Psychopharmacologic Treatment of Schizophrenia

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Abstract

Antipsychotic (neuroleptic) medications continue to be a critical component in the treatment of schizophrenia. Despite numerous advances in brain imaging, genetics, and neurochemistry, the pharmacologic agents routinely used to treat schizophrenia have not changed markedly over the last 30 years. The introduction of clozapine, however, represents an important step in drug development and has stimulated renewed activity in this area. In addition, its novel effects have had a heuristic value in efforts to better understand neuropharmacologic mechanisms.

While we await further advances in treatment development, we are benefiting from clinical research focusing on improving our ability to use available pharmacotherapy in the most effective and least toxic manner. Recent studies reemphasize the potential value of using the minimum effective dosage for acute treatment (e.g., 10–15 mg/day of oral haloperidol) and provide needed data on the benefits and risks of long-term dosage reduction strategies (i.e., continuous low-dose or targeted/intermittent treatment).

The treatment of schizophrenia continues to be a major challenge to clinicians, not only because of the complexity of the disease, but also because of the necessity to integrate and address biologic, psychosocial, and environmental influences. During a time of decreasing health care dollars, the emphasis on cost-effectiveness and community treatment programs will have an important influence on treatment decisions. Despite numerous advances in a variety of areas (e.g., brain imaging, genetics, neurochemistry), the pharmacologic agents routinely used to treat schizophrenia have not changed markedly over the last 30 years. Important advances in the methods used to assess and diagnose patients have improved the reliability and validity of clinical diagnosis. Greater numbers of patients are being maintained in the community with varying degrees of success. Patients who must remain in hospitals are therefore more severely ill or refractory to available treatments. Much recent clinical research has focused on improving our ability to use pharmacotherapy in the most effective and the least toxic fashion. Moreover, the recent marketing of clozapine has stimulated renewed interest in drug development and has led to a search for novel or atypical compounds that have a broader spectrum of activity and/or fewer adverse effects than conventional antipsychotics.

This review will summarize current knowledge regarding the pharmacologic treatment of schizophrenia, highlighting recent developments and identifying areas in need of further clinical observation and research.

Acute Treatment

The acute pharmacologic phase of schizophrenia treatment implies the introduction or reintroduction of...
medication to alleviate an exacerbation of psychosis. These episodes are usually marked by an increase in positive symptoms such as delusions, hallucinations, thought disorder, and agitation; however, an increase in negative symptoms such as extreme withdrawal can also occur. An episode may be rapid or insidious in onset, and the form and content of the symptoms may change over time. Since important aspects of schizophrenic psychopathology involve subjective experience (i.e., delusions and hallucinations), the ability or willingness of the individual to describe these phenomena reliably may also vary over time.

There is no question that antipsychotic (neuroleptic) drugs remain the primary modality in the treatment of an acute episode or acute exacerbation of a schizophrenic illness. At the same time, we are confronted with enormous heterogeneity in drug response, and a substantial minority of patients derive little if any benefit from drug treatment (Davis and Casper 1977). Even among those patients who do benefit, many are left with residual symptomatology, both positive and negative, which contributes to persistent disability, subjective distress, and family burden.

The major considerations in acute pharmacologic treatment (once appropriate diagnostic, neuromedical, and psychosocial evaluations have taken place) are the choice of drug, drug dosage, and dosage escalation schedule, as well as the potential role of concomitant or adjunctive medication. Subsequently the pharmacologic treatment plan should involve the assessment of therapeutic efficacy and adverse effects, the need for further dosage adjustment, and adjunctive or alternative treatments, particularly information on what strategies are potentially effective for those patients who fail to respond. In addition, planning for the maintenance treatment strategy should begin early, even before discharge from the hospital.

Drug Type

Several different classes of antipsychotic drugs have been introduced over the last 35 years. With the exception of clozapine, there are no convincing data that any one drug or drug class is more effective than any other. It is possible that differences do exist, but studies with appropriate methodology have not been conducted to demonstrate these differences. Most comparisons involve random assignment, parallel group designs that contrast one drug with another and demonstrate a lack of significant difference in overall response rate. These results do not necessarily mean that a given individual would respond equally well to either drug.

At present the process of choosing a drug starts with a detailed history of prior drug response. Evidence that a patient has responded well to a particular drug in the past would be a strong indication for using that compound. At the same time, clinicians should be cautious in interpreting some reports of negative response. Some patients will report that they are "allergic" to a particular drug, when in fact they previously experienced a dystonic reaction. Antipsychotics do produce different adverse effects, and those differences should be considered in choosing a medication for an individual with a known history of particular adverse effects.

One notion that continues to be widespread is that sedating drugs, such as chlorpromazine, are more effective for agitated or highly excited patients than nonsedating drugs, such as fluphenazine or haloperidol. The latter, in turn, are supposedly 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 in both types of patients.

Another consideration relates to the long-term treatment plan. In our view, long-acting injectable drugs are advantageous for many patients, and using the oral form of such a compound (in the United States this would mean either fluphenazine or haloperidol) might facilitate the switchover to a decanoate preparation. This would be a particularly important consideration if the most recent relapse was precipitated by noncompliance. At the same time, since noncompliance is very common and not easily predicted, more widespread use of long-acting injectable drugs should be considered before noncompliance leads to a relapse.

Drug Dosage

Despite years of clinical and research experience, we do not have definitive dose-response curves for antipsychotic drugs. However, recent research provides much guidance to clinicians. In the early stages of antipsychotic drug development it became apparent that chlorpromazine doses below 400-600 mg/day were much less likely to prove superior to placebo than doses above that range. Subsequently, particularly in the 1970s, there was considerable interest in
exploring the upper ranges of tolerated doses to determine if such doses might produce any added benefit, either in terms of rapidity of therapeutic effect or the ultimate degree of improvement.

