New Drug Treatment Strategies in Schizophrenia: Editorial Introduction

by Nina R. Schooler and William T. Carpenter, Jr.

Abstract

The recognition of both the value and limitations of antipsychotic drug treatment has led to research on effective alternative strategies for treatment. The authors review assumptions underlying such strategies and introduce five articles pertinent to the topic. These articles address: the use of drugs other than antipsychotic neuroleptics; the use of reduced dosages of antipsychotic drugs; the initiation of antipsychotic drugs early during periods of symptom exacerbation to prevent full relapse; the use of psychosocial treatment strategies in relation to drug treatment; and the development of antipsychotic drugs following models based on restitutive systems in the brain.

This issue of the Schizophrenia Bulletin features five articles describing new pharmacotherapeutic strategies in treating patients with schizophrenia. The topic is timely. Because antipsychotic drug treatment has been in use for almost 30 years, there is a generation of mental health professionals and patients for whom the era before the introduction of these drugs is history, not experience. Much of the initial promise of antipsychotic drugs has indeed been fulfilled. The efficacy of the phenothiazines, and of drugs related to that chemical class in structure and effect, has been demonstrated in treatment of patients with acute exacerbations of schizophrenic psychopathology and in prevention or delay of relapse in patients treated in community settings. However, both research and accumulated clinical experience have demonstrated that antipsychotic drugs are not effective for all patients with schizophrenia, that effectiveness may vary with the phase of the illness, that effectiveness does not extend to all aspects of the illness, and that lack of adequate dose or patient compliance with medication taking is not the sole or even the major cause of this apparent lack of effect.

Awareness of patient populations who are not good candidates for drug treatment, either because they do well without drugs or poorly despite them, has come both from clinical experience and from the research literature. The contribution of noncompliance to apparent drug treatment failure has been clarified through the use of long-acting depot neuroleptics. The availability of such long-acting drugs has revealed that patients may develop symptomatic exacerbation despite medication compliance.

There is an increasing appreciation of considerable risk, especially tardive dyskinesia, associated with the long-term use of antipsychotic drugs. Accompanying the recognition of the therapeutic limitations of standard antipsychotic drug treatment are concerns that these drugs may themselves contribute to a deficit syndrome or otherwise undermine social and psychological function in the long term. Furthermore, the effectiveness of antipsychotic drugs may diminish

1 We use the term schizophrenia, but the discussions are relevant to DSM-III schizophrenia, schizophreniform psychosis, schizoaffective psychosis predominantly schizophrenia, and some instances of atypical psychoses. The articles deal with pharmacotherapy of psychotic illness in which standard treatment relies extensively on long-term antipsychotic drugs.

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with chronic exposure, and even positive symptoms may have an iatrogenic component (the tardive dyskinesia hypothesis).

While the neuroleptic or antipsychotic drugs have been preeminent in the pharmacologic treatment and management of schizophrenia, attributes of illness that might be responsive to other drugs have not been vigorously pursued. From time to time, clinicians choose antianxiety drugs to treat anxiety symptoms in schizophrenic patients, antidepressant drugs to treat depression, antiseizure medication when the nature of illness seems analogous to ictal and interictal phenomena, or lithium when some similarity to bipolar affective illness is seen. However, there have been relatively few well-designed studies to elucidate the role of psychoactive drugs other than neuroleptics in the treatment of schizophrenia. In fact, many workers assume that therapeutic responsiveness to other classes of medication challenges the diagnosis of schizophrenia. 

The growing recognition of both the value and limitations of antipsychotic drugs has led to inquiries concerning effective strategies for the use of these drugs—alternatives to the common practice of treating and maintaining schizophrenic patients indefinitely on substantial doses of medication.

