

New Antipsychotic Agents

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ABSTRACT

Due to the severity caused by schizophrenia, it is important to develop effective treatments. The current antipsychotics, including both typical and atypical, are at best effective only partially effective. Response is usually defined as a 20% to 30% reduction in the positive symptoms (delusions, hallucinations) with a lesser effect on the negative and cognitive symptoms. There has been a tremendous effort to develop newer antipsychotics to improve outcome. This article describes the current antipsychotics in the pipeline being clinically tested. The article also describes preclinical and clinical studies on a variety of agents that affect multiple receptors that are thought to be related to etiology.

INTRODUCTION

Schizophrenia and other forms of psychotic illness have plagued mankind for centuries. The conceptualization of psychosis as a "mental illness," however, has only occurred recently. The development of effective pharmacotherapy began with the development of chlorpromazine in 1952,¹ which revolutionized the treatment of schizophrenia. Older agents such as haloperidol and chlorpromazine (first-generation antipsychotics [FGAs]) are very effective for managing the positive symptoms of schizophrenia but display relatively poor long-term efficacy for negative symptoms, mood disturbances, and cognitive deficits. They are also associated with debilitating extrapyramidal

Needs Assessment: Schizophrenia and other forms of psychotic illness have plagued mankind for centuries. It causes a deterioration in patients afflicted. The current agents, though helpful, only diminish the frequency and severity of positive psychotic symptoms by 20% to 30% and have less of an effect on the negative symptoms and the cognitive deterioration. There is a tremendous need to develop novel agents with unique mechanisms of action for the treatment of psychotic disorders.

Learning Objectives:

- Identify drugs in the pipeline for the treatment of schizophrenia
- Understand the need for new medication treatment of psychotic disorders
- Understand the mechanisms involved in the development of new antipsychotics

Target Audience: Primary care physicians and psychiatrists.

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Off-label disclosure: This article includes discussion of investigational treatments for schizophrenia or psychotic illness.

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symptoms (EPS) and tardive dyskinesia, thus often nullifying their therapeutic effect. There were no new agents approved by the Food and Drug Administration from 1977–1988. However, the introduction of clozapine from Europe in 1989² dispelled the notion that EPS and tardive dyskinesia were inevitable conclusions of antipsychotic therapy.

The FDA approval of clozapine led to a new generation of antipsychotics which seemed to provide a broader range of efficacy (both positive and negative symptoms and less cognitive decline) with a lower risk of EPS and tardive dyskinesia versus the older agents.³ Recent work⁴ has suggested that the newer agents cause a great risk for the metabolic syndrome—including diabetes, weight gain, and hyperlipidemia—which might be (in the long-run) more problematic than EPS or tardive dyskinesia. Thus, the continuing need for newer, safer, more efficacious antipsychotics continues.

SECOND-GENERATION ANTIPSYCHOTICS

The original agents, FGAs or typical antipsychotics, were thought to act by blocking striatal dopamine (D)₂ receptors; indeed, the antipsychotic potency was positively correlated with in vitro potency of the D₂ receptor.^{5,6} The evidence for this was that positron emission tomography positively demonstrated that *N*-methylspiperone (a radiolabeled ligand of the D₂ receptor) blocked striatal dopamine receptors.

The second-generation antipsychotics (SGAs) which included risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole were characterized by strong or stronger antagonism for the serotonin (5-HT)₂ receptor than for the D₂ receptor.⁶ These newer agents (which also include clozapine) only partially block striatal dopamine receptors and more potently block serotonin receptors in the frontal cortex.

