

Developing Therapeutics for Schizophrenia and Other Psychotic Disorders

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Summary: Although the second-generation or atypical antipsychotic drugs have been breakthrough medicines for the treatment of schizophrenia and other psychotic conditions, cognitive dysfunction and to some extent negative symptoms of the disease continue to be the main cause of poor vocational status of the patients. Thus, the majority of investigational drug development efforts today target these unmet medical needs. This review postulates that the field of schizophrenia research has advanced sufficiently to develop biochemical hypotheses of the etiopathology of the disease and target the same for revolutionary disease modifying therapy. This postulate is based on recent studies that have begun to provide a testable etiopathology model that integrates interactions between genetic vulnerability factors, neurodevelopmental anomalies, and neurotransmitter systems. This review begins with a brief overview of the nosology and etiopathology of schizophrenia and related psy-

chotic disorders to establish a context for subsequent detailed discussions on drug discovery and development for psychotic disorders. Particular emphasis is placed on recent advances in genetic association studies of schizophrenia and how this can be integrated with evidence supporting neurodevelopmental abnormalities associated with the disease to generate a testable model of the disease etiopathology. An in-depth review of the plethora of new targets and approaches targeting the unmet medical need in the treatment of schizophrenia exemplify the challenges and opportunities in this area. We end the review by offering an approach based on emerging genetic, clinical, and neurobiological studies to discover and validate novel drug targets that could be classified as disease modifying approaches. **Key Words:** Genetic etiopathology, neurodevelopmental etiology, investigational drugs, animal models, neurotransmission, neuroimaging, proof of concept clinical studies.

INTRODUCTION

Schizophrenia is a debilitating illness that affects up to 1% of the population around the world. Despite aggressive efforts to decrease hospital stays by managed care in the U.S., this psychiatric syndrome accounts for a disproportionate burden upon medical resources, including hospitalizations. Although treatments for the most obvious psychotic delusions and hallucinations have been available for over 50 years, little change in the vocational status of schizophrenic patients has occurred. This appears to be due to a pervasive cognitive dysfunction for which pharmacological agents have minimal impact. Among investigators in this field, a growing appreciation has emerged for an etiological neurodevelopmental hypothesis for schizophrenia in step with the rapidly advancing neurobiology underlying this clinical syndrome. Thus, a central question facing the psychopharmacolog-

ical advancements for this disorder is the degree to which symptomatic treatments can make further inroads on remaining negative symptoms and cognitive dysfunction. Recent breakthroughs in genetic studies of schizophrenia offer, for the first time, a hypothesis-driven approach for development of disease-modifying therapy for this debilitating disorder. This review is focused on providing a brief background on the nosology and etiopathology of schizophrenia and other psychotic disorders as well as a historical summary of available therapeutic agents. After setting this context, we will discuss new approaches for drug discovery and development of drugs that target the unmet medical need in the field.

NOSOLOGY

Schizophrenia is the most frequent and debilitating of the psychotic disorders. The psychotic disorders are characterized by a loss of contact with reality where patients have beliefs or perceptual experiences not shared by other members of their culture (delusions and hallucinations, respectively) or they engage in bizarre

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behavior. These symptoms comprise the so-called positive symptoms or psychotic domain of schizophrenia. Negative symptoms of blunted affect, anhedonia, apathy, and a reduced quantity or content of speech (alogia) are a second symptom domain in schizophrenia. These symptoms may be ameliorated partially (or at least not exaggerated) by second-generation antipsychotic (SGA) drugs, which tend to have a higher potency at the 5-HT_{2A} than dopamine D2 receptors. The third symptom domain involves cognitive impairment evident in the population of schizophrenic patients with problems in attention, learning, and memory, and a variety of executive functions (e.g., abstract thinking, problem solving, response inhibition). A cardinal feature of schizophrenia emphasized historically by Bleuler is disorganized thinking (e.g., loose associations) that is a dimension ranging from derailment (e.g., loose associations where the subjects moves from one topic to another largely out of context) to tangential thinking (where answers to questions are only indirectly related to the question) to especially severe dysfunction of incoherence or a word salad (the patients' speech or writing shows no obvious connections to objective observers). These "loosening of associations" have been redefined over the last 10 years as a "misconnection syndrome" or cognitive dysmetria due to dysfunction of cortico-cerebellar-thalamic-cortical circuits (CCTCC).¹ The cognitive deficits associated with schizophrenia have been relatively unimproved by currently approved antipsychotic drugs, although there is some evidence for the superiority of second-generation antipsychotic drugs such as olanzapine and risperidone over first-generation antipsychotics.²⁻⁴ Unfortunately, this symptom domain appears to be most responsible for the poor vocational status of schizophrenic patients.^{5,6} Thus, cognitive impairment has been targeted by a joint academic, industry, and National Institute of Mental Health (NIMH) initiative termed MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia), which in turn has spawned a corresponding treatment initiative, TURNS (Treatment Units for Research on Neurocognition and Schizophrenia).⁷