Conceptual Basis for Treatment Strategies

The use of any drug treatment strategy depends in part on assumptions that are made regarding the nature of the illness being treated. For instance, the use of continuous antipsychotic medication at standard doses follows from one of two assumptions: either that the symptoms being treated are continuously present and are being kept under control by the medication, or that continuous medication may prevent the unpredictable reemergence of symptoms. A reduced dosage strategy accepts both the maintenance and prophylactic premises of continuous antipsychotic drug treatment but attempts to achieve that goal while minimizing the exposure to medication. This model assumes further that the presence of a continuous low dosage of medication serves to cushion the severity of symptom exacerbation when it does occur and to enhance the speed of response to medication when symptoms appear. A drug holiday approach also assumes both the maintenance and prophylactic benefits of continuous drug treatment but attempts to achieve them through the imposition of a fixed schedule of alternating medication and medication-free intervals. Determination of such schedules is based on general clinical and/or research experience rather than on clinical change in individual patients. A targeted medication strategy assumes that medication is not continuously required to suppress psychotic symptoms in many patients and that medication will prevent or delay the emergence of symptoms if administered early during an exacerbation. This strategy depends on the early identification of prodromal symptoms to provide intervention with medication to treat the symptoms and prevent a full relapse. Medication is again discontinued once clinical stability is reestablished.

It has been postulated that decreasing neurotransmission in mesolimbic or mesocortical dopamine neurons is therapeutic in patients with schizophrenia. A paradoxical effect of continuous administration of dopamine-blocking antipsychotic drugs may be the induction of new postsynaptic dopamine receptors in an adaptive response to the drug blockade. In either case, downregulation of dopamine receptors may enhance clinical stability or augment neuroleptic treatment.

The use of drugs other than the conventional antipsychotic neuroleptic drugs challenges another assumption underlying neuroleptic drug use—that they are a broad-spectrum treatment of schizophrenia and that other classes of drugs are not effective in schizophrenic patients. Indeed, response to another agent may call into question the diagnosis. Approaches using other drugs make a counter assumption that specific psychopathologic attributes or symptoms may occur in a number of diagnostic classes (e.g., depressive symptoms in schizophrenia) and that therefore other drugs may be useful either as a supplement or an alternative to continuous antipsychotic drugs.

All these strategies are alternative drug treatment approaches. The direct comparison of interpersonal therapeutics to pharmacotherapeutics is not addressed here. We find little basis for conceptualizing these two categories of treatment as alternatives, nor do we find any impressive research data supporting a generalized efficacy for psychosocial treatments given exclusive of antipsychotic drugs. Of concern in this discussion is the interplay between drug and psychosocial treatments. When efforts are undertaken to reduce reliance on antipsychotic drugs, an increased need for effective interpersonal strategies may be seen. Specific supplemental, additive, and synergistic effects are also addressed.

Nature of the Schizophrenic Illness

We have noted that the recent attention to new drug treatment
strategies for schizophrenia is not rooted in theory. However, attention to such strategies is also suggested by current concepts of the nature of schizophrenia.

An interactive, developmental model of schizophrenia is based on several assumptions. First, multiple factors are associated with vulnerability to schizophrenia. Second, among those vulnerable to illness, various factors may serve a protective role or may be involved in inducing psychotic episodes. Finally, in those individuals who have become psychotic, a number of factors will influence the subsequent course and outcome of illness. It is assumed that interindividual variability is considerable, and that a combination of factors at each of the three stages will operate in each case. If such a multifactorial model is correct, then multiple therapeutic modalities may be required, and the therapeutic requirements of patients would vary both among individuals and over time.

Bleuler recognized the syndromal aspect of schizophrenia when he referred to “the group of schizophrenias.” The field has generally regarded schizophrenic patients as representing a heterogeneous diversified illness group comprising more than one distinct disease entity. In the absence of methods to confirm such distinctions, however, patients diagnosed as having schizophrenia have generally been approached as though it were a single disease. If one accepts the heterogeneity of schizophrenia, then one needs to consider the likelihood that therapeutic requirements would vary according to the specific disease entity.

