either case these findings argue for the avoidance of premature closure and the need for systematic research with appropriate controls. Labeling a patient as treatment refractory does not automatically eliminate the need for appropriate controls as evidenced by the improvement seen on standard treatments.

We are also concerned about the premature application of treatments to this patient population based on anecdotal reports. There is a particular responsibility to do carefully controlled clinical trials in refractory patients, not only because of the potential to improve our treatments, but also because we are dealing with an area of considerable desperation where the application of premature conclusions or preliminary data to large numbers of patients is extremely common and potentially unfortunate.

Table 2. Therapeutic response in neuroleptic-resistant schizophrenia

Investigator	Drug(s)	Dosage	Overall improvement Combined groups	
Itil et al. (1970)	Fluphenazine	30 mg	9/17	53%
	Fluphenazine	300 mg		
McCreadie & McDonald (1977)	Haloperidol	100 mg	7/20	35%
	Chlorpromazine	600 mg		
Quitkin, Rifkin & Klein (1975)	Fluphenazine	30 mg	13/31	42%
	Fluphenazine	1200 mg		
Bjorndal et al. (1980)	Haloperidol	15 mg (mean)	10/23	43%
	Haloperidol	103 mg (mean)		

Our own recommendation is that two or three different classes of antipsychotic drugs be used, for at least 4 weeks each, in dosages in excess of 400–600 mg chlorpromazine equivalents before the initiation of more unproven approaches. Obviously, this requires a relatively lengthy period of ongoing observation and evaluation; however, there is no shortcut in providing appropriate therapeutic trials in this subgroup.

Psychological and Psychosocial Treatment

Though an enormous amount has been written about various forms of psychotherapy and psychosocial treatments for patients with schizophrenia, there is remarkably little systematic, controlled research. Clearly, this type of research is extremely difficult to conduct, but clinicians would like to base their treatment efforts on evidence supporting their utility and specific indications. Research in this area has been the subject of several excellent review articles (May 1968; Schooler 1978; Mosher and Keith 1980; Schooler and Hogarty, in press).

As Schooler and Hogarty (in press) suggest, research over the past decade has shifted in focus from earlier studies, to some extent in response to developments in the neurosciences, environmental psychology, and deinstitutionalization. We have also seen a shift in focus from attempts to alleviate the schizophrenic illness itself with various forms of psychotherapies to attempts to improve the social adaptation, vocational functioning, and subjective well-being of individuals with schizophrenia, a distinction

well-articulated by Klein (1980). Along the same lines, therapeutic approaches involving families have shifted from viewing the family as a factor in the etiology of the condition to recognizing the potential influence of the family on the course of illness and providing strategies to assist in promoting the positive aspects of that influence.

At the same time, the appropriate increase in emphasis on providing necessary information to patients and families about the nature of the illness, the available treatments, and their respective benefits and risks has also influenced the nature of psychosocial strategies.

With accumulated data on the efficacy of antipsychotic drug treatment in schizophrenia, most research on psychological and psychosocial interventions has involved the concurrent use of medication. There are a variety of ways in which these modalities can interact, making research in this area particularly complex. (Research methodology in this context has been recently discussed by Schooler and Hogarty, in press.)

May (1976) has reviewed many of the studies conducted in chronically hospitalized schizophrenic patients to determine the value of analytically oriented psychotherapy or behavior therapy with and without medication. He concluded that there was no, or only minimal, advantage to psychological treatment with chronically institutionalized patients.

Stanton et al. (1984) and Gunderson et al. (1984) have reported a 2-year, multihospital study on the effects of psychotherapy for nonchronic schizophrenic patients. This study is among the most sophisticated done to date. The intention was to provide a fresh examination of whether intensive psychotherapy added appreciably to the benefits of standard treatment of schizophrenic patients. Investigators compared exploratory, insight-oriented psychotherapy (EIO) to a control treatment which consisted of a high-quality but more standard form of psychotherapy called reality-adapative-supportive (RAS) therapy.

Of the 164 patients who entered the study, 42 percent dropped out before qualifying as study patients (minimum of 6 months' participation). By 2 years, only one third of the initial sample remained in their assigned treatment. Across all three settings, the average length of hospitalization for patients who dropped out of therapy was 2 months as compared to nearly 6 months for those who remained in therapy (a significant difference). To ensure that the results would not be criticized by advocates of psychotherapy with schizophrenic patients, therapists with a commitment to and experience with one of the two forms of treatments being offered were selected. All study patients were placed on antipsychotic medication chosen by the treating inpatient psychiatrist. To ensure an overall high level of drug management and consistency in the prescribing behaviors for both study groups, any plan to change or continue prescription of antipsychotic medications was given an external, independent review by a senior consultant.

The investigators included a very comprehensive and sophisticated battery of antecedent measures, process measures, and outcome measures. In general, this effort represented an enormously ambitious and important task carried out by the investigators with considerable diligence and dedication.

