EDITORIAL

Treatment of Schizophrenia and Spectrum Disorders: Pharmacotherapy, Psychosocial Treatments, and Neurotransmitter Interactions

The Primacy of Dopamine and Focus on Positive Symptoms

The modern era in the biological treatment of schizophrenia was initiated with the observation that chlorpromazine, originally studied for its sedative effects, had the ability to treat delusions and hallucinations. The hypothesis that the antipsychotic action of chlorpromazine was caused by its ability to block the stimulation of brain dopamine receptors (Carlsson and Lindqvist 1963), along with the hypothesis that amphetamine-induced psychosis was caused by the increased availability of dopamine (Randrup and Munkvard 1972; Snyder 1973), were the pivotal ideas that catalyzed the intense effort to link dopamine and schizophrenia and to understand the role of dopamine in brain and behavior. The group of neuroleptic drugs that resulted from the dopamine hypothesis of schizophrenia shaped not only the treatment of schizophrenia but also the basic conception of the disease process itself. The neuroleptic drugs facilitated the closing of vast numbers of psychiatric beds and the initiation of community treatment for schizophrenia, two factors that have had enormous consequences for patients and their families, for the mental health professions and psychiatry in particular, and for society as a whole. Unfortunately, the challenge of treating patients with schizophrenia in the community using neuroleptic drugs as the mainstay of treatment has not been adequately met, as evidenced by only modest advances in improving outcome in schizophrenia and the large numbers of people with schizophrenia in the United States who are homeless or incarcerated.

The usually successful treatment of the positive symptoms of schizophrenia with neuroleptic drugs led directly to diagnostic criteria for the disorder (DSM III, IV) that emphasized these symptoms and focused both preclinical and clinical research more on understanding the etiology of positive symptoms and developing better treatments for them than on other aspects of schizophrenia (e.g., the cognitive deficit) than was warranted in terms of their importance for outcome. Many embraced the reductionist view that the core aspects of schizophrenia might result from one or more abnormalities of the dopaminergic system, leading to models that characterized the onset and course of schizophrenia—negative symptoms and cognitive deficits, for example—as the consequence of abnormalities in dopaminergic activity. Interest in the cognitive deficits of schizophrenia waned as evidence accumulated that the neuroleptic drugs were ineffective in their treatment. The concept that any new treatment of schizophrenia had to be effective in controlling positive symptoms rather than, for example, the cognitive deficit in this disorder came to dominate new drug development. Many of these views are still widely held.

Beyond Positive Symptoms and Dopamine in the Treatment of Schizophrenia: The Importance of the Atypical Antipsychotic Drugs, Negative Symptoms, and Cognition

Beginning in the 1980s, interest in the negative symptoms of schizophrenia (i.e., lack of spontaneity, anhedonia, affective flattening, and avolition) reemerged as a primary goal of the treatment of schizophrenia. An early influential model of the etiology of negative symptoms ascribed them to supposedly irreversible structural changes in the brain (Crow 1980). Subsequently, the possibility that these symptoms were the result of decreased cortical dopaminergic activity emerged (Davis et al 1991; Meltzer 1985).

There is now enough evidence concerning schizophrenia and its treatment to be able to fairly confidently move beyond the disease model shaped by the dopamine/positive and negative symptom mold, however. It has become abundantly clear that treating positive symptoms with typical neuroleptics, even when successful, leaves the majority of patients with schizophrenia significantly disabled from a functional point of view (Hegarty et al 1994; Meltzer 1997). The major reason for this, probably the most important for many patients, appears to be the cognitive deficit present in most but not all patients who meet contemporary criteria for schizophrenia (Green 1996; Meltzer and McGurk 1999). For example, Palmer et al (1997) reported that 85% of patients with schizophrenia are cognitively impaired compared with the general population, although it is likely that the other 15% are less capable cognitively and from a functional perspective than they might have been had they not become psychotic. There are now numerous studies indicating that clozapine, the prototype of the group of atypical antipsychotic drugs, produces much less blockade of striatal dopamine receptors than typical neuroleptics or even the atypical antipsychotics that are most closely related to it such as olanzapine, quetiapine, and risperidone (Farde et al 1992; Kapur

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and Remington 1999). Indeed, some of the key benefits of clozapine, such as the ability to improve cognition and the negative symptoms of schizophrenia, may be due, in part, to the ability to increase dopaminergic activity in the prefrontal cortex, a brain region that, together with temporal lobe regions such as the hippocampus, is essential for cognition. We have now found, however, that olanzapine is able to block extrastriatal dopamine receptors at doses that spare many striatal dopamine receptors. This may be the case for other atypical antipsychotic drugs with similar pharmacology as well. Thus, dopamine receptor blockade may be more important to the action of the atypical antipsychotic drugs than previously thought and may contribute to the limited efficacy of selective 5-HT2a receptor antagonists, such as M100907, that do not block D2 dopamine receptors.

