Pharmacologic Treatment of Schizophrenia

by S. CHARLES SCHULZ, MD and CARLOS N. PATO, MD

When chlorpromazine was introduced, it represented the first specific antipsychotic medication. Previous treatments for schizophrenia and manic depressive disorder were useful in calming irritable or distressed patients but had no specific use in reducing hallucinations, delusions, or thought disorder. Early studies using chlorpromazine and antipsychotics introduced quickly thereafter focused on the establishment of efficacy when compared to placebo.1,2

The introduction of the antipsychotic chlorpromazine and the development of similar specific antipsychotics revolutionized the care of schizophrenic patients.

During the 1950s, the use of the clinical trial methodology for establishing medication usefulness was in its infancy. Not only was there a need to establish the efficacy and dose/response relationship of the new antipsychotics, but also a need to introduce the classical clinical trial methodology to psychiatry. This was accomplished through the large National Institute of Mental Health (NIMH)1,2 collaborative studies, which clearly demonstrated the usefulness of the classical antipsychotic (neuroleptic) drugs.

A group of investigations then followed to determine whether specific medicines were more useful than others. For example, was perphenazine a better antipsychotic than haloperidol, or were certain patients with clinical characteristics best treated by a specific antipsychotic. These studies were never able to establish that one of the agents was better than the other—probably because they work through a similar mechanism.

As clinical trials methodology was applied to the antipsychotic medications, such problems as the minimal dose to be tried for a psychotic patient with schizophrenia were tested. The design of those trials

---

1. Schulz, S. Chief, Schizophrenia Research Program, Division of Clinical Research, National Institute of Mental Health, Rockville, Maryland.
2. Patto is Chief, Genetics Research Program, Schizophrenia Research Branch, Division of Clinical Research, National Institute of Mental Health, Rockville, Maryland.

The authors wish to thank Sharon Liu for assisting in preparation of this article.

Address reprint requests to S. Charles Schulz, MD, Department of Psychiatry, Case Western Reserve University, 2074 Abington Rd, Cleveland, OH 44106.
focused on the lowest dose that would produce the greatest percentage of responders. As a rule, little attention was paid to tailoring the doses for specific patient needs.

During these early trials, the strategy of using very large doses (mega doses) was introduced to speed up the response time and to attempt to help nonresponsive patients. Both of these types of studies were important to the field because they gave evidence to the minimum dose required for an adequate trial of neuroleptic treatment and also demonstrated that, in most cases, markedly high doses of antipsychotic medicines may not be required.

In the 1980s maintenance treatment with neuroleptics has been the routine for many years. In an earlier era in which schizophrenia was labeled schizophrenia-reaction, the concept of long-term or even lifelong antipsychotic medication treatment was not a foregone conclusion. However, the efficacy of maintenance treatment also needed to be demonstrated by careful controlled clinical trials. Studies in the early 1970s demonstrated the powerful interaction of maintenance treatment with specific content-oriented psychosocial interventions.

This article highlights three areas of investigation that have current clinical applications. These three areas are, by and large, extensions of the last 35 years of work and include:

- determining the lowest effective dose of antipsychotic medication for both acute and maintenance treatment for schizophrenia,
- the efficacy of non-neuroleptic augmenting medications, and
- the efficacy of atypical (antipsychotic but non-neuroleptic) medications.

**DOsing Strategies**

As has been noted, dosing strategies in the early era of the investigation of antipsychotics focused on the dose that produced the greatest number of responders with the aim being the achievement of an adequate trial of neuroleptic treatment. This strategy may have been caused partly by an underrecognition of tardive dyskinesia (TD) and that the prevention of TD may be accomplished by exposing patients to the lowest amount of medicine possible.

Davis' review of the use of antipsychotics demonstrated that when placebo-controlled studies of antipsychotics were pooled, all studies using antipsychotics in doses higher than 300 to 500 chlorpromazine equivalents per day demonstrated antipsychotic efficacy greater than placebo. Below that dose, the antipsychotics were not statistically significantly superior to placebo. As has been said, this design does not address the question of whether there are a certain number of responders to antipsychotics below 500 chlorpromazine equivalents. In addition, despite the results of this review, surveys on the use of antipsychotics in the United States have shown that the average daily dose may be as high as 1500 chlorpromazine equivalents. This may be a result of a clinical habit of increasing the neuroleptic dose with each exacerbation and not lowering the dose during periods of stability.