In addition, newer antipsychotics may have more unique actions. They appear to enhance glutamatergic function at the *N*-methyl-D-aspartate (NMDA) receptor and block the behavioral and physiologic effects of phencyclidine, a non-competitive NMDA receptor antagonist that produces a syndrome in normal individuals that closely mimics schizophrenia.⁷ In addition, SGAs, while alike, often show differences that may lead one to different mechanistic possibilities. For example, aripiprazole is a high affinity partial agonist of the dopamine receptor. It displays both dopamine agonist and antagonist properties.⁸ The partial dopamine agonist may thus reduce dopamine synthesis and release by stimulating presynaptic dopamine autoreceptors. They may also diminish the dopaminergic signal at postsynaptic sites by competing with dopamine for postsynaptic receptors.⁹

NEWER DRUGS AND STRATEGIES IN SCHIZOPHRENIA

A fundamental barrier to the discovery of novel treatments remains that our level of the biologic processes involved in schizophrenia is not sufficient to predict the therapeutic value of novel drug targets. Newer agents usually represent drugs that hit known and validated targets (“me too type drugs”). It is important to note that it is important to look at specific symptoms in schizophrenia. FGAs and SGAs are efficacious in treating the positive symptoms (delusions, hallucinations, thought disorganization, and loose associations), but even here the response rate is 67% to 75% with response being a 20% to 30% reduction in overall symptoms.

However, it is the negative symptoms (alogia, avolition, flat affect, and anhedonia) along with cognitive impairments that contribute disproportionately more to the long-term disability in patients with schizophrenia.¹⁰ The negative symptoms lead to particularly poor functional capacity and quality of life. Despite the fact that there was high optimism that the SGAs represented a breakthrough for the treatment of negative symptoms, a complete response has not been shown clinically.^{4,11} The cognitive impairments are significant in that patients with schizophrenia have been known to have documented problems with attention, working memory, and learning in addition to executive level functions such as abstract thinking and problem solving.^{12,13} Thus, improved efficacy with negative symptom relief and improvement in cognition remains unsolved.

DOPAMINERGIC APPROACHES

Of note, all marketed drugs to date have efficacy at the D₂ receptor. Many of the drugs in Phases II and III clinical trials have the same mechanism of action as the already available agents, that is, 5-HT_{2A} and D₂ antagonism.

Iloperidone

Iloperidone, which is currently in placebo-controlled, phase III trials, affects multiple receptor sites. It is an antagonist at D₂ and D₃ receptors, as well as an antagonist at the 5-HT_{2A} and 5-HT_{1A} receptor site. It has had a long developmental process after being dropped by Novartis due to concerns that the drug may cause cardiac arrhythmias (specifically, it might increase the QT interval of the heart-beat). A study¹⁴ in the November 2001 issue of *Psychiatric Times* noted no cardiac abnormalities in 10 patients receiving 0.5–6.0 mg of iloperidone; however, this is an extraordinarily small sample size, and the study was sponsored by

Novartis. In other words, these safety concerns have yet to be resolved in the public domain. However, iloperidone is still in development (currently in phase III FDA clinical trials). Because it acts as an antagonist on many different receptors—including several different classes of dopamine, serotonin, and norepinephrine receptors—it has the potential to alleviate a wide range of symptoms.

Bifeprunox

Bifeprunox was in phase III clinical trials until recently. It is a partial dopamine agonist/antagonist as well as a serotonin receptor agonist. It is expected that partial dopamine agonist action will have beneficial effects for positive, negative, and cognitive symptoms, while the serotonergic agonist action will help alleviate some side effects and possibly combat depression and anxiety that can accompany schizophrenia treatment. Early results report little to no weight gain, and no cardiac effects or EPS. Efficacy was uncertain, and the company investigating it has discontinued the trials.

Blonanserin

Blonanserin [AD 5423] is a combined D and 5-HT receptor antagonist currently undergoing development in Japan with Dainippon Sumitomo Pharmaceutical as a potential antipsychotic. Blonanserin is unrelated structurally to typical antipsychotics or to newer agents such as risperidone. It is hoped that the combination of receptor blockade possessed by blonanserin will be effective against both the positive and negative symptoms of schizophrenia, with a low tendency to cause EPS. Blonanserin is expected to have minimal sedative and hypotensive effects, as its adrenaline receptor-blocking function is weak.

Dainippon is conducting phase III clinical trials with oral formulations (tablet and powder) of the compound in psychotic disorders in the United States.

Ocaperidone

Ocaperidone is a D₂ and 5-HT antagonist. Due to the dual-action mechanism of the drug, early research reports it to have “haloperidol-like effects” on the positive symptoms of schizophrenia, but with a lower incidence of EPS (more like the side-effect profile of risperidone). Neuro3d, the France-based developers of the medication, report that they are nearing the end of phase II clinical trials.