Prominent among the deficiencies in the project was the high attrition rate, which had a definite impact on the investigators' ability to draw meaningful conclusions. For analyses requiring complete followup data, the effective sample was 72 patients (35 EIO and 37 RAS) at 12 months and 47 patients (22 EIO and 25 RAS) at 24 months.

The results of the study suggested remarkably small outcome differences between the patients who received the EIO treatment and those who received the RAS treatment, regardless of the type of outcome measure examined. The most striking advantages were for the RAS patients who over a 2-year follow-up period spent more time functioning independently, spent less time in the hospital, and were more likely to be employed. The longer patients remained in RAS therapy, the fewer days they spent in hospitals, the more days they spent working full time, the higher the occupational level they reached, and the more household responsibilities they assumed, although they did make more job changes. For all but the last measure, the opposite relationship was observed with the EIO patients.

It is quite striking that the EIO treatment for the group as a whole was not significantly better than RAS on any variable. For those patients who remained in the study for the entire duration, there was only one statistically significant advantage for the EIO treatment at 12 months (retardation-apathy) and this had completely disappeared at 24 months. As May (1984) suggested, the finding that "throughout the followup period, RAS patients spent considerably more days ... in full-time employment than the EIO patients" (p. 607) has important implications for the cost-benefit analysis of different types of treatment. Klerman (1984) concluded: "Whatever criteria one uses, whether box

score, scholarship, or meta-analysis, the evidence from at least half a dozen studies would indicate that no further research on the intensive individual psychotherapy of schizophrenics based on psychodynamic or interpersonal principles is warranted" (p. 611).

Many clinicians have suggested the value of group therapy during the inpatient phase of the treatment of schizophrenia. Several review articles have appeared on this topic (Luborsky, Singer, and Luborsky 1975; Parloff and Dies 1977; Keith and Matthews 1982). By and large, the results from studies designed to assess the impact of group therapy when used with or without medication have not been positive, though there are some exceptions (Malm 1982).

The extent to which traditional individual therapy, group therapy, or milieu therapy may have an impact during the acute phase of the illness does not appear striking. This is not to suggest that patients should be left completely alone while medication is taking effect but, rather, that treatment during this phase should be supportive and psychoeducational. It is particularly important to use the inpatient experience to establish as firm a ground as possible for subsequent treatment efforts. As inpatient stays become shorter and shorter, the major goal would be the most effective use of medication with the best possible aftercare planning and initiation of long-term treatment efforts.

Given the deficits which many individuals with schizophrenia exhibit in social role functioning, various strategies have been developed to address these problems. Most of these strategies are based on premises derived from learning theory and behavior therapy paradigms (e.g., modeling, problem solving, and reinforcement).

Schooler and Hogarty (in press) identified four studies involving social skills training that were restricted to or allowed analyses of effects in schizophrenic individuals (Eisler et al. 1978; Brown and Munford 1983; Bellack et al. 1984; Wallace and Liberman 1985). A recently published investigation by Hogarty et al. (1986), which included a social skills training component, is reviewed by Goldstein in this *Special Report*. These studies suggest that social skills training can lead to improvement in some targeted behaviors, but the question remains as to how enduring these efforts are once the treatment is discontinued and how generalizable the results are to the array of social skills in which many patients are deficient.

In addition, Schooler and Hogarty (in press) have emphasized that with only two exceptions (Bellack et al. 1984; Hogarty et al. 1986) all of these studies have been conducted with male inpatients, primarily chronically hospitalized. The extent to which these findings are generalizable to other populations remains to be established. They also remind us that there may be gender differences in long-term response to antipsychotic drugs (Goldberg et al. 1966) as well as psychosocial treatments (Goldberg et al. 1977).

There have been several major studies of family treatment strategies over the past decade, and these are reviewed by Goldstein elsewhere in this *Special Report*.

Clearly, much remains to be learned about the specific indications for and effects of various therapeutic strategies. There continues to be a lack of clarity as to whether treatments should be continuous, intermittent, or may in fact be time-limited with sustained benefit following termination. It should also be kept in mind that not all forms of therapy are benign; indeed, some psychotherapeutic strategies may have a negative impact depending on the individual, the social environment, phase of illness, and presence of somatic treatment (Hogarty et al. 1974).

The available data do not support the feasibility of substituting any psychotherapeutic strategy for drug treatment on an indefinite basis. The strategies that appear promising involve various combinations of somatic and nonsomatic treatments, with awareness of potential interactions and additive effects, as well as recognition that different strategies may vary in those aspects of schizophrenic psychopathology and disability to which they are directed. The study currently being directed by Schooler and Keith (1983) represents a major advance in research in this area in being able to address many of these issues.