During the early 1980s two studies served as examples of how a relatively low antipsychotic dose leads to as rapid a recovery and as low a level of symptoms as higher doses. The studies by Donlon et al and Neborsky et al have shown that 10 mg/day of haloperidol (equivalent to 500 chlorpromazine equivalents) is as effective as doses ranging from 50 to 100 mg/day. As there had been some enthusiasm in the field for so-called loading doses or rapid neuroleptization for the treatment of psychosis, the findings of these studies encouraged others to search for the most specific antipsychotic dose that was neither too low nor too high.

As an example, early studies using the new techniques to determine blood levels of haloperidol demonstrated that most patients would respond to treatment in blood levels between 5 and 15 ng/mL, which resulted from low to moderate doses of the drug. Other blood level clinical response studies have been performed with relatively consistent results indicating either a therapeutic range on the order of magnitude of the Extine et al study or a clear therapeutic window with diminishing returns with higher doses, although not all studies show positive results. In the two recent Van Putten et al studies those patients who developed a blood level above the therapeutic range improved with dose lowering.

An interesting study by Garver et al demonstrated that a group of schizophreniform patients required relatively low blood levels of antipsychotic medication to achieve full remission, thus indicating a clinical characteristic that might predict the success of lower dose strategies. A specific or tailored dosing strategy is that of a “neuroleptic threshold” in which the dose is adjusted to the amount required to lead to minimal rigidity. This idea, first introduced by Haase nearly 35 years ago and dismissed shortly thereafter, has been revived by McEvoy and colleagues. Closer examination of their preliminary results, however, show this to be, as yet, an unproven technique. In this early report McEvoy et al showed that in patients who had previously responded to medication, 67% showed a response when their dose was titrated to the neuroleptic threshold. Unfortunately, this means that 33% of patients previously
responsive to antipsychotic medications did not remit. However, the idea that antipsychotics might be given until a biological endpoint is reached is an interesting and exciting one. The possibility exists that plasma homovanillic acid (HVA), which has been demonstrated to be associated with neuroleptic response, might serve as a marker for depolarization blockade. A study by Bowers et al. has shown that changes in HVA may be associated with patterns of response. Also, innovative work with positron emission topography (PET) scans shows neuroleptic receptor blockade is achieved at relatively low doses, which may be a way to monitor dopamine receptor blockade in the brain rather than at the periphery.

In the long run, the most useful dosing strategies are indicated by studies demonstrating that low doses may be as effective as routine doses of medication for maintenance of schizophrenia. Kane and colleagues performed the first study in which low doses of maintenance treatment were compared to standard treatments. The results were somewhat discouraging in that the lowest dose was associated with a 56% relapse rate in the first year. However, a significant improvement in quality of life kept this concept alive.

The research field persisted, and Marder and colleagues demonstrated that doses of one fifth of standard treatment, ranging between 5 and 10 mg of fluphenazine decanoate every 2 weeks, were as effective as standard doses (25 to 50 mg/wk every 2 weeks) for maintenance treatments up to 1 year. This study is important not only because it gives empiric support to the low dose hypothesis, but also by the empiric demonstration that the quality of life of patients on lower doses is better than those of standard doses.

A cautionary note to the enthusiasm engendered by these studies is necessary, however. During the second year of treatment, in the Marder et al. study, the patients originally taking low doses began to have significantly more relapses than those taking standard doses. Although the investigators suggest that added doses of neuroleptics can help such patients, it might be important for clinicians to note that if they embark on such a treatment plan, special attention is required for the second year.

In addition, a recent British study questions the generalizability of the low dose strategies as designed by Marder et al. As can be noted in the Marder et al study, only patients able to be managed on 25 mg every 2 weeks are allowed in the protocol. In the British study, all subjects—regardless of the dose required for stabilization—were then entered into a low dose versus standard dose strategy. The study was carried on for 3 years rather than just 1 year. At the end of 3 years it was demonstrated that the low dose group had required the same amount of medication as the standard dose group. Thus, the generalizability of the Marder et al. study requires further examination.

Another strategy for diminishing the exposure of patients to higher doses of antipsychotics is the intermittent dosing strategy currently investigated by Herz et al. and Carpenter et al. In both these studies patients were given placebo replacement during the study and, when they began to have premonitory symptoms of psychosis, they were treated with antipsychotic drugs. Although these trials are still in their early stages, both have demonstrated that during the first year the group in the intermittent dosing strategy received less medication. The Herz et al study also has demonstrated some of the clinical characteristics of patients who might be optimal for this type of management. Those patients whose ability to work with the therapist appears to be of prime importance while those whose psychosis becomes full blown very rapidly are not very good candidates, as might be suspected.

