Schizophrenia Pharmacology: Past, Present, and Future Targets for Intervention

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The first medication for schizophrenia was discovered serendipitously. Years later, it was shown that the medication worked by blocking dopamine, and to this date, all available antipsychotic medications also work by blocking dopamine. They differ, however, in many other respects. The so-called first-generation medications have a wide range of receptor affinities, but in all cases, they have a higher affinity for dopamine receptors than for serotonin receptors. In contrast, so-called second-generation medications have a higher affinity for serotonin receptors than for dopamine receptors. A third category of medication acts as a partial agonist at the dopamine receptor. It is likely that a fourth category will also become available and these medications will act as agonists at the *N*-methyl-D-aspartate receptor, although clinical trials thus far have struggled to demonstrate efficacy. In addition to medications that treat symptoms of psychosis, medications are under development to directly target some of the more fundamental aspects of cognition that are impaired in schizophrenia, including memory, sensory processing, attention, and executive function. Several promising strategies are discussed.

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FIRST-GENERATION AND SECOND-GENERATION ANTIPSYCHOTIC MEDICATIONS

Midway through the previous century, chemists were looking for a compound that would blunt the body's autonomic stress response during surgery. This search led to the synthesis of chlorpromazine (1), a modification of a phenothiazine core that had been shown to have antihistaminic properties. To the surprise of the physicians who first used brought this molecule to the clinic, it appeared to have the novel property of creating a sense of indifference among patients. Prescient psychiatrists guessed that this unique effect might lend chlorpromazine some clinical utility beyond blocking catecholamines in the operating theater, and indeed, chlorpromazine proved astonishingly useful, both as a medication and as an illuminator of neuropsychiatric pharmacology itself.

The first report of chlorpromazine in psychiatric literature appeared in 1952, when it was described as having an immediate "calming effect" on an agitated, manic patient. This fortunate soul was restored to his normal state of health after just 20 days of treatment (2). Subsequently, chlorpromazine was shown to be effective in treating hallucinations and delusions. Such a specific antipsychotic effect by a medication had never been seen before, and its significance within the history of schizophrenia cannot be overstated: The discovery of antipsychotic medications contributed directly to the end of the asylum era and the beginning of effective outpatient treatment for psychotic disorders.

Within several years, laboratory models were developed that allowed predictions of antipsychotic efficacy on the basis of animal behavior. Two important determinants were the inhibition of conditioned responses and the provocation of neuromuscular rigidity. In due time, the efficacy of chlorpromazine was discovered to come from its blockade of dopamine receptors (D_2 type) in neural pathways extending from the ventral tegmental area in the midbrain to cortical regions associated with emotion, motivation, judgment, decision making, reward, and memory. Other structurally similar compounds followed, along with chemically dissimilar molecules, such as haloperidol.

As a class, these medications share the property of delivering antipsychotic efficacy through blockade of dopamine at the D_2 receptor, but they differ in their relative affinity for other central nervous system neurotransmitter receptors (Table 1) (3, 4). So-called high-potency antipsychotics are relatively specific for dopamine receptors, whereas low-potency medications have relatively higher affinity for other receptors, such as those in the adrenergic, cholinergic, and histaminic systems.

As can be predicted, the high-potency medications have effects that are specific to the dopamine system, which include both acute and chronic effects on movement through dopaminergic blockade in the extrapyramidal motor system. (Pyramidal neurons, also known as corticospinal and corticobulbar neurons, pass through the medullary pyramids and innervate motor neurons directly; in contrast, the extrapyramidal

TABLE 1. Relative Receptor Affinities for Selected Antipsychotic Medications[a]

Receptor, Ligand, and Typical Biological Effects	First Generation		Second Generation (Serotonin-dopamine selective)			Third Generation (D_2 partial agonist)
	Chlorpromazine (low potency)	Haloperidol (high potency)	Clozapine	Risperidone	Olanzapine	Aripiprazole
D_2 (dopamine): Movement-related effects, increased prolactin	+++	++++	+	+++	++	(+/−)[b]
α_1 (catecholamines): Sedation, orthostatic hypotension	+++	+	+++	+++	++	++
H_1 (histamine): Sedation, weight gain	+	−	+++	+	+++	+
M_1 (acetylcholine): Dry mouth, constipation, blurred vision, memory impairment, urinary retention	−	−	+++	−	++	−
$5HT_{1A}$ (serotonin): Reduced movement-related effects	−	−	+	+	−	+
$5HT_{2A}$ (serotonin): Reduced movement-related effects	+	−	++++	++++	+++	++++