The three articles in this issue of *Biological Psychiatry* concerning the treatment of schizophrenia and the related condition, borderline personality disorder, as well as the article by Carlsson and colleagues summarizing some of their current thinking about the neurotransmitters involved in the etiology of schizophrenia and the implications for developing superior treatments, reflect in varying degrees that breakdown of the old dopamine-based paradigm. In its stead is a new model that has, in my opinion, tremendous heuristic value to shape how we conceptualize, study, and treat what is now called schizophrenia. The limitations and, perhaps, approaching end of the neuroleptic era in the treatment of schizophrenia is documented in John Kane's treatment overview article, which cites the influential review of Hegarty et al (1994) that showed only about a 20% increment in moderate-good outcome in schizophrenia after the addition of the neuroleptic drugs, reaching an overall rate maximum of 55% over a decade ago, followed by a significant decrease in the proportion of good responders. The evidence for the greater benefits of the atypical antipsychotic drugs, such as clozapine, risperidone, olanzapine, and quetiapine, is quite strong in many outcome domains, even though effect sizes are relatively modest (Fleischhacker 1999; Leucht et al 1998). The mean changes obscure the fact that these agents have been of incredible value to many patients who did not respond to, or could not tolerate, the typical antipsychotic drugs. Near miraculous improvement occurs in a limited number of fortunate individuals. The majority of patients, however, remain moderately to severely disabled, despite full or partial control of positive symptoms. The most exciting findings with these drugs are that 1) clozapine can significantly diminish positive symptoms in more than 50% of the patients who fail to respond to the typical neuroleptics; 2) it does not produce tardive dyskinesia; and 3) it can improve some domains of cognition, especially verbal fluency, secondary memory, and some measures of attention (Fleischhacker 1999; Kane et al 1998; Meltzer 1997; Meltzer and McGurk 1999). Risperidone, olanzapine, quetiapine, and ziprasidone share these characteristics to various extents (Leucht et al 1999; Purdon 1999; Tandon et al 1997). Much further research is needed to understand how best to use these agents and to gain a fuller appreciation of their efficacy in schizophrenia and other conditions.

My view that these agents can improve some types of both primary and secondary negative symptoms, albeit to a modest extent in most patients and usually only in those patients with high initial levels of negative symptoms at the start of treatment (Meltzer 1991, 1995) is still controversial (Carpenter et al 1995; Remington and Kapur 1999). There should be no dispute, however, that they can markedly improve negative symptoms per se in some patients. To varying extents, the additional advantages these agents have with regard to compliance, superior effects on mood and suicidality, decreased hospitalization, and improved functional outcomes, which are based in part on improved cognitive function, leads to both reduced overall direct costs of treatment and indirect costs, making them a dominant treatment. As such, they should be the sole drugs prescribed for schizophrenia, especially when long-acting formulations become available within the next few years. Further research to optimize the use of these agents for their numerous indications are necessary. For example, the concept that they owe some of their advantages to low D2 dopamine receptor blockade relative to 5-HT2a receptor blockade in the mesolimbic and mesostriatal systems, if true, dictates that concomitant treatment with neuroleptics should be avoided. The duration of trials with the atypical agents in treatment-resistant patients and the use of concomitant medication or ECT to augment response has not been adequately investigated. The possible use of these agents in the prodromal period of schizophrenia, before the emergence of psychosis (McGorry 1998), is perhaps the most important issue to clarify in the next decade because it is clear that for many patents, the newer drugs, although superior to the neuroleptics, are unable to fully reverse already-established impairment in cognition, negative symptoms, and social disability. A recent study of Tsuang et al (1999) has shown that risperidone has some benefit to improve cognition and mild functional disability in first-degree relatives of people with schizophrenia who meet no diagnostic criteria for psychiatric illness. This is consistent with the possibility of preventing the poor outcome of schizophrenia by identifying individuals with prodromal schizophrenia and utilizing the antipsychotic agent with the best risk-to-benefit ratio available, recognizing that long-term treatment over a course of many years, at least through the peak years of risk, may be needed.

