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Limitations of Dopamine-D_2 Antagonists and the Search for Novel Antipsychotic Strategies

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Significant advances have been made during the past decade in both understanding the pathophysiology of schizophrenia and in identifying more effective pharmacologic treatment strategies for the disease. Before the 1990s, antipsychotic drug development focused exclusively on agents with substantial activity at dopamine-D_2 receptor sites. Although agents that block these receptors result in decreased positive symptoms, such as hallucinations and delusions, these agents have important limitations that result from properties that are inescapable with D_2 antagonists. First, D_2 antagonism is associated with discomforting neurological side effects often present at their clinically effective doses. Second, these drugs have limited efficacy for important symptom dimensions in schizophrenia, particularly negative and cognitive symptoms.

The difficulty with these agents was apparent in a study we conducted in Los Angeles (Van Putten et al. 1991). Seventy-two neuroleptic-free male patients with schizophrenia were assigned to receive 5, 10, or 20 mg of fluphenazine daily for 4 weeks. Patients were excluded from the study if they had a history of nonresponse to neuroleptic drugs or a history of intractable EPS with high-potency neuroleptics. Figure 1 shows the logistic regression function that describes the relationship between disabling side effects and global improvement by plasma fluphenazine concentration (ng/ml). The dashed line represents the percentage of patients who showed improvement, and the solid line represents the percentage of patients who had disabling side effects, most commonly akathisia. This figure shows that at a plasma level of 0.5 ng/ml, which is approximately equal to 10 mg of fluphenazine, about 50% of patients showed symptom improvement and about 20% had disabling side effects. Higher plasma fluphenazine levels were associated with a greater rate of global improvement. However, the data also indicate that these two dose–response curves are perilously close together, and, according to patients, these disabling side effects often negated or compromised any improvements in psychosis (Van Putten et al. 1991).

Fortunately, these dose-limiting side effects have proved to be less important with the introduction of serotonin-dopamine antagonists (SDAs), which are characterized by substantial serotonin-5-HT_{2A} antagonism and some D_2 antagonism (Table 1). In fact, a major effect of SDAs has been to separate the dose–response curves for global improvement and disabling side effects. Initial clinical experience with clozapine in the early 1990s suggested that it would have broad effects in schizophrenia, with efficacy against negative symptoms and greater improvements in overall outcome. Although the broad effects of clozapine have proved to be true, recent data suggest that only a small proportion of patients on clozapine actually show improvement in functional outcomes (Zito et al. 1993) and negative symptoms (Buchanan et al. 1998). Thus, the search continues for more effective compounds to treat the various dimensions of schizophrenia.

The core symptom clusters of schizophrenia as well as mood symptoms are shown in Figure 2. Mood symptoms are included, because mood disorders, particu-

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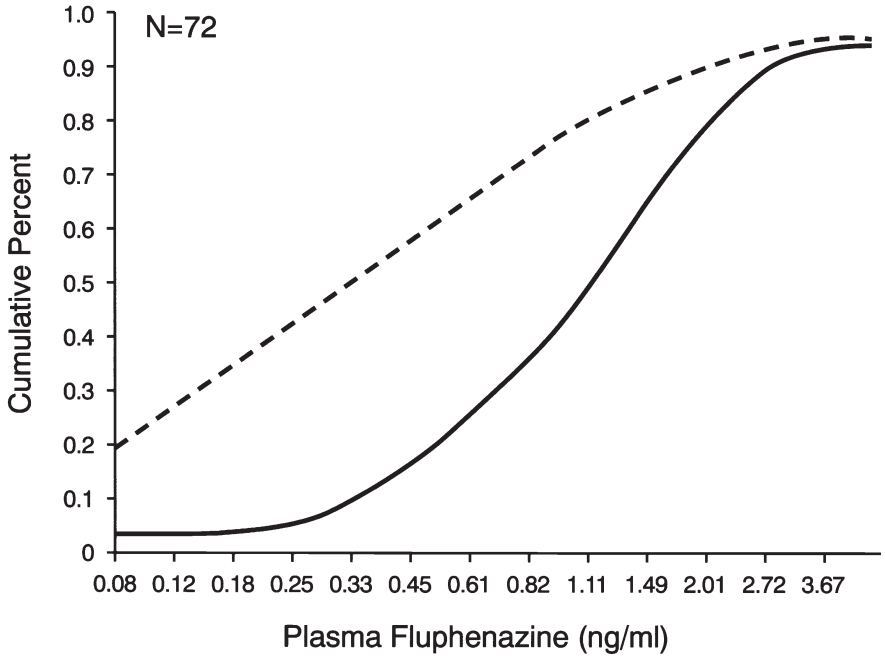