Schizoaffective disorder is a relatively closely related clinical syndrome in which a mood disturbance is present concurrent with the active phase of schizophrenic symptoms, and the delusions or hallucinations are also present for at least 2 weeks in the absence of prominent affective symptoms. The diagnosis of schizophrenia also requires the presence of symptoms meeting full diagnostic criteria for at least 1 month (including a prodromal syndrome). If this duration is not met or functional impairment is not observed, the symptoms are classified as a schizophreniform disorder. Delusional disorder differs from schizophrenia primarily in that the age of onset is typically in the fifth to sixth decade of life (*vs* onset of the first break in the second to fourth decade) and symptoms are largely

limited to paranoid delusions without prominent disorganized speech, bizarre behavior, flat or inappropriate affect. Patients with delusional disorder also present with a history of relatively good premorbid function. A substantial problem in the differential diagnosis of psychosis often is between a manic or mixed episode of bipolar disorder *versus* schizophrenia where the initial presentation to an emergency room physician can be quite similar, and primary clues to the correct diagnosis depend on a careful premorbid history, family psychiatric history, and the treatment response of the patient to mood-stabilizing drugs.⁸ Mood disorder with psychotic features (or psychotic depression) is characterized by delusions with depressive themes. Psychosis can be secondary also to medical conditions (e.g., untreated hypothyroidism, steroid treatment) or drugs of abuse. The long-lasting psychotic symptoms that are sometimes seen subsequent to hashish or marijuana, phencyclidine or ketamine, or hallucinogen (LSD, mescaline) use may reflect symptom exacerbation in individuals with an underlying disease vulnerability. The focus of this chapter will be on schizophrenia, although with pertinent discussion of bipolar disorder, given some of the genetic and pathophysiological overlap between these two major psychiatric syndromes.

ETIOPATHOLOGY

Genetic epidemiology

Evidence from family, twin, and adoption studies clearly indicates that genetic susceptibility plays a key role in the etiology of schizophrenia.⁹⁻¹¹ These studies have led to the conclusions that the heritability for schizophrenia liability is around 80%,¹² and have provided the strongest rationale for continued molecular genetic studies as well as a search for common environmental factors contributing to the etiology of this disease. However, there do not appear to be Mendelian (monogenic) forms of the disease. Rather, it is now well accepted that multiple susceptibility genes, each of small effect, may act in concert with environmental factors to cause the disease.¹³ The high concordance rate of schizophrenia in monozygotic twins, and significantly reduced relative risk for the disease in distant relatives of schizophrenia probands, have led to the hypothesis that etiopathology of schizophrenia may involve fewer than 10 genes.^{14,15} Recent progress in genetic studies has led to identification of several replicated linkages and gene variants associated with the disease^{16,17} that may justify cautious classification of the susceptibility genes as "schizophrenia genes" (see Molecular Genetics of Schizophrenia). In addition, molecular linkage studies also suggest that schizophrenia and bipolar disorder share some of the genetic susceptibility.¹⁸ Multiple genomic loci represent areas of shared genetic suscepti-

bility between schizophrenia and bipolar disorder. Taken together with common epidemiological characteristics of these diseases and recent evidence that olanzapine, an atypical, second-generation antipsychotic, reduces recurrence rates of depression as well as mania¹⁹ in bipolar patients indicates the nosology of the disorders may have to be modified in the near future on the basis of genetic findings and treatment responsiveness. Schizoaffective disorder and other schizophrenia spectrum disorders are more prevalent among families of probands with schizophrenia suggesting shared genetic etiology. However, sufficient replicated data are not available to conclude whether and which genetic susceptibility factors are shared by these psychotic disorders with schizophrenia.