Studies comparing high-dose (defined as > 2,000 mg chlorpromazine equivalents) to standard-dose treatment showed no statistically significant advantage for the high dose (Wijsenbeek et al. 1974; Quitkin et al. 1975; Donlon et al. 1978; Ericksen et al. 1978; Donlon et al. 1980; Neborsky et al. 1981; Rifkin et al. 1991). These findings do not rule out the possibility that some patients may benefit from higher than usual dosages, but such patients appear to be in the minority and better means are needed to identify those individuals who might be appropriate candidates for high-dose treatment.

As Reardon et al. (1989) have shown, there had been an increase in the use of high dosages of high-potency neuroleptics during the late 1970s and 1980s despite the lack of clinical research data supporting such use. The use of these high-dose regimens may have resulted from increasing pressure to treat patients rapidly, the increasing acuity and severity of those being hospitalized, and the fact that many clinicians believe that high doses of high-potency drugs are well tolerated. As a result of these trends, several studies in recent years have focused on clarifying the benefit-to-risk ratios of different neuroleptic dosages. The following factors also promoted this type of research: observations that adverse effects such as akathisia may be frequently misdiagnosed and lead to noncompliance; the hope that the use of lower doses may help to reduce the risk of other adverse effects (particularly tardive dyskinesia); the realization that maintenance dose is highly influenced by acute dose; and the suggestion that higher doses may even impede therapeutic response.

Levinson et al. (1990) studied 53 patients with acute exacerbations of schizophrenic, schizoaffective (mainly schizophrenic), and other nonaffective psychoses. Patients were randomly assigned to fixed-dose, double-blind treatment with either 10, 20, or 30 mg/day of oral fluphenazine. After 24–28 days of treatment, improvement in the sample as a whole was not related to dosage. However, among patients who showed a 40 percent or greater improvement in positive symptoms, dosages ≥ 0.3 mg/kg were associated with the most clinical improvement, but also with a higher incidence of extrapyramidal side effects (EPS). Levinson and colleagues suggested that a linear relationship between fluphenazine dosage and clinical response exists among patients who respond to a certain degree, and that the nonresponder group may include many patients in whom dose is not a factor because they would be unresponsive to any of the dosages studied. The authors concluded that while the best clinical response was seen at dosages of 0.3 mg/kg/day, the increase in adverse effects was such that they would recommend daily dosages in the lower end of the 0.2–0.3 mg/kg range. (A dosage of 0.2 mg/kg would result in 10 mg/day for a 110-lb. patient and 18 mg/day for a 200-lb. patient.) Interestingly, the authors also found that the presence of akathisia during the study (regardless of whether or not it was treated) also predicted poor response. Antiparkinsonian drugs were given as needed, not prophylactically.

Van Putten et al. (1990) reported on the treatment of 80 newly admitted men with schizophrenia who were assigned openly by cohort to receive 5, 10, or 20 mg/day of haloperidol for 4 weeks. Patients with a history of nonresponse to neuroleptic drugs were excluded, and patients with a history of severe dystonic reactions (28%) were given prophylactic benztropine mesylate 2 mg b.i.d.

After 7 days of treatment, the proportion of patients who remained in the study and were described as “much improved” for the 5-, 10-, and 20-mg doses were 6 percent, 33 percent, and 47 percent, respectively. Although the 20-mg dose appeared superior in efficacy during the first week or two, subsequently the highest dosage group experienced a worsening in emotional withdrawal and psychomotor retardation as well as a higher incidence of akinesia and akathisia. In addition, the 20 mg/day group had a 35 percent dropout rate (leaving hospital against medical advice) in comparison to only 5 percent for the 5- and 10-mg dose groups. These investigators concluded that 20 mg may be more effective for controlling psychoses in the first week or two, but that subsequently a higher incidence of adverse effects undermines this benefit. It is important to note that this was an open study (investigators were not blind to dosage), and it is possible that the prophylactic or early use of antiparkinsonian agents or propranolol to treat akathisia could improve the therapeutic index.

Rifkin et al. (1991) randomly assigned 87 newly admitted patients meeting Research Diagnostic Criteria (RDC; Spitzer et al. 1978) for schizophrenia to receive 10, 30, or
80 mg/day of oral haloperidol on a double-blind basis for 6 weeks. All subjects were given benz-tropine mesylate 2 mg t.i.d. (Among these patients, 93% received DSM-III [American Psychiatric Association 1980] diagnoses of schizophrenia and 7% schizophreniform disorder.) Although 22 percent of the subjects dropped out, there was no difference in dropout rate between the treatment groups. Nor were there any significant differences between the treatment groups either in terms of clinical response or the occurrence of EPS. Thus, these investigators found no advantage to treating patients with haloperidol dosages > 10 mg/day, but they also did not find a significant increase in EPS among patients treated with higher dosages and prophylactic antiparkinsonian medication.

There is a considerable degree of consistency in these studies despite differences in patient populations and methodology. It would appear that there are no significant advantages to using dosages of haloperidol or fluphenazine > 10–20 mg/day for acute treatment and that even dosages of 20 mg may be associated with a substantial number of neurologic adverse effects if prophylactic antiparkinsonian medication is not used.

McEvoy et al. (1991) used the “neuroleptic threshold” to determine optimal dosage for neuroleptic treatment of patients with acute schizophrenia. This involved a hypothesis first proposed by Haase (1961) suggesting that the lowest neuroleptic dosages on which patients develop slight increases in rigidity are also the lowest dosages at which the patients will attain maximum therapeutic benefit.