Nemonapride

Nemonapride (international nonproprietary name [INN]; tradename Emilace) is a dopamine receptor antagonist

approved in Japan for the treatment of schizophrenia. Its mechanism of action is proposed to involve both D₂ and D₃ antagonism. Nemonapride is a substituted benzamide antipsychotic with general antipsychotic properties—with effects on positive and negative symptoms of schizophrenia. The average daily dose of nemonapride was 18 mg/day. Plasma prolactin concentrations are significantly ($P < .01$) increased.

Perospirone

Perospirone (INN; trade name Lullan) is a neuroleptic in Japan. It is a D and 5-HT_{2A} receptor antagonist. Clinical trials show that EPS tend to occur less often and were generally milder than with haloperidol.

Zuclopenthixol

Zuclopenthixol (marketed as Cisordinol, Clopixol, or Acuphase) is a typical antipsychotic neuroleptic of the thioxanthene group. It mainly acts by antagonism of D₁ and D₂ receptors, though it also has some antihistamine activity. It is produced and marketed by Lundbeck pharmaceutical company. It is available in three forms, namely, zuclopenthixol decanoate (clopixol), a long-acting intramuscular injection; zuclopenthixol acetate (clopixol acuphase), a shorter-acting intramuscular injection; and zuclopenthixol dihydrochloride (clopixol tablets), a tablet taken orally. Side effects, such as EPS and elevated prolactin levels, are similar to many other typical antipsychotics. In addition, the taking the drug may occasionally result in amenorrhoea or galactorrhoea in severe cases. Neuroleptic malignant syndrome is a rare but potentially fatal side effect. Zuclopenthixol is available worldwide. None of the findings suggest any clear difference between zuclopenthixol and other typical antipsychotics across a wide range of adverse effects. When compared with the newer generation of drugs, those taking zuclopenthixol were associated with no greater risk of being unchanged or worse compared with those taking risperidone.

Lurasidone

Lurasidone is an atypical antipsychotic in Japan. As of 2008, it is undergoing a Phase III clinical trial. Lurasidone blocks D₁, D₂ and 5-HT_{2A} receptors. It seems to cause fewer EPS than current antipsychotics.

ACP-104

ACP-104, or *N*-desmethylclozapine, is the major metabolite of clozapine and is being developed by ACADIA as a novel, stand-alone therapy for schizophrenia. It combines an atypical antipsychotic efficacy profile with the added potential

benefit of enhanced cognition, thereby addressing one of the major challenges in treating schizophrenia today. ACP-104 combines muscarinic (M)₁ agonism, 5-HT_{2A} inverse agonism, and D₂ and D₃ partial agonism in a single compound and, therefore, uniquely addresses what ACADIA believes are the three most promising target mechanisms for treating schizophrenia. As of this writing it is in phase II clinical trials. Two clinical studies^{15,16} showed the drug was safe with the major side effects being sleepiness, increased salivation, constipation, and tachycardia. No significant changes were observed in safety parameters such as electrocardiograph measures (including QT/QTc interval) and clinical chemistries. No EPS were observed in the patients. The Phase IIb study of ACP-104 for the treatment of schizophrenia did not meet its primary endpoint of antipsychotic efficacy (improvement in Positive and Negative Syndrome Scale (PANSS) or any of the secondary endpoints). Neither dose of ACP-104 600 mg or 800 mg demonstrated improved efficacy compared to a placebo. The drug's future is uncertain.

BL-1020

BL-1020 is an orally available γ -aminobutyric acid-enhanced antipsychotic clinical candidate for the treatment of schizophrenia. It is a dopamine receptor antagonist. Data from preclinical and Phase I studies demonstrated that the compound may retain the efficacy of currently available typical and atypical antipsychotics while achieving a much higher safety profile as evidenced by a lack of metabolic or EPS. In an open-label, multi-center, 6-week trial¹⁷ conducted in hospitalized patients with treatment-resistant schizophrenia, BL-1020 showed statistically significant efficacy with minimal side effects. Overall, BL-1020 treatment reduces the PANSS total score by 26.1 points from the baseline ($P < .001$; baseline=85.6, day 42=58.2). There was a significant ($P < .001$) improvement in PANSS negative score by 7.1 points when compared to baseline values (baseline=20.5, day 42=13.4). Furthermore, computer-generated imagery results showed that 92.35% of patients improved by at least one category by the end of this part of the study.