Neurodevelopmental disorder

The most prevalent hypothesis for the pathogenesis of schizophrenia posits that the disease is a neurodevelopmental disorder associated with abnormal connectivity resulting from defects in synaptic pruning and migration of neurons.^{20,21} There are a plethora of anatomical findings such as cortical cytoarchitectural abnormalities that would implicate events in the second trimester of gestation. A number of other early brain developmental abnormalities are seen with a higher frequency in schizophrenic patients such as aqueductal stenosis, arachnoid and septal cysts, agenesis of the corpus callosum, and reversal of normal structural cerebral asymmetries.²² When looking back at schizophrenic patients compared with normal probands or in prospective assessments of healthy adolescents, cognitive impairment, subtle motor dysfunction, and poor school performance often are evident before the first psychotic break or an obvious prodromal stage.^{23–25} These early, premorbid characteristics of schizophrenic patients combined with structural brain changes observed in first-episode neuroleptic-naïve patients are consistent with a neurodevelopmental pathophysiology for schizophrenia.^{26–32} An example of cellular evidence for neurodevelopmental defects in schizophrenia is present in the altered distribution of interstitial neurons in the white matter underlying the prefrontal cortex reflecting either abnormalities in migration of subplate neurons or programmed cell death.³³ These premorbid neuropsychological and neuroanatomical changes combined with the usual onset of schizophrenia between the ages of 16 and 30 are consistent with the knowledge that a number of developmental tasks remain to be completed for the maturation of brain function (e.g., synaptic pruning) through the early third decade of life.³⁴

The neuroanatomical changes in the prefrontal cortex and neocortex largely appear to be due to a pruning of the neuropil (synaptic space) rather than a change in the number of neurons. Modern stereological methods have found an abnormally high neuronal density in the schizo-

phrenic prefrontal and neocortex.³⁵ These changes in the schizophrenic brain appear different from those observed in bipolar disorder where there is a decreased neuronal and glial density associated with glial hypertrophy.³⁶ At the level of individual cell types, the basilar dendritic area surrounding the principal cortical output cell, the layer V pyramidal neuron, is decreased in schizophrenia.³⁷ A decreased spine density on deep layer 3 pyramidal neurons, unlike superficial layer 3 pyramidal neurons, was observed in the prefrontal cortex of schizophrenic patients.³⁸ These observations with layer 3 pyramidal cells are consistent with a decreased thalamic input from the mediodorsal thalamic nucleus (see below) and/or decreases in cortical afferents. Further detail in the cortical microcircuitry has revealed that a special type of GABAergic interneuron, the chandelier cell (one of 20 or more types of cortical interneurons), each of which projects to the initial axon segments of the pyramidal cells, appear to provide a compromised inhibitory regulation over ensembles of cortical output cells.³⁹ These findings may be relevant to the observations from functional imaging studies showing that not only do schizophrenic patients have a hypofunction of prefrontal regions, but that there is an abnormal recruitment of cortical activity during different cognitive tasks.⁴⁰

The thalamus, a structure with multiple channels of thalamocortical and corticothalamic connections in addition to providing afferents to the amygdala, the striatum and subiculum, increasingly is being implicated in the pathophysiology of schizophrenia.⁴¹ Beginning with Andreasen and colleagues,⁴² about half of the magnetic resonance imaging (MRI) reports have found a reduced thalamic volume, which may be restricted to nuclei such as the dorsomedial, pulvinar, central medial, anterior and posteromedial thalamic nuclei. Five of six different groups using postmortem studies stereological studies have found a decreased number of mediodorsal thalamic neurons, especially in those regions projecting to the dorsal and lateral prefrontal cortex, the striatum and premotor cortical regions. Some of the studies have also suggested cell loss in the pulvinar, the anteroventral/anteromedial thalamic, and the ventral lateral posterior nuclei. Consistent with these findings, positron emission tomography studies examining subjects performing cognitive tasks reported reduced thalamic metabolic rates.