Of the 106 patients who participated, 25 had schizoaffective disorder and 32 had no prior exposure to neuroleptics. On day 1 of the protocol, 2 mg of oral haloperidol was given and the daily dosage was subsequently increased by 2 mg every other day until the neuroleptic threshold was crossed (i.e., rigidity increased from baseline) or a dosage of 10 mg/day was reached. Once the neuroleptic threshold was reached within the first 10–12 days (very few patients failed to show an increase in rigidity on 10 mg/day), the dosage was fixed and the patient was treated openly for 14 days. After 24 days, patients were randomly assigned, double-blind, to either continue at their neuroleptic threshold dosage or to have the dosage increased by 2 to 10 times. The average “high” dosage between days 24 and 38 was 11.6 ± 4.7 mg/day versus 3.4 ± 2.3 mg/day for those continuing at their neuroleptic threshold dosage. Interestingly, neuroleptic-naive patients crossed the threshold at a significantly lower (2.1 mg/day) average dosage than those who had been previously treated (4.3 mg/day). After 24 days (14 at the neuroleptic threshold dosage), 54 percent were considered responders. After the double-blind comparison was completed at day 38, 42 percent of those who hadn’t responded at day 24 had become responders, but there was no difference between those remaining on the neuroleptic threshold dosage and those randomized to a higher dosage. The only therapeutic measures on which the higher dosage was superior were ratings of hostility and suspiciousness. However, higher dosages were associated with more EPS. In addition, the authors reported a significantly poorer response rate in those patients who had been actively psychotic for more than 6 months before treatment was initiated compared to those with shorter periods of psychoses.

It is somewhat difficult to reconcile these findings with those of Levinson et al. (1990) and Van Putten et al. (1990), who found clear advantages in terms of therapeutic efficacy for the 10-mg dose in comparison to lower doses. It may be that the inclusion of more first-episode and drug-naive patients in the McEvoy et al. (1991) study could account for this if we assume that such patients may require lower initial doses to achieve a therapeutic effect since they apparently develop EPS at lower doses as well. We would also question whether average doses above 11.6 mg would have produced better results in those patients who were initially categorized as nonresponders. In addition, the extent to which these findings are generalizable to routine clinical practice in terms of reliably identifying the neuroleptic threshold remains to be established.

It is also essential to recognize that generalizability remains an important concern because patients participating in these trials usually represent a small subgroup of the population from which they are recruited. In addition, it is frequently difficult to compare results across studies that differ in patient selection criteria, design, and methodology. At the same time, however, these results can be useful in helping to establish some clinical guidelines. In this case there is a strong consensus that dosages above 15–20 mg/day of haloperidol or fluphenazine should not be the first-line treatment in patients who are judged to be capable of responding (i.e., those without an
established history of neuroleptic refractoriness). It is also clear that neuroleptic side effects such as akathisia and akinesia are serious clinical problems even with dosages in this range, and efforts to prevent and treat them should be a high priority for clinicians.

Managing Partial or Nonresponding Patients

A substantial proportion of patients with schizophrenia derive little if any benefit from a 4–6 week treatment trial with neuroleptic drugs regardless of dosage, and the treatment of such patients remains a major clinical dilemma (Davis and Casper 1977).

Kinon et al. (1992) have reported preliminary results from a study designed to compare commonly applied alternative neuroleptic treatment strategies in such patients. In our experience the three most frequently employed approaches to patients who have failed to respond to 3–4 weeks of treatment are to (1) raise the dose substantially, (2) switch to a different class of neuroleptic, or (3) allow more time on the original treatment. (Even though the third alternative may be the least frequently employed, it is critical to have such a group as a control for the other two manipulations.)

These investigators have reported on schizophrenia, schizoaffective, or schizoaffective patients openly treated with fluphenazine 20 mg/day for 4 weeks. Those patients who failed to meet a priori response criteria and consented to participate were randomly assigned, double-blind to fluphenazine 80 mg/day, haloperidol 20 mg/day, or to continue on fluphenazine 20 mg/day. The double-blind phase lasted an additional 4 weeks. Only 7 percent of those who had not met response criteria at 4 weeks responded after 8 weeks, and there were no significant differences among the three alternatives. Some refractory patients might benefit from substantial increases in dosage or switching to a different class of compound, but better methods to identify such patients are sorely needed.

Christison et al. (1991) extensively reviewed alternative somatic treatments for nonresponders including clozapine, benzodiazepines, electroconvulsive therapy (ECT), reserpine, carbamazepine, propranolol, and L-dopa. They concluded that for patients with significant refractory positive or both positive and negative symptoms, clozapine, adjunctive lithium, and adjunctive benzodiazepines have the best documented benefit, but that clozapine is the treatment that appears capable of producing the most dramatic benefit. If clozapine proves either ineffective or impractical, these authors recommend a trial of adjunctive lithium as the next alternative. If lithium produces little improvement, a trial of adjunctive benzodiazepines in moderate dosages would be the third alternative, particularly for those patients who are agitated and are not substance abusers. Unfortunately good predictors are not available for identifying patients who might respond to specific alternatives. Although ECT is not as effective as medication across the range of schizophrenia patients, it has been shown to be of some value (Salzman 1980), and its relative merits in refractory patients deserves further study. Those patients with illness duration > 6 months, significant affective symptoms, or catatonia are most likely to benefit from ECT. Propranolol has been helpful in some patients with aggressive behavior.

In treating such patients it is critical that clinicians have a well-thought-out treatment plan in terms of target symptoms, dosage, and duration in order to assess the impact of a particular treatment trial. It is recommended that only one change in a given patient's pharmacologic treatment be made at a time. It is also important to give patients an adequate amount of time to respond to an intervention. Some patients may require 4 weeks or more before they demonstrate a response to a new drug regimen. Given the fact that many alternative treatments used in refractory patients do not have approved indications for schizophrenia, it is important that the rationale as well as potential benefits and risks be discussed with the patient and significant others and that these discussions be documented in the medical record.