In conclusion, an important area of study in recent years has been to find ways to reduce neuroleptic dosage so tardive dyskinesia and other movement disorder side effects are diminished. In addition, the lower dose strategies also have shown an improvement in quality of life and one would assume an increased ability to participate in psychosocial treatment. During acute treatment, blood levels of antipsychotics give promise of usefulness in determining whether there is enough or too much antipsychotic medication. The preliminary studies, especially by Van Putten et al. and others, indicate that dose lowering can be an effective way to manage some putatively refractory patients.

The idea of biological endpoints to determine when antipsychotic medication is at its optimal dose for an individual patient is a new and exciting idea. Although the neuroleptic threshold strategy is unproven at this time, such strategies as radio receptor ligand measurement of dopamine receptor occupancy in brain may be a clue into medication strategies for the future. It appears, at this point, that many patients in the United States have received higher maintenance doses of neuroleptics than necessary. Although more research is indicated before recommending certain low dose strategies and before one can feel confident in predicting which patients can receive such low doses, trying to find the lowest effective dose for each individual appears to be an important
part of pharmacologic management of schizophrenia.

**AUGMENTATION STRATEGIES**

Although polypharmacy (the use of multiple antipsychotics in the same patient) was discouraged in the 1970s, recent attention has focused on the use of non-neuroleptics added to regular antipsychotic treatment for persistently psychotic patients. The concern for such patients has led to better strategies for the classification of nonresponse so that researchers and clinicians can communicate more effectively about the type of patients being treated. Such strategies have focused on criteria for an adequate trial of antipsychotic medicine and what level of symptoms constitutes a remission. As augmenting strategies have been useful in other branches of medicine, such as cancer and arthritis therapy, enthusiasm has been building for augmenting treatments for the last 12 years in psychiatry.

In the mid-1970s, Small and colleagues demonstrated that chronically ill schizophrenic patients could have their symptoms reduced by the addition of lithium carbonate given in doses used for bipolar patients. Subsequent trials have demonstrated the usefulness of lithium in this fashion, although some controversy remains as to whether the success in the reduction of overall symptoms is through the reduction of affective symptoms or schizophrenic symptoms. Of note in one of these studies, by Carman and colleagues, is that patients successfully treated with lithium carbonate, who were then withdrawn from neuroleptic, relapsed. This indicates that the added lithium strategy is a synergistic treatment and not the treatment of occult affective illness.

The anticonvulsant mediation carbamazepine has been tried in schizophrenic patients with some success. Early trials focused on patients suffering from schizophrenia with specific clinical patterns, such as violence or abnormal EEGs. When used in this fashion, studies conducted by Hakola and Laulumaa and Luchins have demonstrated that adding carbamazepine to antipsychotic medication is a useful intervention. It not only reduces symptoms of psychosis, but also reduces violent episodes. The prototype of using carbamazepine for schizophrenic patients who have an abnormal EEG was pioneered by Neppe, who found that patients with abnormal EEG localized to the temporal lobe benefited from the addition of carbamazepine to neuroleptics.

It appears, however, that the use of carbamazepine for the general group of nonresponsive patients is not as helpful. The studies by Herrera et al. and by Dose et al. indicate that for patients who are not fully responsive, the addition of carbamazepine to neuroleptic treatment is of little benefit. An additional cautionary note is that recent studies have all shown that when carbamazepine is added to haloperidol treatment, there is a significant reduction in the neuroleptic blood level. This would indicate that careful monitoring of both the carbamazepine blood level and the neuroleptic blood level need to be done if this type of treatment is to be undertaken.

Lastly, Nesteros demonstrated that some patients with persistent psychosis could be helped by adding relatively high doses of diazepam (eg, 50 mg/day) to their neuroleptic regimen. For some reason, these studies were largely ignored. However, pioneering work by Wolkowitz and colleagues, as well as by Cernansky et al., have shown that for some patients the addition of alprazolam can lead to a significant reduction in both positive and negative symptoms of schizophrenia. Of scientific note from the Wolkowitz et al study is the reduction of plasma HVA when alprazolam was added. This was correlated with symptom reduction and may show that certain patients need an additional non-neuroleptic agent to bring about dopaminergic depolarization arrest in the presynaptic neurons.

In conclusion, the use of non-neuroleptic medications for persistently psychotic patients has gained momentum during the 1980s. A number of different types of medication have been found to be useful, thus indicating there may be a common mechanism for the reduction of psychosis. Lithium carbonate has the most empiric support for an augmenting agent and appears to be a safe medication for this use provided that the lithium level is carefully watched and the dose of neuroleptic medication is not too high. Carbamazepine appears to be a useful augmenting agent, but not for every nonresponder. Its greatest utility appears to be those patients who have the specific target symptoms of violent behavior, despite neuroleptic treatment, or an EEG abnormality.