Integrating Psychosocial Treatment and the Atypical Antipsychotic Drugs

The role of psychosocial treatment in the treatment of schizophrenia is well reviewed by Lauriello et al, who rightfully emphasize the importance of the larger domains of outcome, such as social adjustment and employment, and correctly conclude, in my judgement, that psychosocial treatments may be the means of achieving these goals. At the same time, they note how little data there are supporting the conclusion that the current modalities of psychosocial treatment are effective in this regard, having shown mainly a time-limited effect on relapse prevention. It should be noted, however, that all of the studies they review date from the neuroleptic era. The efficacy of these modalities in patients treated with the atypical antipsychotics could be significantly superior because of the greater ability of these agents to improve cognition and negative symptoms and because of better compliance and the ability to delay or even prevent recurrence of positive symptoms. Future research with psychosocial treatment should examine the differential benefit of intensive application during the first years of the illness, including the prodromal period if possible, if they are to have their maximal impact. This is not to diminish their potential value in conjunction with the atypical agents in more chronic patients. Controlled research in this area is most difficult but deserves to be supported because of the importance of satisfactorily demonstrating an additive or synergistic effect of psychosocial treatment and pharmacotherapy. The resources to provide psychosocial treatment to patients with schizophrenia and their families have diminished in the absence of convincing evidence for their efficacy and the increased expenditures for the atypical antipsychotic drugs. Studies to demonstrate the benefit of the various forms of psychosocial treatment used in conjunction with the novel antipsychotic drugs are urgently needed. Positive results in such studies are the only way that society will provide funding for this form of therapy for the vast majority of patients who cannot support it with their own resources.

Novel Uses of the Atypical Antipsychotic Drugs: Personality Disorders

Further testing of the atypical antipsychotic drugs in conditions other than schizophrenia in which neuroleptic drugs previously have been shown to be effective but poorly tolerated should also be a high priority. Clozapine and quetiapine have been found to be highly effective and very well tolerated in treating dopaminomimetic psychoses in Parkinson's disease (Scholz and Dichgans 1985). Borderline personality disorder would seem to be a condition in which the atypical antipsychotic drugs would be of major benefit because the elements of this disorder (e.g., psychosis, mood instability, depression, impulsivity and anger) have been found to be responsive to atypical antipsychotic drugs in patients with schizophrenia and major mood disorders. Further, there is evidence, reviewed in the article by Schulz et al in this issue, that the neuroleptic drugs are effective in some patients with this syndrome but poorly tolerated. It is disappointing that there are no published controlled studies to validate the efficacy of the atypical antipsychotic drugs in borderline personality disorder because there is equivocal anecdotal evidence to support this indication. The study reported here is another open, small trial. Because the authors found a high placebo response rate in this condition in a previous double-blind study with risperidone, it is surprising that they did not go directly to a placebo-controlled study with olanzapine. What one can glean from this report is that the weight gain with olanzapine (8.9 $\pm$ 6.0 lb during the eight week trial) led to its discontinuation in four of nine patients (44%), suggesting that tolerability for this agent may not be high in individuals with borderline personality disorder, regardless of efficacy. It should be noted, however, that the majority of patients with schizophrenia treated with olanzapine, as well as the patients in the Schulz et al study, have only slight weight gain, so this side effect does not preclude its use in many patients. Pharmacologic and other means of controlling weight gain with drugs such as clozapine, olanzapine, and quetiapine are a high priority. An atypical antipsychotic drug with lesser weight gain propensity than olanzapine (e.g., ziprasidone and low-dose risperidone) should be tested in a placebo-controlled trial, with a neuroleptic as an active comparator and a maintenance phase, in patients with borderline personality disorder, as well as schizotypal and schizoid personality disorders.

The Role of Serotonin, Glutamate, GABA, and Acetylcholine in Schizophrenia and the Pharmacotherapeutics of Schizophrenia and Related Conditions

The widespread adoption of the atypical antipsychotic drugs and their undeniable clinical advantages for many patients with schizophrenia and other indications has provided encouragement for the development of additional novel strategies to obtain new antipsychotic agents with superior efficacy and fewer side effects, such as weight gain, sedation, hypotension, and so forth, that are shared by many, if not all, the available agents. Much attention has been given to the importance of 5-HT2a receptor antagonism, together with weak D2 receptor antagonism, in their action (Altar et al 1986; Meltzer 1999; Meltzer et al 1989). There have been at least six additional series of