Clozapine

When clozapine was marketed in February 1990 it was the first time that a compound was approved on the basis of evidence of superiority over other drugs for treatment refractoriness or treatment intolerance. Clozapine's availability, as suggested previously, provided the most effective alternative to date for unresponsive patients. The guidelines most clinicians have followed in prescribing clozapine are derived from a multicenter study published by Kane et al. in 1988. However, a variety of important questions would benefit from fur-
Further research. Although the Kane et al. study employed an average daily dose of 600 mg of clozapine, it is not clear whether this is the optimal dose for most patients (some do well on lower doses) and if there is any benefit of using doses higher than 600 mg if patients fail to respond. In addition, this study lasted only 6 weeks, and it remains to be established what trial duration will succeed in identifying most or all responsive patients (current estimates = 12–26 weeks).

Although clozapine’s labeled indication is for the treatment of refractory schizophrenia, there are many schizoaffective and bipolar patients who are unresponsive to standard treatment, and there is evidence to suggest that clozapine may be effective in some such patients (Lindstrom 1987; Owen et al. 1989). Clozapine is also being used with some success to treat patients suffering from severe tardive dyskinesia or tardive dystonia (Lieberman et al. 1991), and controlled trials are under way to more systematically assess clozapine’s potential in this regard.

Current experience with clozapine now extends to over 25,000 patients in the United States. The cumulative incidence of agranulocytosis after 1½ years of clozapine treatment is 0.91 percent (Lieberman and Alvir 1992). There have been seven deaths from presumed clozapine-induced agranulocytosis as of July 31, 1992 (J. Schwimmer, Sandoz, personal communication, 1992).

If not for its relatively high risk of agranulocytosis, clozapine would likely be the first choice antipsychotic because of its reduced risk of neurologic side effects. (The most common adverse effects of clozapine are sedation, hypersalivation, tachycardia, dizziness, and hypotension, but most of these effects subside over time.) If further research efforts are successful in identifying risk factors or mechanisms involved in clozapine-induced agranulocytosis, perhaps the condition can be prevented or the risk reduced (Lieberman et al. 1990).

Clozapine’s availability has also helped to renew interest in antipsychotic drug development, particularly stimulating efforts to identify other putative atypical compounds (described below). In addition, clozapine’s novel profile has provided a new paradigm for looking at mechanism(s) of action.

**Atypical Antipsychotic Medication**

EPS and tardive dyskinesia (TD) are probably the most important factors limiting treatment with conventional antipsychotic drugs. Until recently, it was believed that all antipsychotic drugs caused EPS (albeit to varying degrees) at clinically effective dosages. This belief was first challenged by clozapine and subsequently by the development of a number of other potentially atypical antipsychotic medications. The term “atypical” is probably inappropriate since the drugs that have claimed this label only need to be different from conventional drugs. Nevertheless, the term has been used to characterize a number of compounds that share the attribute of being associated with less EPS at antipsychotic dosages. Meltzer (1990) has defined atypical antipsychotics as drugs that produce weak catalepsy in rodents, cause minimal EPS in humans at clinically effective dosages, and result in minimal plasma prolactin elevations in humans. The only atypical drug that is currently available in the United States is clozapine. However, a number of atypical drugs are available elsewhere, and others are likely to be introduced to the U.S. market in the near future.

One strategy for developing these drugs has been to reproduce some of the biological activities of clozapine. However, there is considerable controversy regarding the explanation for clozapine’s novel clinical profile. As a result, a number of strategies have been proposed for developing effective drugs without EPS. To evaluate the results, various preclinical paradigms have been developed to screen potential compounds. In the rat model, for example, inhibition of conditioned responses and apomorphine-induced hyperactivity are associated with antipsychotic efficacy in humans. Inhibition of oral stereotypies and the induction of catalepsy are believed to be caused by blockade of striatal dopamine (DA) receptors and consistently predict EPS liability in humans. In general, atypical agents inhibit stereotypies and induce catalepsy only at 3 to 10 times the dose necessary to inhibit hyperactivity.

Sulpiride, raclopride, remoxipride, and amisulipride are members of the substituted benzamide chemical class of neuroleptics. These four drugs have the common properties of (1) high specificity for D₂ receptors with minimal D₁ activity and (2) antipsychotic activity with reduced EPS. Moreover, these drugs are relatively free of other troublesome side effects such as sedation and orthostatic hypotension. Sulpiride is the oldest and most widely used of the substituted benz-
amides. Since this drug does not readily cross the blood-brain barrier, it is administered in relatively high doses (800–2,300 mg/day). These high doses cause substantial elevations in plasma prolactin concentrations, which result in a greater likelihood of women developing galactorrhea and amenorrhea. Remoxipride is likely to be the first benzamide to reach the U.S. market. Since it passes the blood-brain barrier more readily than sulpiride, it can be administered in doses that are less likely to cause galactorrhea and amenorrhea. Clinically, remoxipride appears to qualify as an effective atypical neuroleptic (Lewander et al. 1990). At dosages > 100 mg/day it combines atypical psychotic activity with relatively few EPS or other side effects (tiredness, tremor, or akathisia occurred in a small proportion of patients). At this point a number of important questions remain to be answered, including whether remoxipride has superior efficacy in any specific subgroup of psychoses and whether it is less likely than conventional neuroleptics to cause TD.

Another strategy for developing atypical antipsychotic drugs is based on the theory that clozapine’s unique properties are related to its relatively high affinity for serotonin type 2 (5HT₂) receptors. A number of drugs, including risperidone, sertindole, and ICI 204-636, combine D₂ and 5HT₂ activity. Currently, the clinical development of risperidone is the most advanced among these compounds. Risperidone is a benzisoxazole derivative that is pharmacologically characterized by potent central antagonism of both 5HT₂ and D₂ receptors. The drug was developed with the idea that 5HT₂ activity, which is clearly high with clozapine, would give the drug two important advantages: decreased EPS and increased activity against negative symptoms. The drug has undergone extensive trials in the United States, Canada, and Europe. The findings indicate that risperidone is an effective antipsychotic drug that is at least as effective as haloperidol and may be more effective at dosages of 4–8 mg/day. Moreover, in this dosage range risperidone results in approximately the same amount of EPS as a placebo (Marder 1992).