RGH-188

RGH-188 (INN; generic cariprazine), discovered by researchers at Gedeon Richter, is a novel antipsychotic which preferentially binds to D₃ receptors and acts as a dopamine system stabilizer. It is also a D₂ antagonist. A phase II study¹⁸ involving 389 schizophrenia patients, evaluating a primary endpoint change from baseline to Week 6 on the PANSS and RGH-188 demonstrated a nominally statistically significant (ie, not adjusted for multiple comparisons) therapeutic effect compared

to placebo in the treatment of schizophrenia in the low-dose arm and a numerical improvement compared to placebo in the high dose arm that did not reach nominal statistical significance. RGH-188 was generally well tolerated and overall premature discontinuation rates (all causes including adverse event related) were 47% for patients receiving low dose of RGH-188 up to 4.5mg/day, 46% for patients receiving high dose RGH-188 up to 12 mg/day, and 47% for patients receiving placebo.

ACR-325

ACR-325 is a dopaminergic stabilizer (primarily a dopamine agonist), a new class of compounds with a unique ability to either enhance or inhibit dopamine-controlled functions depending on the initial level of dopaminergic activity. ACR-325 has also demonstrated an ability to strengthen the glutamatergic and noradrenalinergic (agonistic) functions, which is an important aspect in novel treatments of psychosis and motor dysfunctions.

In June 2008 NeuroSearch has completed Phase I evaluation ACR-325 with a highly positive outcome. The results of single- and multiple-dose studies¹⁹ in healthy volunteers show that ACR-325 has a linear and predictable pharmacokinetic profile after oral administration. Further, the compound proved very well tolerated at doses and plasma levels exceeding by far the predicted therapeutic levels.

SLV-313

SLV-313 is a combined D₂ receptor antagonist and 5-HT_{1A} receptor agonist that may improve efficacy and alleviate some side effects associated with classical antipsychotics. As a full 5-HT_{1A} receptor agonist and full D_{2/3} receptor antagonist possessing characteristics of an atypical antipsychotic, it represents a potential novel treatment for schizophrenia. A phase I study randomizing patients to fixed doses of 2 mg, 5 mg, and 10 mg is currently underway.

YKP-1358

YKP-1358 is a novel 5-HT_{2A} and D₂ antagonist that, in preclinical studies, fits the general profile of an atypical antipsychotic. It is currently undergoing phase I trials.

Asenapine

Asenapine is a 5-HT and D₂ antagonist, part of a class of atypical antipsychotics that have typically been more effective than medications that act only at D₂ receptors. For example, clozapine, risperidone, and olanzapine all have serotonin-dopamine antagonist properties, and these drugs are popular for their low incidence of side effects (par-

ticularly EPS) and their efficacy against both positive and negative symptoms. Early data from previous trials shows good tolerability and superior efficacy when tested against placebo. Schering-Plough Corp. acquired Organon in 2007—now asenapine is currently pending FDA approval for both mania and schizophrenia.

The problem with the above drugs is that they have the same mechanism of action as the already available agents.

ATTEMPTS TO LOOK AT VARIOUS NEUROTRANSMITTER SYSTEMS TO DEVELOP NEW ANTIPSYCHOTICS

Other Dopamine Strategies: D_1 , D_3 , and D_4 Receptors

The D_1 receptor plays an important role in schizophrenic illness as it is thought to have a role in cognitive dysfunction.²⁰ Chronic blockade of D_2 receptors leads to down regulation of D_1 receptors in the prefrontal cortex, and this produces severe working memory impairment in non-human primates. Thus, novel compounds targeted at stimulating the D_1 receptor may be of great value in treating the cognitive symptoms of schizophrenia. Many drugs have been proposed, such as ZD-3638, a 5-HT_{2A}/ D_2 , D_1 agent developed by AstraZeneca in phase II development; BSF-78438 (Abbott); and LE-300 (sanofi-aventis), the latter two in preclinical development.²¹