The medial temporal lobe is a region of the brain that appears to be differentially involved in schizophrenia as compared with bipolar disorder.⁸ The amygdala appears to be decreased in size for schizophrenic patients compared with control patients,^{43,44} and certainly so for schizophrenic patients compared with bipolar patients.⁴⁵ Changes in neuronal or glial density, however, have not been reported. Evidence has also accumulated that all portions of the hippocampal formation (subiculum, parahippocampal gyrus, and entorhinal cortex) are involved

in schizophrenia.^{8,44,46} There also has been evidence for either abnormally placed neurons in the entorhinal cortex or disarray of pyramidal neurons at the boundaries of the hippocampal field CA1 with CA2 and the subiculum. A clinical context for these findings are the repeated association of schizophrenia with obstetrical complications with preeclampsia (an indicator of fetal malnutrition) high on the list of neuropathological insults.⁴⁷

Consistent changes in the neostriatum of schizophrenic patients with no or minimal antipsychotic drug treatment have not been seen. However, an increased striatal volume does appear in patients treated with first-generation or typical antipsychotic drugs.⁴⁸ There is also some evidence that striatal volume tends to return to normal when a second-generation antipsychotic drug is substituted for a first-generation typical antipsychotic drug.^{49,50}

From a functional standpoint, hypotheses of dopaminergic hyperactivity have been prominent in the field of schizophrenia. A recent series of neuroimaging studies from Laruelle, Abi-Dargham, and colleagues⁵¹⁻⁵⁴ have suggested that schizophrenia is characterized by an enhanced amphetamine-induced dopamine release during the initial onset and in patients previously not exposed to antipsychotic drugs.

Cerebellar abnormalities also have been noted in schizophrenia. Functional magnetic resonance spectroscopy has found reduced cerebellar N-acetylaspartate in schizophrenic patients.^{55,56} An MRI study reported increased volume of the vermis and greater vermis white matter volume from a cohort of schizophrenic patients compared with normal subjects.⁵⁷

MOLECULAR GENETICS OF SCHIZOPHRENIA

Positional cloning and candidate gene association studies

The high heritability of schizophrenia has spawned a number of linkage studies. Despite the failure to replicate all linkages, sufficient data have emerged and recent meta-analyses^{58,59} have identified linkages at the following loci: 8p, 22q, 2q, 3p, 6p, 1q, 11q, 5q, 13q, and 20p. This led to application of modern molecular genetic studies to identify single nucleotide polymorphisms (SNPs) within the linked loci, establish the association of the SNPs with schizophrenia and identify candidate genes containing the SNPs (i.e., the classical positional cloning approach). This path has led to the breakthrough identification of several schizophrenia susceptibility genes. Thus neuregulin 1,^{60,61} dysbindin,^{62,63} G72,⁶⁴ deaminoadic oxidase, regulator of G protein signaling-4,^{65,66} catechol-O-methyltransferase (COMT),^{67,68} and proline dehydrogenase⁶⁹ represent results of the molecular genetic breakthroughs in schizophrenia research. Although the results are to be viewed with caution until further repli-

cation is documented unequivocally, the association of these genes with schizophrenia offers an unprecedented opportunity to understand the pathogenesis and pathophysiology of this disease. In fact, Harrison and Owen¹⁶ have proposed a hypothetical construct of pathophysiology of the disease that involves convergent interactions among the seven genes listed above. This approach holds tremendous promise. For the first time, hypothesis-driven schizophrenia research is likely to lead to better therapeutic strategies, both by enabling better animal models and by potentially offering the ability to assess biochemical pathways associated with the disease pathophysiology.