There are a number of other compounds that have been synthesized and are currently undergoing testing for atypical activity. Among these agents are unusual D₂ blockers that cause little or no catalepsy (e.g., melperone); DA autoreceptor agonists (e.g., 3-[3-hydroxyphenyl]-N-n-propylpiperidine [3-PPP]); partial DA agonists (e.g., HDC-912); selective D₁ antagonists (e.g., Sch 39166); and selective 5HT₂ antagonists (e.g., ritanserin).

Many of these drugs may prove to have less efficacy or more adverse effects than expected and only extensive, well-controlled clinical trials will determine their usefulness. In addition, the recent identification, cloning, and sequencing of D₈, D₉, and D₃ DA receptors raise new possibilities regarding novel mechanisms (Seeman 1990; Sokoloff et al. 1990; Sunahara et al. 1991; Van Tol et al. 1991). The two compounds that are likely to be available in the near future in the United States are risperidone and remoxipride. A number of important questions about these drugs are unlikely to be answered until they are available for widespread clinical use: Are the advantages of these drugs in reduced EPS and perhaps superior efficacy likely to translate into improved psychosocial outcome and quality of life? Will these newer compounds be effective for patients who have previously been treatment refractory in a manner similar to clozapine? Will these drugs have reduced liability for causing TD? Although these important questions remain unanswered at this stage, it is reasonable to predict that the effects of clozapine and other atypical drugs will be substantial and that the drug treatment of schizophrenia could be significantly improved in the near future.

Antipsychotic Drug Plasma-Level Measurement

In some respects, antipsychotic drugs would appear to be well suited for plasma-level monitoring. There are large differences in plasma concentrations among patients given an oral dose of a given drug. This probably results from large interindividual differences in drug absorption and metabolism. In addition, there is frequently a delay of days or weeks from the time patients are first treated with antipsychotics until they demonstrate a clinical response. During this period, clinicians are unable to titrate clinical response against drug dosage. If measuring a patient’s plasma level enabled clinicians to select a drug dosage more scientifically, this would decrease the amount of time it takes to arrive at an appropriate dosage. These observations have led to numerous studies focusing on relationships between plasma concentrations and clinical response. Recent studies have helped to characterize the potential usefulness and the limitations of...
plasma-level measurement of antipsychotics.

Early studies focused on drugs, such as chlorpromazine, that have a complex metabolism. These drugs are problematic for plasma-level measurement since some of the antipsychotic activity in the plasma may result from metabolites of the drug. Drug selection and methodological errors may explain why early studies failed to find a reliable relationship.

A number of more recent studies have focused on drugs other than chlorpromazine and have had more promising results. Moreover, recent studies have also employed improved methodology, including the use of fixed dosages. Haloperidol has received the most attention in this context. This is partially due to the fact that this drug has only a single important metabolite, which may not have significant antipsychotic activity. As a result, measuring the plasma level of haloperidol may provide an accurate representation of the amount of effective drug. Five studies have found a "therapeutic window" relationship between plasma levels and clinical response, and five have not. In most cases, failure to find a relationship may be explained by methodologic shortcomings such as the use of patients with a history of poor drug responses or the use of doses which were either too high or too low. At the same time, those studies reporting poor response at higher blood levels may reflect an increase in adverse effects rather than a true decrease in efficacy.

Figure 1 displays data from the study by Van Putten et al. (1992). These findings indicate a curvilinear relationship between plasma haloperidol levels that were averaged during a fixed-dose treatment period and change in psychosis on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962; Woerner et al. 1988). Patients demonstrated the most improvement when their levels were between 5 and 12 ng/ml. Patients with levels above 12 ng/ml also improved as a group, suggesting that some patients tolerate these higher levels. However, when relative nonresponders had their levels increased above 12 ng/ml they failed to improve, and some actually worsened. Volavka et al. (1992) randomized 176 acutely ill schizophrenia patients to one of three plasma ranges of haloperidol: low (2-13 ng/ml), medium (13.1-24), and high (24.1-35). This is an innovative design that permits clinicians to evaluate the usefulness of targeting a particular plasma concentration. Overall, the three groups had approximately the same rate of response, although there was a suggestion that higher levels were associated with less improvement. However, the low plasma level range overlapped with what others consider the optimal range (e.g., 2-12 ng/ml; Van Putten et al. 1991). The findings of this study may indicate that there is no advantage to raising haloperidol levels above the low plasma range.

Given the array of studies in this area and their varying results, it is understandable that there is no consensus as to whether or not plasma levels of antipsychotics should be monitored by clinicians. However, some conclusions may reasonably be drawn from an evaluation of the most recent generation of studies. There is probably little to be gained by monitor-
ing plasma concentrations on a routine basis since a high proportion of patients will respond when they are prescribed moderate doses of antipsychotics. On the other hand, a plasma level may provide useful information in the following circumstances: (1) when patients fail to respond to what is usually an adequate dose; (2) when it is difficult for the clinician to discriminate drug side effects—particularly akathisia or akinesia—from symptoms of schizophrenia such as agitation or negative impairments (a high blood level might be associated with increased adverse effects); (3) when antipsychotic drugs are combined with other drugs that may affect their pharmacokinetics, such as fluoxetine, beta blockers, cimetidine, barbiturates, and carbamazepine; (4) in the very young, the elderly, and the medically compromised, groups in which the pharmacokinetics of neuroleptics may be significantly altered; and (5) if non-compliance or poor compliance is suspected.

Plasma-level measurement for antipsychotic drugs may also be useful for long-term maintenance treatment. During this stage, the goal of treatment is to prevent relapse in stabilized patients. One of the problems of maintenance treatment is that clinicians are unable to titrate drug dosage against clinical response in patients who are already stable. Moreover, this is a time when treating patients with the lowest effective drug dosage can be particularly important since EPS, particularly akathisia and akinesia, may cause substantial personal discomfort or non-compliance, or interfere with rehabilitation efforts (Marder et al. 1987).