Figure 1. Improvement and disabling side effects as a function of plasma fluphenazine (Van Putten et al. 1991). The dashed line represents the percentage of patients who were much improved ($p = .0154$), and the solid line represents the percentage of patients who had disabling side effects ($p = .0008$).

larly depression, are not just a comorbidity in schizophrenia, but rather a key feature of schizophrenic relapse for many individuals. This figure shows that negative symptoms, cognitive dysfunction, and mood impairment all play a greater role than positive symptoms in social and vocational dysfunction and the overall outcome of schizophrenia. The severity of negative symptoms and cognitive impairments have been shown to be strong determinants of the functional outcome of patients, especially the ability of patients to go back to work or school (Fenton and McGlashan 1991; McGlashan and Fenton 1993). Thus, the greatest opportunities for improving functional outcomes in schizophrenia may result from the development of drugs that lead to improvements in negative symptoms and cognitive deficits.

New treatment approaches to schizophrenia will most likely result from understanding the neuropharmacology underlying the subsyndromes of schizophrenia. Historically in psychiatry, clinicians found effective treatments and then took the drugs into the laboratory to explain how they worked. Currently, the drug development process in schizophrenia has progressed, identifying basic mechanisms of disease pathology and targets for new drug treatments. A number of hypotheses regarding the neuropharmacologic mechanisms involved in the pathophysiology of schizophrenia and a number of proposed treatment strategies have been developed.

This supplement to *Neuropsychopharmacology* is based on the proceedings of a symposium entitled "Is D_2 Antagonism Required for Antipsychotic Activity?" held February 14 to 16, 1999 in Washington, DC. This set of articles assimilates recent and ongoing research on the neuropharmacologic mechanisms of schizophrenia and new approaches to antipsychotic drug treatment. Novel research was presented that provides a rationale for non-D_2 mechanisms in pharmacologic treatments for schizophrenia, including serotonin 5-HT_{2A}, dopamine D_1, glutamate, and cholinergic mechanisms.

Table 1. Novel Antipsychotic Drugs and Receptor Affinities (Adapted from Pickar 1995)

	Dopamine D_1	Dopamine D_2	Serotonin 5-HT_{1A}	Serotonin 5-HT_{2A}	Alpha$_1$	Alpha$_2$	Histamine H_1	Muscarinic M_1
Clozapine	++	++	+	+++	+++	+++	++++	+++++
Risperidone	++	++++	++	+++++	++	+++	++	−
Olanzapine	+++	+++	−	++++	+++	−	++++	+++++
Quetiapine	+	++	−	+	++++	+	++++	+
Sertindole	+++	+++++	++	++++	+++	−	+	+
Ziprasidone	+	++++	*	++++	++	−	+	−

+++++ = High; + = Low; *5-HT_{1A} agonist.

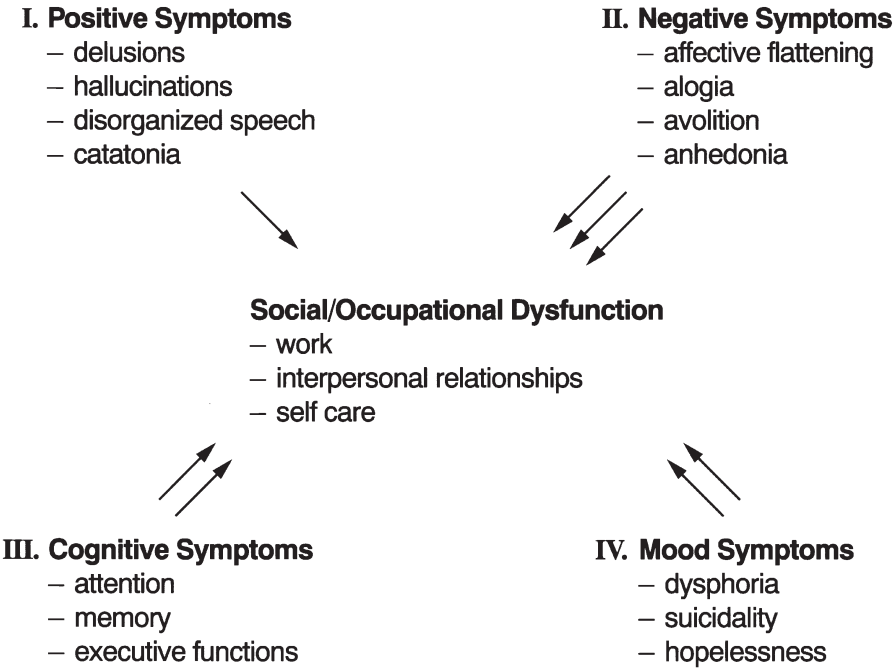

Figure 2. The core symptom clusters of schizophrenia and their influence on occupational and social dysfunction (adapted with permission from Michael F. Green, Ph.D.).