When patients with schizophrenia are viewed from a long-term perspective, it is clear that many patterns of course are to be found and that patients change remarkably in their clinical status over time. For instance, the concept of “burned-out schizophrenia” refers to end stages of illness where episodic exacerbations of positive symptoms are diminished and the deficit syndrome is enduring. Some patients have continuing psychotic symptoms, while others run a course of remission and relapse. The different patterns of course among patients suggest the need for individualization of long-term treatment. Further, the fact that patients vary over time in their own therapeutic requirements also argues for the individualization, rather than simple perseveration, in treatment.

There is a broad range of psychopathology expressed in patients with schizophrenia. Significant pathologic disturbances are found in many areas of functioning. There are disturbances in subjective experience, perception, and thought that form the usual basis for recognizing the presence of schizophrenia. Patients vary widely in the degree of premorbid disturbance (perhaps best conceptualized as early morbidity). Some forms of schizophrenia appear to undermine intrapsychic and interpersonal functioning early in life. In following the course of schizophrenia, a number of investigators have shown that impairments in various domains of functioning are only modestly linked. During acute phases of illness, antipsychotic drugs exert a therapeutic impact on a wide range of symptomatology but, even then, patients may have important psychopathologic attributes which remain unresponsive. During less acute phases of illness, it is not yet clear what the interaction is between antipsychotic drugs and functional attributes such as the amotivational syndrome. This consideration further calls attention to the requirement of individualizing treatment decisions and the potential benefit of integrating pharmacotherapy with other therapeutic endeavors.

Acceptance of any (or all) of the above-described current theoretical ideas regarding schizophrenia—its multifactorial etiology, vulnerability, and course; the heterogeneity of the patients called schizophrenic; the range of functioning that is disrupted in the disorder; and the variability of its course both within an individual and across individuals over time—could lead to attention to a range of psychopharmacologic treatment strategies and the effort to determine for which patients specific strategies are the most appropriate.

Treatment Strategies

Among the many important issues in drug treatment in schizophrenia, we have chosen to highlight the following:

- The use of drugs other than the antipsychotic neuroleptic agents is reviewed by Susan Donaldson, Alan Gelenberg, and Ross Baldessarini. Their article focuses on drugs that are marketed and available to the clinician rather than on experimental agents. As has been discussed above, psychotherapeutic drugs may not be disease specific. Extant data provide some guidance to the clinician in this area.

- The low dosage strategy is presented by John Kane. Drawing on work of others, but focusing primarily on recent studies in progress by Kane and his colleagues, he draws attention to the variability and the range of strategies that are encompassed within the general category of substantial dosage reduction. The profile of benefits and risks is different for low and standard doses, and the clinician will find the reported data important in
evaluating the best fit between patient and treatment.

- The targeted medication approach is described by one of us (William T. Carpenter, Jr.) and Douglas Heinrichs. The importance of a psychosocial component to this approach is highlighted, and the specific psychosocial method is described. Here, also, work in progress supports the feasibility of an alternative to standard treatment, and a different set of risks and benefits begins to be appreciated.

- A review of psychosocial strategies in relation to drug treatment is provided by Ian R. H. Falloon and Robert P. Liberman. They analyze the relationship of drug and psychosocial treatment modalities (i.e., independence, additivity, interaction) and focus on recent work with a specific model of family intervention.

- Last, Arnold Friedhoff returns to models of the illness of schizophrenia drawn from a common biochemical characteristic of antipsychotic neuroleptic drugs—their ability to block postsynaptic dopaminergic receptors. Noting that this observation alone has not led to the development of novel drug treatments for schizophrenia, he calls attention to general principles of brain physiology and postulates a method for developing antipsychotic drugs. Work in progress based on an aspect of this theory (down-regulation) reveals supporting clinical effects.

All the articles share a common element. They describe work in progress. This issue of the Bulletin is far from the last word on drug treatment strategies in schizophrenia. Rather, we attempt to bring together a wide range of research under a rubric that we hope will stimulate clinicians and investigators to refine these and initiate other strategies to improve the treatment of schizophrenic patients.

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