A recent study (Marder et al. 1991) suggests that measuring plasma concentrations of fluphenazine may be useful for monitoring patients who are receiving fluphenazine decanoate. In this study, plasma concentrations were measured after 6 months on an assigned dose when patients had reached a stable steady state. The rates of relapse (or psychotic exacerbations as the authors called it) were relatively low when fluphenazine levels were above 0.8 or 0.9 ng/ml, suggesting that this is a reasonable plasma level for maintenance. However, very few patients with levels above 1.2 ng/ml experienced exacerbations, suggesting that if the clinician had given priority to preventing relapse and was less concerned about side effects, then this higher level might be preferable. On the other hand, patients with fluphenazine plasma levels that are lower than 0.9 ng/ml may be on the ascending part of the curve and would benefit from a dosage increase. Patients who received 25 mg of fluphenazine decanoate every 2 weeks had mean levels of about 1.4 ng/ml, and nearly all were on the flatter part of the curve. If this relationship is confirmed with fluphenazine and found with other antipsychotics, particularly haloperidol or haloperidol decanoate, it would indicate that plasma-level monitoring may be helpful for the routine monitoring of maintenance patients, particularly when dosage reduction is being considered.

Comorbid Syndromes

Recent attention has focused on psychopathologic syndromes that commonly coexist with schizophrenia. Relatively common examples are depression, obsessive-compulsive disorder, panic disorder, and substance abuse. Since the last “Special Report” (Kane 1987), there has been increased recognition that these comorbid conditions are common and often difficult to treat. With the possible exception of depression, the literature provides relatively little guidance for the clinician in the pharmacologic treatment of these disorders.

The most common syndrome comorbid with schizophrenia is probably depression. Often the suffering resulting from these depressive episodes equals or exceeds the suffering from psychotic symptoms. Signs and symptoms of depression can occur when patients are experiencing a worsening of their psychosis or when psychotic symptoms are stable. When depression is associated with the prodrome or onset of a psychotic episode, antipsychotic medications are usually the most effective treatment. Recent attention has focused on depressive syndromes that occur in patients with stabilized schizophrenia. Siris et al. (1987) studied 90 patients with either schizophrenia or schizoaffective disorder who had been stabilized on a depot antipsychotic drug. EPS mimicking depressive symptoms, specifically akinesia, were ruled out with the use of antiparkinsonian medications. Patients were randomized to receive either imipramine or a placebo as a supplement to their antipsychotic drug. The findings demonstrated that the patients receiving imipramine were more likely to experience an improvement in depression than those receiving a
placebo, but they were not more likely to experience a psychotic exacerbation. It is interesting to note that patients in this study were treated with 200 mg or more of imipramine, which is the same dosage used for treating depression. These findings clearly support the use of antidepressants for stabilized schizophrenia patients. They do not give guidance to clinicians who are treating depressive syndromes in patients who are acutely psychotic or those who are just recovering from psychotic episodes.

The management of syndromes that commonly coexist with schizophrenia, such as anxiety disorders, obsessive-compulsive disorder, and alcohol or cocaine abuse, clearly deserve attention in the near future. Without systematic research clinicians will need to rely on isolated clinical reports or uncontrolled pilot studies for guidance in treating some of the most difficult schizophrenia patients.

**Maintenance Treatment**

The efficacy of antipsychotic medication for the long-term maintenance treatment of schizophrenia has been established in numerous clinical trials over the last three decades (Davis 1975; Kane and Lieberman 1987). In recent years maintenance treatment studies have focused on improving the benefit-to-risk ratio of long-term treatment and exploring alternative maintenance strategies as well as improving our understanding of how environmental and psychosocial factors interact with drug treatment.

The risk of TD has been a major impetus for dosage-reduction strategies, but it is also important to recognize that the alleviation or minimization of adverse effects such as akathisia and akinesia are also important goals in maintenance treatment. It is likely that these and other side effects contribute to the high rates of non-compliance in medication-taking among many patients being treated for schizophrenia on a chronic basis (Kane 1985).

Attempts in recent years to establish minimum effective dosage requirements for maintenance treatment have focused on two approaches: (1) the comparison of different fixed dosages of medication on a double-blind random assignment basis; and (2) the comparison of continuous drug treatment with an “intermittent” or “targeted” maintenance strategy.

In comparing the results of these studies, it is important to recognize that outcome measures such as prodromal signs (of relapse), exacerbation, and relapse may be defined and applied in different ways by different investigators. Despite this variability, there is considerable consistency in the results across many of these reports.

**Continuous Low-Dose Medication.** Four studies have been reported involving outpatients followed for at least 1 year on different dosages of maintenance medication. Kane et al. (1983, 1985) studied 163 patients randomly assigned to three different dosage ranges of fluphenazine decanoate: 1.25-5.0 mg, 2.5-10.0 mg, or 12.5-50 mg given every other week (antiparkinsonian medication was given as needed). At the end of 1 year the cumulative relapse rates, defined by changes in psychosis on the BPRS, were 56 percent on the lowest dose, 24 percent on the intermediate dose, and 14 percent on the highest dose.

Despite the significantly greater relapse rate in the lowest dosage range, few patients had to be rehospitalized, and on average patients had returned to their baseline state within 9 weeks of having the dosage increased in response to the relapse. In addition, patients receiving the lower dosage achieved better ratings on some measures of psychosocial adjustment as well as ratings of emotional withdrawal, tension, blunted affect, and psychomotor retardation. The fact that these differences were apparent to family members suggests that they were not trivial. Although some of these signs are associated with negative symptoms, it would appear that their improvement in this context was likely due to a reduction in EPS.