[a] Adapted from Roth et al. (3) and Holmes and Zacher (4). This table is not intended to be a complete list of antipsychotic medications, and it is not a complete list of central nervous system receptors and their biological activity. Rather, it includes selected agents and properties to illustrate the variability between molecules used for treating psychosis, whereby plus signs indicate degree of affinity and a minus sign indicates no affinity. Note that the second-generation medications and aripiprazole have proportionally greater affinity for the serotonin 5-HT_{2A} receptor than for the dopamine receptor.

[b] Aripiprazole is a partial agonist at the D_2 receptor.

neurons pass outside the pyramids and control involuntary motor activities, such as posture, balance, and coordination.) Moreover, lower-potency antipsychotics have more activity at nondopamine receptors. Depending on their specific combination of receptor affinities, the medications can cause effects such as sedation (histamine blockade); orthostatic hypotension (adrenergic blockade); as well as dry mouth, constipation, hyperthermia, and cognitive dysfunction (cholinergic blockade).

These days, receptor occupancy can be measured with methods such as positron emission tomography and radiolabeled ligands. In the era before that was possible, the twin animal effects of conditioned response inhibition and neuromuscular rigidity were thought to be both necessary and sufficient for predicting antipsychotic efficacy in human beings. Such was the strength of this belief that when clinicians were treating patients, they would deliberately increase the doses until either clinical improvement was noted or limiting extrapyramidal effects appeared (5). It was thought that any antipsychotic would begin to show extrapyramidal effects when pushed to a sufficiently high dose. This belief changed with the discovery of clozapine, which acted as an antipsychotic but did not have the predicted neuromuscular effects on animals.

Because clozapine did not induce catalepsy, whereas all other antipsychotics did, it was called an "atypical" antipsychotic. It was the first of many atypical compounds to follow. Its novel lack of motor activity occurs because the molecule blocks serotonin at the 5-HT_{2A} receptor in a ratio such that serotonin blockade is much greater than dopamine blockade. Blocking serotonin at the 5-HT_{2A} receptor modulates both dopaminergic and glutamatergic neurotransmission, leading to increased dopamine release in the striatum and thus less effective dopaminergic antagonism in the basal ganglia and motor system (6). As a result, atypical antipsychotics have fewer movement-related effects than first-generation antipsychotics as well as a lower liability of late-occurring (or "tardive") involuntary movements to become permanent. Similarly, 5-HT_{2A} receptor blockade modulates dopamine release in the prefrontal cortex, which may have beneficial effects on cognition.

These combined serotonin-dopamine antagonists came to be known as second-generation antipsychotics. However, it is worth noting that the so-called atypical effects of the medications actually fall on a spectrum. Some low-potency, first-generation medications actually resemble second-generation medicines with respect to extrapyramidal effects. Muddying the waters a bit more, some medications thought to be of the first generation were later found to have some degree of serotonin antagonism (7). Thus, categorization can be somewhat challenging. There is a consensus, however, that combined serotonin-dopamine blocking agents, as long as their affinity for the 5-HT_{2A} receptor is greater than their affinity for the D_2 receptor, are reliably superior to other agents when it comes to movement-related effects.

It is worth noting at this point that purely selective 5-HT_{2A} antagonists have also been tried as antipsychotics but,

somewhat surprisingly, without seeing any robust clinical effects. This lack of success with 5-HT_{2A} antagonists was a bit unanticipated because specific 5-HT_{2A} agonists have been shown to precipitate psychotic experiences in human beings. Two common recreational psychotomimetics, lysergic acid diethylamide and psilocybin, both work by acting as agonists at 5-HT_{2A} receptors. This development led to useful descriptions of a serotonin model for psychosis, despite the fact that strictly selective 5-HT_{2A} antagonists do not deliver meaningful clinical efficacy compared with combined serotonin-dopamine antagonists (8). Dopamine thus remains an integral part of the story.