Finally, it is exciting that the benzodiazepines may help in the reduction of symptoms of schizophrenia as they are both safe and reduce negative as well as positive symptoms. Despite all of these studies, very few (if any) compare one added medicine to the other. In one trial, lithium and carbamazepine were basically equivalent, although the number of responders to lithium was higher. Thus, other than the clinical characteristics of those patients who might be helped by carbamazepine, there is little to suggest which patient may do well with which specific augmenting drug.

**ATYPICAL ANTIPSYCHOTIC MEDICATION**

The medication clozapine was discovered in the early 1960s along with other compounds, such as amoxapine and loxapine. Clozapine was nearly discarded in its early stages of development because it did not exhibit the usual profile of an antipsychotic used by the pharmaceutical industry. Fortunately, the lack of a cataleptic response in animals was recognized as a possible advantage for patients as it might be specifically antipsychotic without causing symptoms of dystonia, parkinsonism, and tardive dyskinesia.

Clozapine trials were begun in the early 1970s and showed the drug to
be an effective treatment of psychosis. In the mid-1970s clozapine was associated with fatal cases of agranulocytosis, and the US clinical trials were stopped. Although the drug continued to be used in Europe and China, it was not tested in the United States until the early 1980s when a protocol to investigate the efficacy of clozapine as a treatment of last resort was initiated. It was through this innovative trial focusing upon the most seriously ill psychotic patients that the specific usefulness of clozapine for schizophrenics unresponsive to usual treatment was demonstrated.

In a landmark study by Kane and colleagues, 30% of patients who had shown no signs of remission for the previous 5 years could be classified as responsive after 6 weeks of treatment with clozapine. Only 5% of the patients who were assigned to the chlorpromazine and benzotrione comparison group were responsive. The Psychiatric Rating Scale (BPRS) data demonstrated an advantage in favor of clozapine over chlorpromazine in the reduction of negative symptoms.

This study not only provided evidence for a new treatment for patients with persistent psychosis, but also may give scientists a pharmacologic profile of a specific subtype of schizophrenic patients, eg, those treatment resistant to typical antipsychotic but responsive to atypical antipsychotics. It has also given the pharmaceutical industry a new avenue of investigation and so-called “atypical” medications currently are being developed.

In addition to its use for patients who are refractory to usual treatment, clozapine may be useful in the treatment of TD because of its lack of motor side effects. Early studies by Lieberman et al have demonstrated reduction in disabling TD, and current trials are underway to see if patients with TD can have their psychosis successfully treated with clozapine as well as experiencing a reduction in TD. Again some caution is indicated in that there is a report showing withdrawal dyskiniesias after 1 year of treatment with clozapine—thus bringing into question whether clozapine allows the brain to “heal” or whether clozapine only suppresses TD. It is known that clozapine has a mild affinity for the basal ganglia receptor and can cause a transient rise in prolactin in the first week of treatment. Whether this amount of blockage can lead to or is associated with the withdrawal dyskiniesias at 1 year is unknown at this time. Further, because of its lack of side effects, clozapine may be of use for the small number of patients who are intolerant to neuroleptic treatment—meaning that they are unable to achieve an effective dose of antipsychotic before side effects become overwhelming.

**CONCLUSIONS**

The introduction of the antipsychotic chlorpromazine and the development of similar specific antipsychotics revolutionized the care of schizophrenic patients. This revolution was characterized by the success of treatment of a number of patients, allowing many to return to work or psychosocial treatments. The routine use of antipsychotics has become part of the armamentarium of psychiatrists around the world.

In this article, the authors discuss the concept of neuroleptic treatments focusing on the use of clozapine. The authors discuss the use of augmenting drugs, points to the ability to help reduce symptoms of schizophrenia for those patients who have not responded previously. It might soon be part of the routine treatment of schizophrenia rather than continued neuroleptic treatment in the face of poor response.

Finally, Kane and colleagues have demonstrated the specific niche for a new specific antipsychotic, clozapine. As approximately 30% of patients previously unresponsive to neuroleptics are helped by clozapine and as this may represent 300,000 to 600,000 patients, clozapine is one of the more exciting findings for patients with schizophrenia in the last three decades. Taken together, these three groups of investigations are in a positive direction and all have immediate clinical use.

**REFERENCES**