Marder et al. (1984, 1987) studied 66 male outpatients in a Veterans Affairs clinic who were randomly assigned to 5 mg or 25 mg of fluphenazine decanoate given every other week and followed for 2 years. The investigators defined three levels of outcome: psychotic exacerbation, relapse, and rehospitalization. A psychotic exacerbation was defined as an increase of 3 or more points on the BPRS cluster scores for either thought disturbance or paranoia. A relapse occurred if patients could not be returned to their baseline state by an increase (up to 100%) in dosage. Following an exacerbation, the treating clinicians were allowed to increase the dose up to 10 mg for the 5 mg group and 50 mg for the 25 mg group. At the end of 1 year, the exacerbation rates were 35 percent on 5 mg and 43 percent on 25 mg, whereas the relapse rates were 22 percent versus 20 percent. These differences were
nonsignificant. After 2 years of followup, however, the two dosages resulted in different rates of exacerbation—69 percent on 5 mg compared to 36 percent on 25 mg. In terms of relapse, however, the difference remained nonsignificant (44% on 5 mg and 31% on 25 mg could not be controlled by a dosage increase following the initial exacerbation). These results emphasize the importance of a long-term perspective in assessing the impact of maintenance strategies. However, few studies to date have lasted more than 1 year.

Johnson et al. (1987) studied 59 stable schizophrenia outpatients who had been receiving flupenthixol decanoate up to 40 mg every 2 weeks for at least 1 year. Patients were randomly assigned to either continue their original dosage or undergo a 50 percent dosage reduction; all were followed for 1 year. A significantly higher (32%) relapse rate was seen in the dosage-reduction group in comparison to the controls (10%). After the first year of the study, those originally assigned to their regular dosage had their dosage reduced by 50 percent, and all patients were followed for an additional 2 years. Seventy percent of the patients followed on reduced dosage for 3 years relapsed and 56 percent of those followed on reduced dosage for 2 years relapsed. Three out of every four patients had resumed their previous full dosage by the end of the followup periods. The full dosage employed here is approximately equivalent to 25 mg of fluphenazine decanoate given every other week. Although there were fewer EPS during low-dose treatment, the differences were not statistically significant.

Hogarty et al. (1988) studied 70 stable outpatients who were categorized as living in high expressed emotion (EE) or low EE households. Participants were randomly assigned, double-blind to receive a standard dose of fluphenazine decanoate (mean 25 mg every 2 weeks) or a minimal dose, approximately 20 percent of the original (mean 3.8 mg every 2 weeks).

At 1 year the relapse rate for the higher dosage was 14 percent as compared to 22 percent for the lower dosage. After 2 years the rates were 24 percent and 30 percent, respectively. No significant differences in relapse rates were found between dosages at 1 or 2 years. Differences in EPS were significant (favoring the low-dose group) after the first year, but were not generally apparent after 2 years. These investigators also reported that the lower dosage showed some advantage in terms of less emotional withdrawal and psychomotor retardation, and better psychosocial and vocational adjustment as reported by Kane et al. (1986).

The results of these studies suggest that substantial dosage reduction is feasible for some patients, but many will relapse. The proportion relapsing will increase the longer the dosage gets and the longer the patients are followed. In addition, the less stable the patients are initially, the greater the risk may be (Hogarty 1984). Dosage reduction can lead to a diminution in adverse effects, though reduction in risk of TD is neither consistent nor dramatic. On the other hand, a 1- or 2-year time frame may be inadequate to assess the impact of these strategies on the incidence of TD. It might be useful to study dosage reduction strategies specifically in patients at high risk for this condition in order to fully determine the utility of these strategies.

**Targeted or Intermittent Medication.** Although intermittent treatment may suggest drug holidays of short duration, the term has recently been used to describe a strategy employing medication only at the earliest signs of symptom exacerbation or relapse. The goals of this strategy are somewhat similar to those of the continuous low-dose strategy, that is, to reduce the risk of TD, and to lessen EPS and other side effects that may in turn lead to improved subjective well-being and psychosocial and vocational adjustment. This strategy requires careful clinical monitoring and reinstitution of medication at the earliest signs of relapse or so-called prodromal symptoms. This approach is intended to take advantage of the fact that many patients will not relapse for several months following complete drug discontinuation. At the same time, however, clinicians, patients, and families must realize that prodromal symptoms and exacerbation are very likely to occur at some point, and everyone must work together to ensure rapid intervention with medication to prevent or control a full-blown relapse. This same requirement is true of the low-dose strategy; however, in that context the dosage is increased and some medication is already present.

Herz and Melville (1980) have suggested that some patients have characteristic prodromal periods with specific signs and symptoms preceding a psychotic episode and that patients and families frequently can recall such early signs of decompensation. Examples of prodromal phenomena would
include sleep disturbance, irritability, depression, changes in energy level or attention, and mild or questionable psychotic signs and symptoms.

These aspects of the intermittent strategy necessitate an ongoing therapeutic relationship for patient monitoring and support. As Carpenter and Heinrichs (1983) have suggested, this is not a “no-medication” strategy, but instead an approach to using medication.

Four major studies have been conducted on targeted or intermittent treatment. Herz et al. (1991) have completed a double-blind study in 140 subjects. Patients who had been stable outpatients and had cooperative families were withdrawn from medication for 8 weeks in a single-blind fashion. Twenty percent of the subjects experienced prodromal episodes during this period and were excluded from further study. A group of 101 patients was randomly assigned to restart medication or to receive placebo. Patients were seen weekly in supportive therapy, and prodromal signs were monitored regularly. If a patient experienced a prodromal episode, open active medication was initiated. Once the patient was restabilized, blinded study treatment was continued and open treatment discontinued. Patients were dropped from the study if they had three episodes in 1 year or one episode lasting more than 9 weeks. Intermittently treated patients did receive significantly less medication; however, they were significantly less likely to complete the 2-year study course (38% vs. 72%). Many of the patients who were dropped from the study because of three episodes in 1 year did not experience a full-blown relapse. Patients receiving continuous medication went for significantly longer intervals without prodromal episodes or full relapses. Family informants monitored prodromal symptoms and often were able to detect them before the patient’s self-report.