All of the aforementioned agents, whether first or second generation, have comparable clinical efficacy, with the notable exception of clozapine, which has been shown to be more efficacious among patients with treatment refractory schizophrenia (9–11). All of the medications differ widely in other ways, though, such as tolerability and the incidence of effects (such as sedation) that are not mediated by dopamine pathways. The drugs also range widely across a spectrum of adverse metabolic consequences, ranging in severity from practically none to significant weight gain and detrimental changes in glucose and lipid metabolism. Therefore, although all the agents except clozapine are similar in efficacy, there is still such variability among the medications that choosing a therapy for an individual patient requires thoughtful consideration of the whole picture of the patient's individual health and circumstances.

BEYOND THE FIRST AND SECOND GENERATIONS: NEWER ANTIPSYCHOTICS

To date, all medications with antipsychotic efficacy deliver their action through the aforementioned dopamine blockade at the D_2 dopamine receptor. This occurrence led to a pathophysiological description of schizophrenia that came to be known as the "dopamine hypothesis," in which excess dopaminergic tone in the mesolimbic tracts was held to be responsible for symptoms such as hallucinations and delusions, whereas dopamine hypoactivity in the frontal cortex led to cognitive dysfunction and some affective symptoms.

All current antipsychotic medications block dopamine receptors, but they do not block them in the same way. As we have seen, the second-generation medications add the property of combined serotonin-dopamine receptor antagonism. Then, at the turn of the century, aripiprazole came to market as the first D_2 "partial" agonist. In some ways, the idea of a partial agonist actually extended the dopamine hypothesis. Hyperactive mesolimbic dopamine signaling was thought to contribute to positive psychotic symptoms, whereas attenuated mesocortical dopaminergic signaling was implicated in negative symptoms and cognitive impairment (12). First- and second-generation medications reduce dopamine signaling in the mesolimbic tracts, and in so doing, deliver their clinical efficacy, but they also reduce signal transmission in the mesocortical tracts. This result implies that first-generation medications might worsen cognitive symptoms.

A dopamine partial agonist would increase signal transmission when dopaminergic tone was too low and reduce signal transmission when it was too high. When a full agonist is present, a partial agonist would reduce postsynaptic output by preventing some of the competing ligands from binding, whereas when no agonist is present, the partial agonist would itself bind to the receptor and initiate a response. This process is the proposed mechanism for aripiprazole (13), a drug that has led the way toward a third generation of antipsychotic compounds—other partial agonists have shown promise as well, including cariprazine (14) and brexpiprazole (15).

However, things may not be quite as straightforward as the partial agonist hypothesis would suggest. There is evidence that what appears to be partial agonism might also be the result of "functional selectivity," or the tendency for signaling to be modulated by receptor-ligand combinations that change with variations in the local cell environment. In a practical sense, this outcome means that a biologically active ligand may interact differently under different circumstances with the same receptor isoform (16) or that the intrinsic efficacy of a ligand at a receptor subtype is contextually dependent. Indeed, animal models of antipsychotic response have demonstrated that aripiprazole has full D_2 antagonist properties in regions of the central nervous system with intrinsically low dopamine tone; this finding would seem to contradict the idea that aripiprazole is a dopamine partial agonist in every circumstance (17). Instead, the effects of aripiprazole binding at the D_2 receptor may vary with the environment in which the D_2 receptor is found. This result not only suggests that dopamine signaling is more complex than previously understood but also opens up interesting areas for future drug development as the number and types of potential targets multiply.