Dr. George Aghajanian and Dr. Gerald Marek review the role of 5-HT_{2A} receptors in the cerebral cortex (medial prefrontal and anterior cingulate regions), particularly in relation to their ability to enhance transmission by indoleamine and phenethylamine hallucinogens. These electrophysiological effects are discussed in relation to the N-methyl-D-aspartate (NMDA) antagonist class of psychotomimetics, which were recently reported to produce increased glutamate release in the cerebral cortex. The authors discuss potential new antipsychotic agents based on a hyperglutamatergic model of psychotomimetic drug action. The therapeutic potential of the selective serotonin 5-HT_{2A} antagonist, M100907, and antagonists of other receptors that are coupled through the $G_{q/11}$/phosphoinositide pathway is discussed.

The use of prepulse inhibition (PPI) as a model of the disruptions in attention and cognition observed in schizophrenic patients is discussed in the article by Dr. Mark Geyer and colleagues. Disruptions in PPI have been demonstrated in schizophrenic patients as compared with healthy controls. A variety of pharmacologic (serotonergic, glutamatergic, and dopaminergic) and nonpharmacologic (rearing in isolation) treatments disrupt PPI in animals and are used to characterize and identify antipsychotic drugs. Dr. Geyer and colleagues present original research on the effects of M100907 on apomorphine- and isolation rearing-induced disruption of PPI in rats. Although M100907 was shown to be inactive in the apomorphine model of disrupted PPI, it has been shown to be effective in reversing deficits in PPI produced by 5-HT_{2A} agonists, NMDA-receptor antagonists, and isolation rearing.

Dr. John Krystal presents a novel perspective on the neurobiology and treatment of schizophrenia. This perspective is based on the effects of NMDA-receptor antagonists in animals and healthy humans. The effects of these agents seem to resemble the symptoms of schizophrenia, including disturbances in information processing. Dr. Krystal provides evidence that links NMDA-receptor antagonism to glutamatergic activation and information-processing deficits and reviews evidence that manipulation of dopaminergic systems has limited ability to effect symptoms produced by NMDA antagonists. The value of facilitation of the glycine-B site of the NMDA receptor complex and drugs that attenuate glutamate release as pharmacotherapies for schizophrenia is discussed.

The utility of ketamine-induced psychosis as a model to screen for antipsychotic activity is described by Dr. Adrienne Lahti and colleagues. Administration of ketamine consistently produces both positive and negative symptoms of schizophrenia and impairs memory functioning in healthy subjects. In schizophrenic patients, ketamine-induced delusions, hallucinations, and thought disorders are similar in theme and content to those of the patients' illness. Increased cerebral blood flow and immediate early gene expression following ketamine or phencyclidine administration lend further support for glutamate involvement in the pathology of schizophrenia. These effects of NMDA antagonists are not reversed by haloperidol or olanzapine, suggesting that the ability of novel compounds to reverse these effects may be indicative of enhanced clinical antipsychotic activity.

Dr. Patricia Goldman-Rakic reviews evidence that

the cognitive deficits observed in schizophrenic patients can be attributed to impairment of function in the prefrontal cortex. Specifically, research is presented concerning the localization of dopamine-D_1 receptors and their involvement in cognition and schizophrenia. For example, single-cell recording studies show that D_1 antagonists produce a dose-dependent effect (U-shaped) on the firing rate of cells within memory fields of the prefrontal cortex during delayed-response tasks in monkeys. In addition, autoradiographic and positron emission tomography (PET) studies show that the relative density of D_1 and D_2 receptors in the prefrontal cortex is altered in schizophrenic patients. Further characterization of the role of D_1 receptors in schizophrenia, including the use of appropriate doses of D_1-receptor antagonists or agonists in a clinical trial setting, are identified by Dr. Goldman-Rakic as important areas of future study.

Dr. Göran Sedvall summarizes the current state of our understanding regarding dopamine receptor distribution in the brain based on autoradiographic studies, PET studies, and studies of mRNA expression identified by in situ hybridization. Evidence is presented implicating the dopamine-D_1 receptor in the pathophysiology of schizophrenia. Specifically, the ratio of D_1- over D_2-regulated dopamine signaling in some brain regions is reduced in schizophrenic patients. In addition, this review focuses on emerging evidence concerning the efficacy of pharmacological manipulation of D_1-receptor function in the treatment of schizophrenia. Findings do not support the prediction that selective D_1-receptor antagonism produces antipsychotic effects, however, the possibility of D_1 agonists or a combination of D_1 and D_2 antagonists for the treatment of schizophrenia should be considered.