Carpenter et al. (1990) published a report involving 116 newly discharged patients. Following a 4- to 8-week stabilization period and a 4-week medication discontinuation phase, participating subjects were randomly assigned to continuous treatment or targeted medication for 2 years. Treatment was not blind. Targeted patients received medication only 52 percent of the time; however, significantly more patients in the continuous-treatment group completed the full 2-year study. Patients on targeted treatment experienced significantly more clinical decompensations and were more likely to be hospitalized. For those patients still in treatment after 2 years (targeted = 21, continuous = 36), the degree of job employment was significantly better among continuously treated patients.

A British group (Hirsch et al. 1987; Jolley et al. 1989, 1990) studied 54 schizophrenia outpatients who had been clinically stable for at least 6 months and on injectable fluphenazine decanoate for at least 2 months. Patients were randomly assigned, double-blind, either to continue medication or to have placebo substituted. The trial lasted for 2 years; subjects were seen every 4 weeks. Prodromal signs of relapse were treated with the addition of open oral haloperidol. The investigators reported no differences in the number of patients completing the first year of the trial. Significantly more patients receiving the intermittent treatment (76%) experienced prodromal episodes than those in the continuous-treatment group (27%). In addition, the intermittent group experienced significantly more relapses, but the number of hospitalizations did not differ. At 6 and 12 months EPS were significantly reduced in the intermittent-treatment groups. The results during the second year of followup, however, were rather different. Although the dosage received in the intermittent group was still less overall, both rates of relapse and rehospitalization were significantly greater. Although there had been a trend toward a lower incidence of TD observed at the end of the first year, this was not seen in the second year. The 4-week interval between visits in this study may have been too long to adequately monitor prodromal symptoms.

Pietzcker et al. (1986) have conducted a trial comparing standard maintenance medication, neuroleptic crisis intervention, and prophylactic early neuroleptic intervention. The investigators studied 365 patients from four different clinical sites. The neuroleptic crisis intervention arm included in this study differs from the intermittent treatment in that this group received medication only when a relapse occurred rather than at the identification of early or prodromal symptoms. Therefore, this study provided an opportunity to determine whether or not intervention at the prodromal symptom phase could prevent the development of a full-blown relapse. Patients participating had to have a 3-month period of stabilization following discharge from the hospital. At both 1 and 2 years, patients experienced significantly higher relapse rates in the early intervention group as compared to the standard maintenance treatment.
The rate of rehospitalization was not significantly greater in the first year (23% vs. 16%) but did reach significance in the second year (37% vs. 24%). Patients receiving only neuroleptic crisis intervention had a higher relapse rate than the other two groups.

Although there are some important differences in these studies (e.g., the Herz et al. [1991] and Jolley et al. [1989, 1990] studies were double-blind whereas the other two studies were not), there is considerable agreement in the overall conclusions. It would appear that intermittent-treatment strategies can be implemented in an outpatient setting and can result in reduced cumulative medication exposure and reduced side effects. However, in some cases, the price to be paid for these advantages is a significant increase in the risk of prodromal episodes as well as rates of relapse and rehospitalization. It is particularly important to recognize that no consistent benefits of intermittent treatment have been demonstrated in terms of social functioning or reducing the risk of TD. One also must keep in mind that some patients may not be good candidates for this approach because their relapses are associated with the risk of suicidal or aggressive behavior. In addition, although many patients in these studies returned to previous levels of stability, some patients may not, and it is possible that patients can lose substantial ground if they are allowed to relapse.

Some patients may be particularly good candidates for intermittent treatment, such as those who refuse to comply with medication but who, with proper education, agree to comply when they are showing signs of early relapse. The field is eagerly awaiting the results of a recently completed study, the National Institute of Mental Health Treatment Strategies in Schizophrenia study (Schooler et al. 1989), which is directly comparing low-dose and targeted treatment. Although several studies focusing on these two strategies have been reported, this will be the first to provide a direct comparison in a large sample of patients. It also includes an assessment of the additive or interactive effects of specific psychosocial treatments. Without such a direct comparison, it is difficult to draw conclusions regarding the relative merits of low dose and intermittent dosage-reduction strategies.

Many attempts in recent years to reduce cumulative neuroleptic exposure have served to highlight the importance and efficacy of maintenance medication in reducing the risk of psychotic exacerbation and rehospitalization. Clearly, it is impossible to make sweeping generalizations with regard to the efficacy of these strategies as they might apply to an individual patient. Clinicians must weigh the potential benefits and risks and also consider other factors that may play a role in a given individual's medication requirements. These factors include, among others, level of compliance, retention of insight during the early stages of relapse, family attitudes, environmental stress, and access to good clinical observation. The emphasis that has been placed on monitoring patients for prodromal signs of relapse regardless of the treatment approach should be applied in routine clinical practice.

Further knowledge is also needed to guide clinicians in identifying individual patients who may go for substantial periods of time without psychotic relapse and who would in fact be the best candidates for an intermittent-treatment approach. The work of Lieberman et al. (1987) provides some encouragement in this context.

For those patients experiencing clinically significant EPS or TD, the potential role of dosage-reduction strategies may be even greater. Although no studies have focused specifically on this population, data from outcome studies in TD suggest that dosage reduction may have an impact on reducing the severity of the disorder or in increasing the likelihood of its remission (Kane 1990).
from currently available treatments. We should not lose sight of the fact that even incremental advances in the safe and effective use of currently available treatments can have a major impact on the lives of many people.

Treatment research should proceed in close interaction with many of the perspectives and disciplines represented in this "Special Report" in order to maximize the potential for future breakthroughs. This can happen only if adequate attention is given to both the opportunities and the potential obstacles in advancing clinical research (Kane 1991).

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