Maintenance Neuroleptic Treatment

The "acute" phase in the treatment of schizophrenia involves an attempt to eliminate the signs and symptoms associated with an acute exacerbation. As discussed, antipsychotic drugs generally have a dramatic effect on the symptoms of schizophrenia (e.g., delusions, hallucinations, and thought disorder) within 4–6 weeks, although improvement may continue well after that interval. The response achieved during this treatment phase will to some extent determine the rationale and expectations of subsequent continuation or maintenance treatment. We usually divide the pharmacological treatment of an illness with exacerbations and relative remissions into three phases: acute, continuation, and maintenance (or pro-

phylactic). In those patients who achieve full or substantial recovery during the acute treatment phase, the continuation phase begins when maximal improvement is reached; its intent is to continue the treatment long enough to be sure that the episode for which the original treatment was given is in fact over. Once this period has passed, then further pharmacological treatment would be intended to prevent the occurrence of a new episode rather than the reemergence of the original episode. This model has been applied more readily to affective illness where episodes may be more discrete, but in our view it may be useful in schizophrenia as well. The actual delineation of these phases in the treatment of schizophrenia may be difficult since, for example, some patients do not necessarily achieve a complete remission of psychopathology despite continuous drug treatment. Although, as shown by antipsychotic drug discontinuation studies, many of these patients would experience even more symptomatology without medication, pharmacotherapy may be viewed as controlling or suppressing ongoing manifestations of the illness rather than preventing a new episode. These patients, therefore, may be relatively poor candidates for drug discontinuation or substantial dosage reduction.

Maintenance antipsychotic drug treatment has proved to be of enormous value in reducing the risk of psychotic relapse and rehospitalization. Numerous double-blind, placebo-controlled clinical trials can be cited to support this conclusion and have been the subject of several review articles (Davis 1975; Davis et al. 1980; Kane and Lieberman, in press).

In the last decade we have seen the initiation of much more sophisticated long-term clinical trials that have focused not only on relapse and rehospitalization, but on various other factors relevant to assessing the overall benefits and risks of maintenance drug treatment. Several concerns have influenced the types of studies conducted in recent years: high rates of noncompliance in taking medication for long periods; the frequent occurrence of adverse effects, particularly tardive dyskinesia; the relative lack of substantial improvement in various areas of functioning leading to continued impairment in psychosocial and vocational adjustment in many patients; considerable variability in clinical course and the potential importance of other therapeutic modalities, environmental and personality factors; and increasingly sophisticated methodological and data-analytic strategies being available to assist in the design and interpretation of long-term clinical trials.

Table 3 summarizes the results of double-blind comparisons of either: active drug versus placebo; two different active drugs (or forms of administration, e.g., oral versus long-acting injectable); or the same drug given in different dosages. We have only included maintenance trials of at least 9 months' duration.

There is clearly an enormous variability in relapse rates reported in these studies. Meaningful comparisons are complicated by differences in design and methodology, such as diagnostic criteria, level and duration of remission, patient selection and recruitment methods, and definition of relapse. In addition, not all of these reports have presented cumulative relapse rates or "life table" analyses that allow for appropriate handling of patients with incomplete data (e.g., those who drop out or are discontinued from the trial due to adverse effects). When cumulative relapse curves are presented, then data from different studies can be contrasted even though investigators may have used different assessment intervals, conducted trials for different lengths of time, or encountered different dropout rates.

Guaranteed medication delivery (i.e., long-acting injectable neuroleptics) has played an important role in many of the major maintenance medication studies in recent years because it enables the investigator to be certain that relapse occurring in the context of long-term pharmacotherapy is not due to noncompliance in oral medication taking, and therefore the impact of other patient, treatment, or environmental factors can be considered and explored (Kane and Borenstein 1985).

The use of guaranteed medication delivery in clinical trials has also made quite clear that many patients continue to experience psychotic relapse despite medication, and this has underscored the importance of exploring other factors that might contribute to poor outcome.

Drug Dosage in Long-Term Treatment

The desire to reduce adverse effects, particularly tardive dyskinesia, but also behaviorally manifested parkinsonian side effects, has led to an increasing interest in identifying minimal dosage requirements for the long-term treatment of schizophrenia.

Attempts to identify minimum dose requirements have taken three major paths: (1) exploring the relationship between dosage and relapse in those reported clinical trials that allow such analysis; (2) carrying out prospective studies comparing patients undergoing gradual dosage