The effects of pharmacological manipulation of the cholinergic system on schizophrenia symptomatology and alterations in the cholinergic system of schizophrenic patients are reviewed by Dr. Rajiv Tandon and colleagues. In addition, the results of two original studies on the effects of biperiden, a relatively specific M_1 antimuscarinic/anticholinergic agent, on symptoms and sleep in schizophrenic patients are presented. Biperiden produced a significant increase in positive symptoms and a decrease in negative symptoms in schizophrenic patients. Analysis of sleep measures showed that rapid eye movement (REM) latency was significantly shorter in schizophrenic patients and that biperiden increased REM latency in schizophrenic patients and healthy controls. Furthermore, REM density was decreased in schizophrenic patients as compared to healthy controls. These results provide additional evidence that the cholinergic system plays a role in schizophrenia pathophysiology and suggest a role for dopamine–acetylcholine interactions in the expression of positive and negative symptoms and the production of sleep abnormalities in schizophrenia.

Dr. Richard Mohs compares the cognitive and functional impairments of patients with schizophrenia with those of patients with Alzheimer's disease. In contrast to Alzheimer's disease, schizophrenia does not fit the model of a progressive degenerative process, and patients manifest general cognitive impairment with more visuospatial and language ability deficits. Importantly, functional outcome of schizophrenia is more closely related to cognitive deficit than to positive and negative psychotic symptoms. These findings warrant the development of an assessment tool for cognitive function in schizophrenia and its routine use in the evaluation of new antipsychotic therapies.

Dr. Roy Corbett and his colleagues review animal behavioral models of the negative symptoms of schizophrenia. Data from these studies clearly show that newer antipsychotics, but not conventional antipsychotic agents, are effective in reducing negative symptom-like behavior in the social withdrawal model and phencyclidine (PCP)-induced immobility in the forced swim test. The authors also present new data showing that M100907 significantly reduced PCP-induced immobility in the forced swim test. Further studies of the effects of M100907 in a model of anhedonia are ongoing.

Several papers in this supplement discuss the therapeutic potential of M100907 based primarily on its efficacy in preclinical models of schizophrenia. Recently, the results of three phase III clinical trials of M100907 for the treatment of schizophrenia, two in the United States and one in Europe, were released. The two U.S. studies enrolled patients with acute schizophrenia. These multicenter, placebo- and haloperidol-controlled trials of 6 weeks in duration indicated that the effects of M100907 in acute schizophrenia, although better than placebo, were inferior to haloperidol. In the European study, which enrolled patients with predominantly negative symptoms, M100907 did not demonstrate a statistically significant effect as compared to placebo. Based on the results of these clinical trials, the development of M100907 for the treatment of acute schizophrenia has been discontinued. These data, however, have not ruled out a potential for the use of M100907 for the treatment of chronic schizophrenia. It is important to note that these results bring into question the relative contribution of 5-HT_{2A} receptor activity in the pathophysiology of psychosis in the general population of psychotic patients and perhaps the predictability of preclinical models for clinical efficacy.

Despite the disappointing clinical findings with M100907 in acute schizophrenia, collectively, the papers in this supplement demonstrate an exciting trend in the field of schizophrenia research. The field is abandoning an exclusive focus on dopamine-D_2 receptors and is moving toward an integrative model that encompasses multiple neurotransmitter systems, including se-

rotonergic, glutamatergic, dopaminergic, and cholinergic systems. As hypotheses continue to be generated about the role of these neurotransmitters in schizophrenia pathophysiology, drug development is shifting toward compounds with selective mechanisms of action. Use of selective agents is expected to help identify the contribution of individual neurotransmitters and, potentially, their interactions with other neurotransmitters in the various symptom dimensions of schizophrenia. Ultimately, an individualized treatment strategy may include a single pharmacological agent or a combination of agents that addresses the symptoms of a particular individual. In this manner, a targeted research approach may fulfill gaps in schizophrenia therapy, leading to more effective and tolerable treatment.

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REFERENCES

Buchanan RW, Breier A, Kirkpatrick B, Ball P, Carpenter WT Jr (1998): Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am J Psychiat 155:751–760

Fenton WS, McGlashan TH (1991): Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. Arch Gen Psychiat 48:978–986

McGlashan TH, Fenton WS (1993): Subtype progression and pathophysiologic deterioration in early schizophrenia. Schizophr Bull 19:71–84

Pickar D (1995): Prospects for pharmacotherapy of schizophrenia. Lancet 345:557–562

Van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N (1991): Neuroleptic plasma levels. Schizophr Bull 17:197–216

Zito JM, Volavka J, Craig TJ, Czobor P, Banks S, Vitrai J (1993): Pharmacoepidemiology of clozapine in 202 inpatients with schizophrenia. Ann Pharmacother 27:1262–1269