The D_3 receptor is structurally similar to the D_2 receptor and is, thus, a target for drug development. Interestingly, a study evaluating drug-free schizophrenics found elevated levels of D_3 receptors with normal D_2 receptors. A few agents are being evaluated. A-437203 is undergoing Phase II trials as is SB-773812. BP 4.879a (Bioproject), SB-277011 (GlaxoSmithKline), PD 157533 (Pfizer), U 99194A (Pfizer), and PNU 177864 are in preclinical development. The potential antipsychotic efficacy of D_3 receptor antagonists remains unknown at this time but there is some suggestion that D_3 receptor antagonists have a role in improving negative symptoms²² and working memory.²³

The D_4 receptor was initially cloned. It was noted that clozapine had a higher affinity for this receptor than for the D_2 receptor, leading to speculation that the D_4 receptor might be the receptor responsible for clozapine's unique enhanced efficacy.²⁴ However, clinical trials have not yet demonstrated any appreciable evidence of efficacy of D_4 receptor antagonists in the treatment of schizophrenia.^{25,26} These clinical failures suggest that selective D_4 antagonism alone is not responsible

for the unique antipsychotic efficacy of clozapine but it is possible that D_4 antagonism along with the action of other neurotransmitter receptors may be important in treating psychosis. There is some suggestion that D_4 antagonism may play an important role in impulsivity and working memory.²⁴ Pfizer has three D_4 agents in clinical development, namely, PD 165167, PD 172760, and U99363E.

Serotonergic Issues

Since the atypical antipsychotics bind with higher affinity to the 5-HT_{2A} receptors versus dopamine receptors, selective 5-HT_{2A} receptor antagonists have been evaluated as possible antipsychotics.

EPLIVANSERIN: A 5-HT_{2A/2C} RECEPTOR ANTAGONIST

Adults with schizophrenia or schizoaffective disorder (N=481) were randomly assigned in a 3:1:1 ratio to receive fixed doses of investigational drug, placebo, or haloperidol for 6 weeks. Reductions in the PANSS total and negative scores in the group receiving the 5-HT_{2A/2C} antagonist were equal to haloperidol and were significantly larger than those in the group receiving placebo.²⁷

Another 5-HT_{2A} selective antagonist, M100907, though more effective than placebo in two cumulative studies, was not as effective as haloperidol.²⁸

The above studies suggest that although 5-HT_{2A} receptor antagonists have antipsychotic properties, they are not superior to D_2 antagonists. It does appear that 5-HT_{2A} receptor antagonists may help with negative symptoms by elevating dopamine in the mesocortical region.²⁹

5-HT_{1A} agonists like clozapine have been suggested to boost dopamine levels in the prefrontal cortex. This may be responsible for clozapine's efficacy with respect to negative symptoms and cognitive dysfunction in schizophrenics. So far, attempts to develop 5-HT_{1A} agonists have not replicated the clinical efficacy profile of clozapine.³⁰

The 5-HT_{2C}, 5-HT₄, and 5-HT₆ receptors have also been targets of antipsychotic drug development. Selectively of the 5-HT_{2C} receptor by decreasing dopamine in the mesolimbic and mesocortical region but not the nigrostriatal region suggests it might have antipsychotic efficacy without EPS.²⁹ Since the 5-HT_{2C} receptor antagonism has been shown to cause weight gain, a 5-HT_{2C} receptor agonist may be useful in reducing food intake and weight in patients.³¹

The 5-HT₄ receptor is prominent in the hippocampus, frontal cortex, and amygdala. This receptor is decreased in Alzheimer's disease and, thus, 5-HT₄ receptor agonists may

be helpful in schizophrenia with the mechanism of increasing cholinergic transmission in the hippocampus. Thus, there is the possibility that these agents may be helpful in the cognitive dysfunction in schizophrenics.³² The affinity of clozapine and olanzapine on the 5-HT₆ receptor, which preclinically improves cholinergic neurotransmission, may help with the neurocognitive deficits in schizophrenia.³³

To date, human clinical studies involving the 5-HT_{1A}, 5-HT_{2C}, 5-HT₄, and 5-HT₆ agents have not been published.