Table 3. Maintenance pharmacotherapy in schizophrenia

Author	n	Age (mean or range)	Sex	Prior episodes	Time since discharge (weeks)	Level of remission	Duration	Outcome		Dropout rate
								Treatment	Relapse	
Troshinsky, Aaronson & Stone (1962)	43	40–50	63% female	2–3	2–4 yr	No hallucinations, delusions, or obvious thought disorder. Required 300 mg CPZ	1 Year	Drug PBO	4% 63%	?
Engelhardt et al. 1963, 1964, 1967)	446	18–44	?	?	?	?	48 mo	CPZ PBO	1 yr 15%, 4 yr 20% 1 yr 30%, 4 yr 31%	36% in 18 mo
Leff & Wing (1971)	35	16–55	?	?	6–12	Preadmission level	12 mo	Drug PBO	35% 80%	14%
Hirsch et al. (1973)	81	43	36% female	70% ~4	50% 52	?	9 mo	FD PBO	8% 66%	9%
Crawford & Forrest (1974)	31	20–65 $\bar{X}$ = 40's	71% female	?	?	?	10 mo	Trifl FD	40% 14.3%	7%
Hogarty et al. (1974)	347	34	58% female	60% ~2	?	?	24 mo	Drug PBO	12 mo 31% 24 mo 48% 12 mo 68% 24 mo 80%	8%
Cheung (1981)	30	40	60% female	1 6	3–5 yr	Fully remitted 3–5 yr	18 mo	Antipsychotic Benzodiazepine	13% 62%	7%
Kane et al. (1982)	28	22	50% female	1	$\bar{X}$ = 17	Remitted	1 yr	Drug PBO	0% 41%	35%
McCreadie et al. (1982)	28	55	All male	?	Inpatients	"Well-controlled"	10 mo	Pimozide FD	15% 7%	25%
Odejide & Aderoummu (1982)	70	?	?	~2	?	Well for ≥12 mo	12 mo	FD PBO	19% 56%	25%
Kane et al. (1983, 1986a)	163	29	37% female	3.2	$\bar{X}$ = 64	Remitted or stable plateau	12 mo	FD dose Low Intermediate Standard	 56% 24% 14%	10%
Marder et al. (1984, in press)	50	36	All male	?	$\bar{X}$ = 23 mo	Stable	1 yr	FD dose Low Standard	 1 yr 22% 2 yr 44% 1 yr 20% 2 yr 31%	14%

Crow et al. (1986)	120	26	38% female	1	1 mo	Able to be discharged	2 yr	Drug PBO	58% 70%	11%
Chien (1975)	47	43	57% female	Former long-term inpatients	?	?	12 mo	FE[1] FE[2] PBO	12% 37 86%	?
Rifkin et al. (1977)	73	23	32% female	1.9	$\bar{X}=26$	Remitted or stable plateau	12 mo	FD + oral PBO	5% 75%	11%
Kelly et al. (1977)	60	42	66% female	?	?	?	9 mo	FD Flupen D	10% 10%	2%
Falloon, Watts & Shepherd (1978)	44	17–60 $\bar{X}=39$	55% female	80% ≥2	0	?	12 mo	Pimozide FD	24% 40%	12%
Quitkin et al. (1978)	56	26	44% female	2.7	$\bar{X}=64$	Remitted or stable plateau	12 mo	Pen FD	7% 10%	20%
Hogarty et al. (1979*a*, 1979*b*)	105	34	54% female	4.6	0	?	24 mo	Oral FD	2 yr 65% 12–24 mo 42% 2 yr 40% 12–24 mo 8%	13%
McCreadie et al. (1980)	35	50	All male	?	?	"Well-controlled"	9 mo	Pimoide FD	19% 17%	3%
Schooler et al. (1980)	214	29	41% female	≥2	0	?	12 mo	FHCL FD	38% 46%	25%

[1]Doctor regulated interval.
[2]Patient regulated interval.

Note.—PBO = placebo. CPZ = chlorpromazine. FD = fluphenazine decanoate. Trifl-trifluoperazine. FE = fluphenazine enanthate. Flupen D = flupenthixol decanoate. Pen = penfluridol. FHCL = fluphenazine hydrochloride.

reduction to controls maintained on stable doses of medication; and (3) assigning patients randomly to different fixed dose levels for comparison.

The first type of analysis is complicated by the fact that the dosage employed may have been influenced by a variety of factors and cannot be assumed to be random. Dosage changes may not have been carried out in a systematic, objective, or reproducible fashion. In the second type of study, dosage reduction and time may be confounded. Even if patients discontinue medication completely, a psychotic relapse may not occur for several weeks or months. In a gradual dosage reduction strategy, it is difficult to determine minimal dosage requirements given the unpredictable time frame in which patients relapse. Although the third strategy eliminates some of these concerns, a fixed dose or dose range must be set, and this has generally been done on a somewhat arbitrary basis given the lack of available data. This design does not necessarily identify the smallest effective dose for a given individual, but it does provide some guidelines as to where to begin.

Fixed Dose Comparisons

Caffey et al. (1964) conducted the first controlled dosage reduction study in hospitalized inpatients and demonstrated that those individuals whose dosage was reduced to 3/7ths of their original dosage experienced a 15 percent relapse rate within 4 months as compared to a 45 percent relapse rate for those patients receiving placebo and 5 percent for those continuing on their original dose. The mean dose of either chlorpromazine or thioridazine that patients had been receiving for at least 3 months before the study began was 350–400 mg/day.