Presynaptic autoreceptors form another chapter in the story. Most dopamine receptors are located on nondopaminergic neurons, but D_2-type receptors are also found presynaptically on dopamine neurons themselves, where they function as autoreceptors: When activated, they decrease excitability of the neurons on which they are located and thereby modulate downstream dopamine transmission through feedback inhibition (18). Selective activity at these autoreceptors would be a theoretically useful property in the treatment of psychosis, because one downstream effect would be less limbic dopamine release. The first selective D_2 autoreceptor ligand to be developed, roxindole, resembled a second-generation antipsychotic because it reversed effects of amphetamine and blunted conditioned responses in animals without inhibiting reflexes or causing cataplexy. It also had properties in common with antidepressants (19). Disappointingly, the hoped-for antipsychotic effect was modest at best (20). Research continues, and presynaptic dopamine agonists may eventually play a larger role in the management of psychosis.

BEYOND DOPAMINE: THE GLUTAMATE HYPOTHESIS

Early in neuropsychopharmacology research, dopaminergic agents were discovered that could induce psychosis in otherwise healthy people. One of these agents, amphetamine, increases release of dopamine into the synaptic cleft and thus increases dopaminergic signaling. This finding was discovered alongside the fact that dopamine blockade reduced symptoms of psychosis; both of these findings reinforced the centrality of dopamine neurotransmission to the symptoms of schizophrenia. However, there are other pharmacologic methods of inducing psychosis that are equally intriguing.

Early in the 1980s, the anesthetic agents phencyclidine and ketamine were shown to induce symptoms of psychosis by acting as antagonists at *N*-methyl-D-aspartate (NMDA)–type receptors on glutamatergic neurons (21), a discovery that led to a "glutamate hypothesis" of schizophrenia. According to the glutamate hypothesis, because glutamatergic neurons modulate dopamine release in the brain, impairments in NMDA signaling can explain both positive (hallucinations, delusions) and negative (affective flattening, avolition, etc.) symptoms. Lowering NMDA tone reduces gamma-aminobutyric acid inhibition of glutamatergic interneurons, leading to increased excitation of dopaminergic neurons in limbic cortical regions. This outcome leads to an increase in positive symptoms. Moreover, glutamate interneurons are present in the frontal cortex as well, where hypofunction may impair dopamine signaling (22). Thus, with the observations that NMDA antagonists provoke psychosis, and a plausible theory linking NMDA hypofunction to many of the symptoms of schizophrenia, the search was on for a clinically useful compound that could bind NMDA receptors as an agonist and act as an antipsychotic. In addition to clinical efficacy, there is also much hope that NMDA-based drugs would have fewer unwanted movement-related and metabolic effects than dopamine-blocking drugs. Several agents have made it into clinical trials, frequently with promising results (23). However, to date, there has been no successful phase III trial of any NMDA agonist for the treatment of schizophrenia.

One important side note in the story of new drug development is that the magnitude of the placebo response appears to be increasing significantly over time (24). This occurrence is true for many types of agents, including medications for schizophrenia (25), depression (26), epilepsy (27), and neuropathic pain (28). Because the increase in placebo response has been observed in so many different types of medications, investigators have begun to question whether clinical trial design itself is perhaps obscuring positive results. If true, this finding would be quite disturbing, given the time and expense needed to bring a new drug to market. It is unfortunate that some of the things that make a trial easier to carry out, including shorter study duration, higher number of sites, and a lower number of university-affiliated participants, are associated with an increase in the placebo response (29).

One case study in particular illustrates the challenges of modern clinical trial design. Eli Lilly and Company developed a molecule called mGlu2/3 (also known as pomaglumetad), an NMDA receptor agonist, with high hopes that it would become the first antipsychotic medication with no affinity for dopamine receptors. Early trials showed that it was a safe and effective, with no more weight gain than placebo; however, bioavailability was low, so a similarly safe and effective prodrug form (pomaglumetad methionil) was developed (30). A subsequent trial looking at tolerability across a wide dosing range revealed two significant problems: First, for the first time in the investigation of the drug, a small number of patients reported seizures, and second, the trial failed to show efficacy. The lack of demonstrated efficacy came perhaps because of an unexpectedly large placebo response; this hypothesis is supported by the fact that the trial also failed to show any separation between placebo and an active comparator, olanzapine, which was known to be efficacious (31). This trial showed evidence of the general trend toward increasing placebo response rates, and perhaps in this case, the effects of both the experimental drug and a proven drug were hidden. However, the story did not end there.