OTHER RECEPTORS

α -adrenergic receptors may play a role in improving the cognitive functioning for schizophrenics. Indeed, α -adrenergic-2 receptor agonists such as clonidine and guanfacine have shown some efficacy in improving cognitive function in schizophrenics when added to standard antipsychotics.^{34,35} The problem with this is many α -adrenergic-2 receptor antagonists are traditional antipsychotics and thus a choice between α -adrenergic-2 receptor agonism and antagonism will be challenging.

CHOLINERGIC AGENTS

Acetylcholine is important in various domains of cognition, including attention, learning, and memory. Cholinergic dysfunction is central to the treatment of Alzheimer's disease as cholinesterase inhibitors have been shown to slow down the cognitive decline of Alzheimer's disease and other neurodegenerative disease.³⁶ These agents have been hypothesized to help with respect to cognitive dysfunction in schizophrenia, but the results have been disappointing.³⁷

MUSCARINIC ACETYLCHOLINE RECEPTORS

There are five types of muscarinic receptors (M₁–M₅), with M₁ the most closely linked to schizophrenia. Clozapine and its metabolite *N*-desmethylozapine bind to the M₁ receptor with *N*-desmethylozapine acting as a potent agonist.³⁸

Xanomeline, an agonist at the M₁ and M₄ receptor with activity at 5-HT_{1A} and 5-HT_{2A} receptors, has shown improvement with active psychotic symptoms in a double-blind, placebo-controlled study³⁹ assessing 10 patients receiving xanomeline versus 10 patients receiving placebo. Patients on xanomeline showed greater improvement on Brief Psychiatric Rating Scale (BPRS) and PANSS scores as well as verbal learning and short-term memory function compared with placebo.

Nicotinic-acetylcholine receptors have shown interest as schizophrenics have been shown to have significantly higher

smoking rates than normal control⁴⁰ and smoking has been shown to improve various measures of cognition while easing the side effects of antipsychotics.⁴⁰ Considerable efforts are being made to explore the potential use of nicotinic agents in the treatment of schizophrenia.

GLUTAMATE IN SCHIZOPHRENIA

The role of glutamate in schizophrenia is complex. Since phencyclidine and ketamine—both NMDA antagonists—may cause psychotic symptoms as well as worsen cognition and negative symptoms, it has been hypothesized that schizophrenia may be related to NMDA hypofunction.⁴¹ However, it is also thought that hyperactivity of the NMDA receptor may alleviate psychosis.

The NMDA receptors are ligand-gated ion channels with both a primary glutamate-binding site and an allosteric glycine-binding site. In view of the fact that a direct agonist to the glutamate-binding site may cause excessive excitation possibly giving rise to seizures, the glycine-binding site on the NMDA receptor has been the focus of much attention in the development of new antipsychotics.

NMDA receptor agonists attaching to the glycine site have been evaluated. These include the amino acids such as glycine, D-cycloserine, D-serine, and D-alanine. These agents have been added to either typical or atypical antipsychotics and show some significant benefits in reducing negative symptoms and cognitive impairment in schizophrenia.⁴²

Other attempts to increase glycine is by inhibiting the glycine transporter. A low-potency glycine transport inhibitor, sarcosine, has been investigated in relation to schizophrenia. Early evidence suggests that intake of sarcosine 2 g/day as add-on therapy to certain antipsychotics⁴³ in schizophrenia gives significant additional reductions in both positive and negative symptomatology as well as the neurocognitive and general psychopathologic symptoms that are common to the illness. This was not found to be the case when sarcosine was added on to clozapine.⁴⁴ Sarcosine has been tolerated well. It is also under investigation for the possible prevention of schizophrenic illness during the prodromal stage of the disease. It acts as a type 1 glycine transporter inhibitor. It increases glycine concentrations in the brain, thus causing increased NMDA receptor activation and a reduction in symptoms. As such, sarcosine and other glycine transporters might be interesting treatment options and a possible new direction in the treatment of schizophrenia in the future.