compounds of different chemical classes with this profile that have been shown preclinically to have atypical antipsychotic properties. Other 5-HT receptors, however, such as the 5-HT1a, 5-HT2c, 5-HT6, and 5-HT7 receptors (Meltzer 1999), as well as the D3 and D4 dopamine receptors, and, as pointed out by Carlsson et al in this issue, drugs targeting NMDA- and AMPA-type glutamate receptors also appear promising. The circuitry underlying these strategies is discussed by Carlsson et al here and by others (Jakab and Goldman-Rakic 1998; Wang and Arvanov 1998). The ability of the novel antipsychotics to enhance cholinergic function in the prefrontal cortex (Ichikawa et al 1999; Meltzer et al 1999), as well as other data (Bymaster et al 1998), points to the importance of acetylcholine as well. In my view, drugs that improve cognitive function and negative symptoms, in addition to positive symptoms, are what is needed for the treatment of schizophrenia and related conditions. If they lack the ability to treat positive symptoms, however, they might be effectively combined with low doses of the current generation of agents effective to treat such symptoms unless these effects are incompatible because of pharmacodynamic interactions.

The article by Carlsson et al in this issue provides an excellent overview of the current ideas concerning schizophrenia, its pathophysiology, and its treatment, authored in part by one of the greatest minds in the history of psychopharmacology and biological psychiatry. It is laden with new and old concepts based on the type of thoughtful integration and synthesis of clinical and preclinical data that is essential for rapid progress utilizing updated, classical concepts, as opposed to "fishing expeditions" based on genome scans in patients with schizophrenia or identification of genes activated by various models such as noncompetitive NMDA-receptor antagonists, such as PCP, or by atypical antipsychotic drugs. Carlsson et al provide a concise, interesting update on current concepts of the role of dopamine, serotonin, acetylcholine, glutamate, and GABA in schizophrenia, as well as crucial directions for future preclinical and clinical research in schizophrenia, including biological psychiatry, new drug development, and clinical trials. It is an article worth close study by anyone with an interest in schizophrenia or one or more of its various components, such as delusions, hallucinations, negative symptoms, and cognitive disturbance. Only a few points can be highlighted here, and if I appear to focus on what I take some exception to, it is only because the rest is so cogently argued, one does not need a guide.

Heterogeneity of Schizophrenia

Among the basic concepts that Carlsson et al discuss in this article and other recent publications (Martin et al 1998), now more important than ever in my view, is the notion that there is no single biology of schizophrenia. Heterogeneity due to subtypes, such as paranoia, presence of hallucinations, severity and type of cognitive dysfunction, and different phases of the illness (e.g., florid psychosis vs. the quiescent periods characterized mainly by negative symptoms), cognitive impairment, and functional disability must be taken into account if one is to find biological correlates in such clinical studies as pharmacologic challenge paradigms, PET studies of dopamine and serotonin turnover or receptor density, or postmortem neurochemistry, and, I would add, genetic association and pharmacogenomic studies. The models of schizophrenia that Carlsson et al favor emphasize neurocircuitry that involves multiple neurotransmitters interactions, requiring the integrated activity of various presynaptic and postsynaptic enzyme and receptor-governed processes. It is highly likely in a heterogeneous syndrome such as schizophrenia that there will be a multiplicity of combinations of deficits in basal and stimulus-driven responses that produce the varied phenotypes. Interactions among neurotransmitters may make an apparently normal level of activity at one receptor subtype pathogenic because of the absence of a competing system that normally opposes it. A prime example of this would be the 5-HT2a and 5-HT2c systems that have a crucial role in mediating responses to glutamate and serotonin (Martin et al 1997a). Differences in the forms of 5-HT2a and 5-HT2c genes in schizophrenia may well underlie some of the heterogeneity in response to clozapinelike antipsychotic drugs (Masellis et al 1998) and psychopathology.

Appreciation of heterogeneity by Carlsson et al leads to an interest in the neurochemical differences that underlie periods of intensified positive symptoms as opposed to those period when such symptoms are absent or minimal. It also draws attention to the goal of finding drugs that are capable of "stabilizing" rather than merely blocking dopaminergic function. It is suggested that partial dopamine agonists may be the means to achieve this, a view I do not necessarily share. Drugs of this class that have been clinically tested in schizophrenia have proven to be ineffective for the most part. Others are still in development and testing phases, however, and one hopes that they will fulfill the role that Carlsson et al assign to them. The goal of "stabilized" dopaminergic function has been achieved in many ways, by the atypical antipsychotics that can enhance dopaminergic activity in the prefrontal cortex (Kuroki et al 1998) and diminish it, via limited dopamine receptor blockade, in the mesostriatal and mesolimbic systems, and perhaps more extensive blockade of extrastriatal dopamine receptors.