Two additional trials were then carried out to address these problems. Because of the concerns about seizures, investigators conducted an open-label safety trial in which mGlu2/3 was compared with standard-of-care, second-generation antipsychotics (but not with placebo). The new agent showed safety and efficacy once again, with superior tolerability to the comparator antipsychotics and no increased incidence of seizures (32). To address the placebo issue, a large (N=1,009) phase III study was conducted with elaborate precautions to minimize the placebo effects, including an attempt to recruit participants with a known history of good drug response and to eliminate participants from the trial who responded quickly to placebo. This study was able to demonstrate the efficacy of an active comparator (risperidone), but it did not show efficacy of pomaglumetad (33). Eli Lilly and Company subsequently ended ongoing studies of the drug (34).

There are several possible explanations for the failure of the final trial. Recruitment of patients with a history of good treatment response implies that the patients all had sizable exposure to dopaminergic medications. Perhaps chronic dopamine-serotonin blockade downregulates the glutamate receptors that pomaglumetad targets. This explanation is plausible because NMDA agonism reduces dopaminergic excitability; if there is less dopaminergic activity, then less NMDA agonism is needed, and thus the receptors could downregulate to preserve balance. The end result is that years of exogenous dopamine antagonism could lead a person to be less responsive to NMDA agonists.

Evidence also suggests that glutamatergic dysregulation is more clinically significant early in the course of the illness,

and thus selecting patients with long treatment histories may have excluded people who may have potentially responded well had they been treated earlier in the course of their illness. The clinical effects of pomaglumetad may also be susceptible to genetic variation in receptor expression (35). In any event, the experience with this compound shows the considerable complexity and challenges in modern clinical trial design.

BEYOND PSYCHOSIS: IMPROVING COGNITION

The history of schizophrenia psychopharmacology began at the point when dopamine blockade was discovered to be effective in reducing psychotic symptoms such as hallucinations and delusions. Thus, much of what we later learned about both treatment and neurophysiology follows a path from dopamine signaling, through the effects of dopamine antagonism, through the benefits from combined serotonin-dopamine blockade, to the related glutamate system, and finally to their combined impact on psychotic symptoms. But the positive symptoms are only one facet of the illness.

Functional outcome seems to be more related to another factor, namely cognitive impairment. Many cognitive domains are impaired in schizophrenia, including working memory, declarative memory, sensory gating, executive function, and attention. Indeed, cognitive dysfunction predicts real-world functional outcomes better than the burden of positive symptoms does; cognitive dysfunction is also largely unaffected by treatment with antipsychotic medications (36). There is great interest, therefore, in agents that may enhance cognition.

Several targets for pharmacotherapy have been proposed. One promising target is the alpha-7 subunit of the nicotinic acetylcholine receptor (α7nAchR). This receptor is expressed in areas of the brain that subserve several cognitive domains, including memory, sensory gating, visiospatial construction, and attention (37). It appears that other subunits of the nicotinic receptor are involved in nicotine craving addiction; this finding implies that drugs targeting α7nAchR are not likely to be habit forming or to produce anxiety or withdrawal symptoms when discontinued (38). The association between α7nAchR and schizophrenia-related cognitive dysfunction is plausible because decreased expression of the receptor protein is seen in postmortem studies of patients with schizophrenia, whereas genetic studies show that copy number variations in the region coding for α7nAchR confer additional risk for the disorder; α7nAchR ligands in animal models show improved sensory gating and improved performance on some behavioral tasks. Drugs for humans are not yet available, although several candidates have made it as far as phase III clinical trials (39).

Returning to dopamine, we should note that there are five types of dopamine receptors. Although the D_2 receptor is central to psychotic symptoms, dopamine signaling through the D_1 receptor in the prefrontal cortex facilitates cognitive processes, such as working memory, which is the ability to hold information in short-term memory for immediate manipulation and processing. Both D_1-dependent signaling and working memory are significantly impaired in schizophrenia, and so a D_1-selective agonist would plausibly improve working memory and thus cognitive activities such as reasoning, decision making, and judgment. D_1-selective agents have shown promise in animal models, but drugs that are tolerable and effective in humans have been hard to find. This area remains very active for researchers (40).