GLUTAMATE RECEPTOR

The glutamate receptor family is subdivided into ionotropic receptors and metabotropic receptors which activate G-protein coupled intracellular metabolic processes.⁴⁵ NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate are ionotropic receptors. The NMDA receptor is mainly coupled to the calcium channel while AMPA and kainate are coupled to sodium channels. Allosteric potentiation of the AMPA receptor by a group of compounds known as ampakines may help in alleviating some symptoms of schizophrenia. Indeed, the ampakine CX-516, when added to clozapine, yielded significant improvement in memory and attention,⁴⁶ although when given as monotherapy it had no benefit.⁴⁷

Currently, there are eight metabotropic receptors divided into three classes. Group 1, classified as mGLU R 1 and mGLU R 5, uses inositol 3P as its second messenger; Group 2, classified as mGLU R 2 and mGLU R 3, uses cyclic adenosine monophosphate (cAMP) as its second messenger; Group 3, which includes mGLU R 4, mGLU R 6 (mainly confined to the retina), mGLU R 7, and mGLU R 8, also uses cAMP as its second messenger. Selective allosteric modulators of these mGLU R receptors are being examined in schizophrenia.

NEUROKININ RECEPTORS

First identified in the 1930s, neurokinins are neurotransmitters found in the substantia nigra and striatum areas of the brain. Unlike most of the neurotransmitters identified to date, they are made from peptides rather than amino acids. They are believed to be involved in the control of movement. Their potential as therapeutic targets for drug development has only recently been suggested, but these receptors are seen as an area of rich research. The neurokinins NK₁ and NK₃ have been identified as suitable targets for drug development. Several antagonists to these neurokinins are now in development. Talnetant and osanetant are the two NK₃ antagonists in development for schizophrenia.

NK₁ has been studied with respect to depression but NK₃ receptor antagonists have been evaluated in the treatment of schizophrenia. In one study,²⁷ the group receiving the NK₃ antagonist osanetant showed significantly greater improvement over baseline than the group receiving placebo as measured by PANSS total score, Clinical Global Impressions (CGI) severity of illness score, and BPRS psychosis cluster score. Talnetant has not been evaluated in clinical studies with respect to schizophrenia.

CANNABINOID RECEPTORS

In view of the fact that there appears to be significant correlation between prior cannabis use and the development

of schizophrenia, the study of the endogenous cannabinoid system has been of interest.^{48,49} There are two cannabinoid receptors, namely, CB1 and CB2. A selective CB1 antagonist SR 141716, while showing some preclinical antipsychotic efficacy, did not show antipsychotic efficacy versus placebo.²⁷

NEUROTENSIN RECEPTORS

Neurotensin is a 13 amino acid neuropeptide that is implicated in the regulation of luteinizing hormone and prolactin release and has significant interaction with the dopaminergic system. There is evidence that since neurotensin agonists may reverse amphetamine-induced effects on hyperactivity, neurotensin may have a potential for use in schizophrenia. Clinical trials on neurotensin agonists need to be evaluated. Since there is neurotensin tone in schizophrenia, a neurotensin antagonist may be useful in schizophrenia. A recent study,²⁷ however, showed that the neurotensin antagonist compared with haloperidol and placebo did not equal the group receiving haloperidol or differ from the group receiving placebo on any outcome measure (PANSS total score, CGI severity of illness score, and BPRS psychosis cluster score.).

CONCLUSION

Generally, with clozapine being the ideal drug, it seems we need to develop drugs that mirror clozapine without its side-effect profile. Clozapine as the "ideal drug" has affinities for numerous receptors, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, D₁, D₂, D₃, D₄, α_1 , α_2 , M₁, M₂, and H₁ receptors. It would seem that this might require the use of polypharmacy and augmentation strategies, but the hope is for the development of non-selective single compounds that can target multiple domains, while decreasing side effects. Pursuing diverse molecular targets and validating these targets as effective in the treatment of schizophrenia appears to be the future for developing antipsychotics in the treatment of schizophrenia. **PP**

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