Glutamate-Serotonin Interactions in Schizophrenia

The role of glutamate in schizophrenia is emphasized by Carlsson et al, in part, because of the phencyclidine (PCP) model of psychosis. The preclinical studies done by this group to understand the multiple systems involved in controlling the hyperlocomotion produced by NMDA-competitive and noncompetitive antagonists versus amphetamine are of tremendous interest. They have concluded that increased serotonergic tone is the key to the hyperlocomotion produced by these agents and that the atypical antipsychotic drugs are effective in this model, and hence, by virtue of their ability to block 5-HT2a receptors while blockade of 5-HT2c receptors should have an antagonistic or propsychotic action in schizophrenia (Martin et al 1997a, 1998). This is an idea I had previously proposed based on a multivariate analysis of the pharmacology of the atypical versus the typical antipsychotic drugs (Meltzer et al 1996). Much of this hypothesis by Carlsson and colleagues in this issue is based on the greater effectiveness of the 5-HT2a antagonist M100907 to block hyperlocomotion produced by NMDA antagonists compared with spontaneous locomotion, whereas the D2 receptor blocker raclopride is equally effective in blocking both types of activity (Martin 1997b). Carlsson et al (this issue) expected that M100907 alone should have antipsychotic activity in some patients but that because of heterogeneity, it might not produce such as effect in other patients, who might benefit from combination with a D2 receptor antagonist. The preliminary results of the first large-scale trial with M100907 have now been reported. It was found to be less effective than haloperidol in treating positive symptoms but more effective than placebo in patients with schizophrenia in an acute exacerbation (J. Shipley, personal communication, August 15, 1999), consistent with the predictions of Carlsson et al. Based on our studies using microdialysis, the combination of M100907 with low-dose but not high-dose haloperidol, but not M100907 alone, can modulate prefrontal cortical and mesolimbic dopaminergic activity in a desirable manner. A subgroup of patients with schizophrenia with low dopaminergic activity on endogenous basis might be expected to respond to M100907 alone, whereas others would need some D2 receptor blockade. I have suggested elsewhere that drugs that have as a component of action the ability to stimulate 5-HT2c and 5-HT1a receptors may be a promising approach to the development of novel antipsychotic agents (Meltzer 1999).

In this issue, Carlsson et al propose that the most promising approach to new treatments for schizophrenia may involve enhancing glutamatergic function without causing neurotoxicity. This is most certainly a reasonable conclusion. A thorough understanding of the regulation of pre- and postsynaptic glutamatergic activity will facilitate this probably achievable goal. Drugs that can do this are likely to be multireceptor active agents, in my view, consistent with the complexity of the circuitry that must be manipulated and the heterogeneity of schizophrenia. All is not lost for receptor specific agents such as 5-HT2a, D2, D3, and other antagonists, however. Not only are they invaluable as research tools, they may also be able to augment the activity of other receptor-specific or multireceptor agents in specific patients. One size does not fit all in schizophrenia, an enduring message provided by the neuroleptics vis a vis clozapine and the other atypical antipsychotic drugs.

Conclusions

Although the use of neuroleptic drugs as the sole treatment for schizophrenia should no longer be acceptable because of their risk of tardive dyskinesia and their limited efficacy to treat positive symptoms, negative symptoms, and especially the cognitive disturbance of schizophrenia, they will continue to be useful in low doses as a means of providing D2/D3 receptor blockade when needed to complement other agents that are ineffective by themselves to treat positive symptoms but effectively treat other components of the schizophrenia syndrome. As truly novel drugs for schizophrenia and spectrum disorders become available for clinical testing, one hopes that the trial designs and the clinical investigators who test them, as well as industry and regulatory executives who ultimately must decide on their availability for clinical use, will remember the following: 1) relevant outcome measures encompass more than control of positive symptoms; 2) multiple phases of the disease process should be explored, not just florid psychosis; and 3) these highly sophisticated drugs may be active in only some patients. It is likely that this next generation of treatments for schizophrenia, whether they be based on serotonin, dopamine, glutamate, or other strategies, will require psychosocial interventions to make them maximally beneficial. In addition, they may be most beneficial when given during the prodrome period or even before and also will have widespread application for other neuropsychiatric disorders if they do not have a heavy burden of side effects.

Herbert Y. Meltzer

Department of Psychiatry
Vanderbilt University School of Medicine
Psychiatric Hospital
1601 23rd Avenue, Suite 306
Nashville, TN 37212

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