Goldstein et al. (1978) studied the efficacy of two dose levels of fluphenazine enanthate, with and without crisis-oriented family therapy, in 104 recently discharged schizophrenic patients. These predominantly first episode (69 percent) patients were randomly assigned to fluphenazine enanthate, 25 ml or 6.25 mg i.m. every 2 weeks, and studied for 6 weeks following hospital discharge. Relapse was defined as the need to alter medication substantially or to rehospitalize the patient. Only 10 percent relapsed within the 6 weeks following discharge, but 24 percent of those in the low-dose/no-therapy condition relapsed as compared to none of the high-dose/therapy patients. The low-dose/therapy and the high-dose/no-therapy group had relapse rates of 9 percent and 10 percent, respectively. Although this study involved a relatively brief period of controlled treatment, it is a classic study in suggesting the potential additive affects of medication and such psychotherapeutic strategies as crisis-oriented family therapy.

We have reported (Kane et al. 1983, 1985, 1986*a*) results from a 1-year, random-assignment study of different dosage ranges of fluphenazine decanoate (12.5–50 mg every 2 weeks as compared to 1.25–5.0 mg every 2 weeks) involving stable outpatient schizophrenics. At the end of 1 year, the cumulative relapse rate (determined by the psychotic items of the Brief Psychiatric Rating Scale) on the low dose was 56 percent as compared to 14 percent for the standard dose. An intermediate dose (2.5–10.0 mg every other week) was also studied and produced a cumulative relapse rate of 24 percent. Despite the significantly higher relapse rate among patients receiving the low-dose treatment, most of the patients who did relapse were restabilized with temporary dosage increase and without requiring rehospitalization. On average, patients were back to their baseline state within 9 weeks. In addition, significantly fewer early signs of tardive dyskinesia were observed in the patients receiving the very low dose, and they were performing better on some measures of psychosocial adjustment than the patients treated with the standard dose.

Interestingly, patients receiving the very low dose also manifested less evidence of emotional withdrawal, blunted affect, tension, and psychomotor retardation. These differences were statistically significant in group comparisons of rating scale data, but were not of such magnitude as to be obvious in individual patients. These findings do, however, emphasize the potential importance of ongoing parkinsonian side effects even during the maintenance phase of treatment, and highlight the complexity of assessing so-called negative symptoms.

Marder et al. (1984, in press) studied 66 male veteran outpatients, who were randomly and double-blindly assigned to 5 mg or 25 mg of fluphenazine decanoate administered every 2 weeks. Patients were followed for 2 years and were maintained on the assigned fixed dose of 5 or 25 mg as long as they did well. The investigators defined three levels of unfavorable outcome, which could lead to a dosage change. When patients had an increase of 3 or more points on the Brief Psychiatric Rating Scale (BPRS) cluster scores for thought disturbance or paranoia, they were considered to have had a "psychotic exacerbation." These exacerbations were relatively mild and seldom led to rehospitalization, but the clinician

was allowed to increase the dose up to 10 or 50 mg for the respective groups. When patients' symptoms could not be adequately controlled within this range, they were considered to have had a "relapse." The third level of outcome was rehospitalization. The results from this study highlight the importance of a long-term perspective. At the end of 1 year, the "exacerbation" rate was almost identical in the two treatment groups (35 percent on 5 mg and 43 percent on 25 mg). During the second year, however, the two doses produced different rates of exacerbation. Sixty-nine percent experienced an exacerbation on 5 mg as compared to only 36 percent on 25 mg. When the outcome of "relapse" is considered (indicating those patients who could not be controlled by the dosage increase), the two treatments produced similar results after 2 years: 44 percent relapsing on the lower dose and 31 percent on the higher dose (NS). Relapse rates at 1 year were 22 percent with the lower dose range and 20 percent with the higher.

Hogarty (1984) has reported preliminary results from a study comparing standard dose fluphenazine decanoate (average 20 mg every 2 weeks) and a low dose (averaging 4 mg every 2 weeks) representing 20 percent of the standard. At 1 year, 5 of 20 patients (25 percent) assigned to the low dose relapsed.

Results of these studies suggest that dosage reduction can lead to a diminution in adverse effects and improvement in some subjective and nonsubjective measures of well-being. The risk of psychotic exacerbation does increase, however, and patients must be observed carefully with a readiness to increase medication when appropriate and, one hopes, on a temporary basis. This highlights the importance of viewing this approach as a strategy within the context of flexible, observant clinical management. In addition, there may be patients for whom dosage reduction is not feasible based on past attempts or potential dire consequences of psychotic relapse (e.g., history of serious suicide attempts or dangerousness).

The assumption underlying maintenance pharmacotherapy is that continued medication is necessary to prevent an increase or reemergence of psychotic signs and symptoms. The relative benefits and risks of maintenance treatment in general, or alternative strategies in particular, undoubtedly vary from patient to patient. It is also important to keep in mind that the relative desirability of specific strategies may also vary depending on the stage of illness that a given patient is experiencing. Results from long-term naturalistic followup studies (Bleuler 1978; Huber, Gross, and Schüttler 1979; Ciompi 1980*a*, 1980*b*; Huber et al. 1980; Harding et al., in press) emphasize the heterogeneity of outcome in this illness. Some patients appear to experience a chronic deteriorating course while others may experience a much more benign outcome after 10 or 20 years. Unfortunately, we have relatively little information on the very long-term impact of drug treatment on the course of schizophrenia, despite the dramatic benefits of antipsychotic drugs during a period of several years as demonstrated in controlled clinical trials.