One other area of consideration is the family of serotonin receptors. We have already discussed the role of the 5-HT_{2A} receptor in serotonin-dopamine–blocking drugs, such as the second-generation antipsychotics. However, at least 16 other types of serotonin receptors exist, and several of those are linked closely to cognitive functions. The 5-HT_{1A} receptor, for example, is found to be upregulated in postmortem schizophrenia studies, which may imply decreased receptor functioning in life (41). Its expression clusters most strongly in the hippocampus, a structure that is vital for the encoding of memory, and receptor activation is thought to improve memory. 5-HT_3 receptors have also been extensively studied; these receptors are found in the hippocampus and frontal cortex as well as in the ventral tegmental area. Exogenous 5-HT_3 receptor ligands have been shown to improve performance in memory and learning tasks in animals, and they are under investigation for enhancement of memory in Alzheimer's disease and schizophrenia in humans (42). Moreover, selective $5HT_6$ antagonists have been shown to improve attention, learning, and memory (43, 44).

Many other potential procognitive drug targets exist, including ones within the histaminic and glutamatergic systems, along with agents such as glycine and phosphodiesterase inhibitors. The number of potential targets continues to grow, as does the hope that cognition-enhancing medications will ultimately take their place in clinical practice and contribute to improved functional outcomes of people with schizophrenia.

One final area for consideration is the role of inflammation in the pathogenesis of schizophrenia and the possible drug targets that it suggests. Inflammatory processes have been implicated in schizophrenia through several lines of evidence. Numerous studies have demonstrated that maternal infections during pregnancy increase the risk of the child's developing schizophrenia, and some adults with schizophrenia have higher levels of various markers of inflammation (45). This finding is also supported by animal experiments in which animals exposed to viruses in the perinatal period developed into adults with sensory gating deficits (46) and behavioral abnormalities (47) compared with noninfected control animals.

Among humans, higher maternal levels of proinflammatory cytokines during pregnancy have been associated with increased risk of schizophrenia in the developing child (48). It may also be the case that some childhood infections also increase the risk of developing schizophrenia years later (49). Taken in sum, this body of evidence suggests that preventive strategies may be effective, and indeed, disease

prevention through vaccination may have led to decreased incidence of schizophrenia in some parts of the world. In addition, agents that modify the inflammatory response may prevent the illness, change its course, or ameliorate some of the symptoms. The most widely studied approaches have been omega-3 fatty-acid supplementation and anti-inflammatory drugs such as celecoxib, a cyclooxygenase-2 inhibitor (50), followed by agents such as erythropoietin (51) and minocycline (52). Omega-3 fatty acids and celecoxib have generally been used in conjunction with antipsychotics in the earliest phases of the illness and have shown promise in delaying progression from the prodrome to the full disorder. Results have been mixed, however, and research is ongoing to clarify the role of drugs such as these in schizophrenia treatment and prevention (53).

It is interesting and somewhat surprising that therapy targeting the immune response has shown encouraging results on the so-called negative symptoms of schizophrenia (54). Although hallucinations, delusions, and formal thought disorder may be more commonly associated with the illness (and have historically been more popular targets for treatment), negative symptoms such as decreased emotional expression, avolition, poverty of speech and thought, and the inability to experience pleasure contribute more to daily dysfunction. Unfortunately, these symptoms have also been stubbornly resistant to pharmacologic treatment. It is serendipitous, therefore, that immunomodulators may be helpful here. Results are still preliminary and require replication but have nevertheless been encouraging for people with what remains today a very debilitating illness.

For many patients and many clinicians, the lack of effective treatment options other than the dopamine-blocking medications has been frustrating, considering that chlorpromazine was first synthesized more than 60 years ago and we are still waiting for the first medication that improves symptoms of schizophrenia by a fundamentally different mechanism. That being said, the last half century of research has delivered a wealth of knowledge about the illness itself and has illuminated many promising pathways for future research as well as many potential targets for future pharmacologic intervention.

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