The variability in symptom patterns as well as drug responsiveness (even among patients presenting with similar symptoms) also complicates our attempts to identify true drug effects. The extent to which maintenance medication treatment is actually prophylactic—preventing new episodes as compared to suppressing continuously present symptomatology—may also vary from individual to individual. If this distinction could be made with any reliability, it would clearly be useful in establishing the most appropriate treatment strategy.

The possibility that some patients may not require continuous medication has fostered research on "intermittent" or "targeted" strategies that go well beyond earlier suggestions of "drug holidays" in supporting the possibility that some individuals may do well without antipsychotic drugs for substantial periods of time, and that a full-blown psychotic relapse could be prevented by identifying early or prodromal signs of exacerbation and reinstituting medication promptly.

The targeted or intermittent treatment strategy is a partial outgrowth of observations by Herz and Melville (1980) that many patients experience characteristic signs or symptoms during the early stages of relapse and that the clinician's knowledge of this pattern (obtained from the patient, family, and previous treatment sources) may facilitate early recognition and reinstitution of drug treatment. Implicit in this strategy is the assumption that lengthy interruptions in drug administration may minimize the risks of adverse effects. Although this is clearly the case for many adverse effects (e.g., parkinsonian, cognitive, and neuroendocrine), the impact of the strategy on the incidence of tardive dyskinesia has not been established.

Herz, Szymanski, and Simon (1982) and Carpenter et al. (1982; Carpenter and Heinrichs 1984) have demonstrated the feasibility of targeted or intermittent treatment, but direct comparisons of continuous low-dose versus targeted or intermittent strategies have yet to be completed. The National Institute of Mental Health has recently instituted such a study under the direction of Schooler and Keith (1983)

in collaboration with investigators at five hospitals. The drug treatment component compares standard antipsychotic drug maintenance treatment with these two dosage reduction strategies. Patients and their families also participate in one of two treatment approaches designed to improve social functioning and buffer the increased risk for relapse incurred by medication reduction.

Ideally, we would like to have methods that would enable us to identify specific patients who are best suited for a particular strategy on the basis of their propensity to relapse within a relatively short time following neuroleptic discontinuation. The work of Lieberman et al. (1984) using response to methylphenidate infusions as a potential predictor of relapse is a logical extension of earlier work by Janowsky et al. (1973), Janowsky and Davis (1976), and Angrist, Rotrosen, and Gershon (1980; Angrist et al. 1985). Lieberman's results suggest that those patients experiencing a transient exacerbation of psychotic signs and symptoms following 0.5 mg/kg of i.v. methylphenidate will relapse sooner (following antipsychotic drug discontinuation) than patients not responding to methylphenidate. This strategy does not necessarily identify patients who can be maintained medication free on an indefinite basis, but in our experience this remains a very small subgroup.

Even for patients who have been in remission for a considerable period of time on neuroleptics, the risk of relapse following drug discontinuation appears to be considerable. Table 4 summarizes six discontinuation studies (either open or double-blind) that provide relevant data. Even though patients had been in remission for from 6 months to as long as 5 years, 75 percent relapsed within followup intervals ranging from 6 to 24 months.

Table 4. Relapse rate following drug discontinuation among patients in long-term remission

Investigator	*n*	Time in remission (yr)	Length of followup off drug (mo)	Relapse rate %
Hogarty et al. (1976)	41	2–3	12	65
Johnson (1976)	23	1–2	6	53
Dencker, Lepp & Malm (1980)	32	2	24	94
Cheung (1981)	30	3–5	18	62
Johnson (1979)	60	1–4	18	80
Wistedt (1981)	14	½	12	100

Even among individuals recovering from an acute onset, first episode of schizophrenia, a statistically significant drug effect is apparent in preventing relapse. There are two published double-blind, random-assignment trials focusing exclusively on first episode patients. In a 1-year, double-blind study comparing fluphenazine and placebo, the relapse rate on placebo was 40 percent as compared to none on drug (Kane et al. 1982). Crow et al. (1986) reported a less striking drug effect after 2 years in a population of first episode patients. Fifty-eight percent relapsed on active medication as compared to 70 percent on placebo. The lack of a more dramatic drug effect is surprising.

There are potentially important differences between these two studies. Kane et al. (1982) included only acute onset patients, whereas Crow et al. (1986) included a large proportion of individuals who had a lengthy insidious onset. In addition, Crow et al. (1986) reported a significant relationship between length of time ill before initiation of antipsychotic drug treatment and poor outcome. Crow et al. (1986) randomized patients to drug or placebo only 1 month after hospital discharge, whereas in the Kane et al. study patients were in stable remission for an average of 17 weeks before randomization. The extent to which these differences might account for the striking differences in relapse rate, particularly on medication, remains speculative.

A question has also been raised as to whether antipsychotic drugs have a negative impact on the course of schizophrenia. Chouinard and Jones (1980) have proposed a concept of "supersensitivity psychosis" which implies that following drug treatment, the risk of relapse is increased by an increase in sensitivity of dopamine receptors in relevant brain areas. This could be manifested clinically by more rapid relapse following drug discontinuation than would have occurred without maintenance drug treatment, or by the need for continually increasing dosage of medication to maintain the same degree of remission. There are, at present, insufficient data to allow meaningful conclusions and enormous methodological problems in adequately testing this hypothesis. It is also important to consider that some individuals with schizophrenia do have a chronic deteriorating course despite or without drug treatment rather than as a potential consequence of such treatment. In addition, the lack of, or delay in, pharmacological treatment

may have a negative impact on subsequent course even if medication is ultimately used, as suggested by the classic study of May et al. (1976). This phenomenon may be mediated biologically and/or psychologically, and further work would be necessary to consider potential mechanisms.

Adverse Effects

Given the severity and importance of psychotic signs and symptoms that can be controlled by antipsychotic medication, the saliency of what might appear to be relatively minor adverse effects is easily diminished in the mind of the clinician. This is an attitude, however, that we must guard against. This bias is also evident in clinical trials where much more attention is frequently given to assessing and documenting efficacy than to the occurrence of adverse effects. One consequence is that we know relatively little about dose-response relationships, risk factors, and outcome of adverse effects.

Among the most common and troublesome side effects are those involving extrapyramidal movement disorders including: dystonia, parkinsonism, akathisia, tardive dyskinesia, and tardive dystonia. Estimates of the incidence of these reactions vary enormously, from less than 5 percent to over 90 percent of neuroleptic-treated patients (Ayd 1961; Kane and Smith 1982; Mackay 1982; Rupniak, Jenner, and Marsden 1982).

The relationship between antipsychotic drug dosage and the occurrence of extrapyramidal symptoms is complicated. This should not be surprising since patients vary in their vulnerability to develop these side effects. It is also likely the dose-response relationship and the time of onset are not necessarily similar in dystonia, akathisia, and akinesia. In addition, prior medication exposure, bioavailability, age, sex, other manifestations of central nervous system dysfunction, and even genetic factors may play a role.

Drug-induced dystonia, akathisia, and parkinsonism clearly can occur early in treatment, but there is a frequent misconception that complete tolerance to these effects develops over time and that they do not remain a problem in long-term or maintenance drug treatment. This is clearly *not* the case (Rifkin et al. 1978). As we discussed previously, those studies reporting results of substantial dosage reduction during the maintenance phase of antipsychotic drugs treatment do suggest the impact of this strategy on continued manifestations of extrapyramidal side effects (Marder et al. 1984; Kane et al. 1985).

The prophylactic use of antiparkinsonian drugs remains controversial and is clearly more of an issue when high-potency antipsychotic agents are used. The advantages of instituting prophylactic antiparkinsonian treatment include the avoidance of a potentially frightening neurological reaction (e.g., acute dystonia) as well as the prevention of akathisia or akinesia which can mimic symptoms of psychopathology and result in inappropriate increases in psychotropic medication. In addition, it is quite likely that patients who experience adverse reactions during the acute phase of antipsychotic drug treatment are more prone to become noncompliant subsequently (Van Putten 1974).

The disadvantages of using prophylactic antiparkinsonian medication include the possibility that it is not necessary, given the fact that not all patients will develop these adverse effects, as well as the potential for increasing anticholinergic adverse effects. Earlier suggestions that antiparkinsonian drugs lower the blood levels of neuroleptic agents have either not been substantiated or have been dismissed on the grounds that these effects are relatively minor and not of clinical significance.

As indicated, parkinsonian side effects may continue to be a problem even during the maintenance phase of treatment. The clinician should attempt to discontinue antiparkinsonian drugs, if they are being administered, after the first 1 or 2 months of acute treatment; however, discontinuation should be followed by careful examination for reemergence of often subtle extrapyramidal side effects. If these effects do emerge, reducing the dosage of the antipsychotic drug may be appropriate instead of reinstituting the antiparkinsonian agent. A major problem remains the lack of recognition of extrapyramidal side effects in many clinical settings (Weiden et al. 1986).

Chronic and potentially persistent adverse neurological effects such as tardive dyskinesia and tardive dystonia remain a major concern in the long-term treatment of schizophrenia. Epidemiological data suggest that neuroleptic treatment is an important etiological factor in the development of involuntary movements, although individual vulnerability varies considerably and some patients may exhibit abnormal movements unrelated to neuroleptic exposure. Prevalence estimates vary widely and are influenced by a variety of patient, demographic, and treatment history characteristics as well as methodological issues (Jeste and Wyatt 1982; Kane and Smith 1982; Kane et al. 1984).

Data from an ongoing prospective study of tardive dyskinesia development suggest an incidence of 4 percent per year of antipsychotic drug exposure for at least the first 5–6 years of drug treatment (Kane et al. 1986*b*). Whether or not the incidence continues at this rate beyond 5 years remains to be seen. Note that the majority of these prospectively identified cases were rated as mild and did not increase in severity during the 2- to 3-year followup period despite the fact that many patients continued to receive neuroleptics (Kane et al. 1984, in press *b*). Data reported by Casey (1983) and Gardos et al. (1983) also suggest that tardive dyskinesia is not generally progressive despite the continued administration of antipsychotic drugs. Improvement in abnormal involuntary movements does appear to be more likely, however, if antipsychotic drugs can be discontinued, particularly soon after the first evidence of tardive dyskinesia emerges.

There is a small subgroup of patients who do develop a very severe and progressive form of tardive dyskinesia. The intensive study of these patients might help to identify risk factors. Our current inability to predict this degree of vulnerability emphasizes the need for caution in the use of antipsychotic drugs in general. The single most frequently implicated risk factor for the development of tardive dyskinesia is age, although the normal aging process in itself does not appear to produce a substantial degree of abnormal involuntary movements (Lieberman et al. 1984). Increasing age among drug-treated patients appears to increase not only the risk of developing tardive dyskinesia but also its severity and likelihood of persistence.

At present, there are no proven safe and effective treatments for this condition. Though antipsychotic dosage reduction and, particularly, discontinuation can have a definite beneficial effect, complete drug discontinuation is frequently not feasible. There is at present no convincing evidence that any marketed antipsychotic drug or drug class is less likely to produce tardive dyskinesia or more appropriate for patients who have developed tardive dyskinesia.

Given the potential adverse effects that can be produced by antipsychotic drugs, it is critical that attention be given to the overall benefit to risk ratio when these agents are used. Although antipsychotic drugs may symptomatically improve a variety of conditions, they should not be used when equally effective and safer treatments are available as, for example, in patients with affective or anxiety disorders. Clear documentation of ongoing need and benefit derived from the treatment, as well as documentation that the patient has been informed about the potential benefits and risks, should be reflected in the medical record of any patient receiving antipsychotic drug treatment.

Future Directions

The development of new antipsychotic drugs has proved difficult, though some compounds considered atypical may have promise (e.g., clozapine). A major problem in drug development has been the lack of alternative preclinical models and the inherent difficulty and expense of testing drugs in carefully selected subgroups of patients.

Given the apparent heterogeneity of schizophrenia, it is possible that different types of pharmacological agents may be more or less effective in specific subgroups of patients. As we discussed previously, however, the means by which drugs are tested in clinical populations make it difficult to identify agents which may not have a broad spectrum of activity, but may be potentially superior for a specific subgroup of patients.

Research in the treatment of schizophrenia must proceed along two fronts simultaneously—the development of new, potentially superior treatments, and the development of techniques and strategies to maximize the benefits of currently available treatments. Despite our impatience with the progress of research, and hopes for a major breakthrough, we cannot lose sight of the fact that there are over one million people suffering from schizophrenia whose treatment presents an immediate and ongoing challenge. Even incremental advances in the safe and effective use of currently available treatments can have a major impact on the lives of these individuals and their families. Reducing rates of relapse and rehospitalization by as little as 10 percent per year has enormous public health implications. In addition, much remains to be done in assuring that current knowledge is in fact put into practice on as broad a scale as possible.

Much more research needs to be done with those patients who derive little if any benefit from currently available treatments. Degree of response to medication should provide an important cutting edge for better defining subgroups within schizophrenia, leading to potential advances in our understanding of etiology and pathophysiology.

Although most clinical trials do not carry the glamour of potential scientific breakthrough, very basic questions remain to be answered in daily clinical situations. For exam-

ple, what is the appropriate strategy for a patient who has failed to respond adequately to a course of a particular antipsychotic drug? What is the most appropriate management for patients who relapse despite maintenance pharmacological treatment? The critical factor, I believe, in addressing some of these questions, as well as providing the necessary patient populations for all of the types of research reviewed in this issue, is the development of a well-trained cadre of clinical researchers with a sincere and continuing interest in schizophrenia.

Research in this area is fraught with obstacles, and attention must be given to developing incentives for schizophrenia research careers (Pincus, Shore, and Sirovatka 1986). Development of research facilities with access to a broad spectrum of patients at various stages of the schizophrenic illness is also critical in maximizing the potential for meaningful and generalizable conclusions.

Treatment research should proceed in conjunction with many of the perspectives and disciplines represented in this *Special Report* so that our ability to make inroads toward understanding the heterogeneity of schizophrenia can be maximized. Carefully diagnosed and carefully treated patients followed over time will be essential in applying and testing any new biological hypotheses.

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Acknowledgment

Investigators described in this report were supported by NIMH grants MH-31776, MH-32369, MH-3880, and MH-00537.

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