In addition to these classical studies, several investigators have been performing genetic studies on endophenotypes of schizophrenia. These are intermediate phenotypes that segregate with the genetic risk for schizophrenia.^{70,71} The endophenotypes offer the advantage of using objective neurophysiological measures such as deficits in smooth-pursuit eye tracking,⁷²⁻⁷⁴ or suppression of auditory evoked potentials, such as the P50 wave⁷⁵⁻⁷⁸ as indices of attentional deficits. The genetics of schizophrenia-associated endophenotypes have begun to provide significant insights into biological processes contributing to disease susceptibility⁷¹ and have offered other candidate genes or loci. Thus, Arolt et al.⁷⁹ reported a linkage of abnormal smooth-pursuit eye tracking with a locus on the short arm of chromosome 6 without identifying a gene or gene variants in the locus. Similarly, Freedman et al.⁸⁰ linked the abnormal P50 wave to a locus on the long arm of chromosome 15, which contains the nicotinic $\alpha 7$ gene,⁸¹ a drug target being pursued by several companies. It should be noted that some scientists question the relevance of genetic association with endophenotypes because deficits in eye-tracking and abnormal evoked potentials are significantly more frequent in the general population than schizophrenia.⁸² Another promising research strategy uses molecular imaging to study interactions between genetic and environmental factors that contribute to intermediate phenotypes such as working memory deficits in schizophrenia. Thus, Weinberger and co-workers⁸³ have been exploiting the advances in molecular genetic and noninvasive imaging technologies such as functional MRI to identify functional neural circuitry associated with genetic polymorphisms. These studies provide insights into disease-related neural circuits and their modulation by genetic susceptibility factors. This understanding is critical, in turn, for identification of druggable targets, generation of better animal models, and biomarkers for proof of concept studies.

PHARMACOTHERAPY

First-generation or typical antipsychotics

The modern era of pharmacological treatment for schizophrenia can be dated to the introduction of the

phenothiazine, chlorpromazine, in 1952 by Delay and Deniker.⁸⁴ Within a decade, Arvid Carlsson⁸⁵ had suggested that both chlorpromazine and the butyrophenone haloperidol might act in schizophrenia by blocking brain dopamine receptors. The development of receptor binding techniques led to the discovery that the clinical potency of both phenothiazines and butyrophenones in treating psychotic behavior is related to blockade of dopamine D2 receptors, rather than dopamine D1 receptors.^{86,87} Thus, by the 1980s a number of antipsychotic drugs that shared potent dopamine D2 receptor blockade had been released, including the phenothiazines (chlorpromazine, triflupromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine), the thioxanthenes (chlorprohixene, thiothixene), the butyrophenones (haloperidol), a dibenzoxazepine (loxapine), and a dihydroindolone (molindone). Although this class of drugs worked effectively at treatment of positive psychotic symptoms, they induced dose-limiting extrapyramidal motor deficits as well as exacerbated negative symptoms and failed to affect cognitive deficits.

Second-generation or atypical antipsychotic drugs (SGA)

In an attempt to mitigate against the extrapyramidal side effects (EPS) that range from Parkinsonian symptoms to tardive dyskinesia, an effort to build in more potent 5-HT_{2A} receptor blockade was begun which led to the development of SGA drugs, also known as atypical antipsychotic drugs. Thus, since the introduction of chlorpromazine, well over 30 antipsychotic drugs have become available for the treatment of schizophrenia.⁸⁸ Some of the SGAs such as clozapine, amisulpride, risperidone, and olanzapine have been found to produce greater effect sizes than the first-generation antipsychotic (FGAs) drugs on overall antipsychotic efficacy³ in addition to reduced EPS liability. This greater efficacy for SGAs compared with FGAs was not observed for all SGA class members in the relatively limited sample available (e.g., aripiprazole, sertindole, quetiapine, ziprasidone, and remoxipride). It remains to be seen whether a greater effect size will be seen with this latter group of SGAs as more studies become available. Consistent with reduced EPS load, the SGAs also have a reduced liability toward hyperprolactinemia. With regard to the SGAs, it should be noted that clozapine stands out with respect to efficacy in treatment-refractory patients and for patients at risk for suicide.^{89,90} The relatively infrequent agranulocytosis accompanying clozapine has greatly limited clozapine usage. An additional drawback associated with clozapine is sedation.

Dopamine D2 partial agonists

Thus far, only one dopamine D2 partial agonist has been approved by regulatory agencies for the acute treatment of schizophrenia, aripiprazole.⁹¹ Aripiprazole is a

potent partial agonist at dopamine D2 and 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors among other less potent pharmacological actions.⁹² This atypical antipsychotic appears to have a reduced liability toward weight gain, but it is not yet known if this factor will also translate into a decreased liability for schizophrenic patients to develop type 2 diabetes mellitus. A number of other dopamine D2 partial agonists (e.g., talipexole, roxindole, and SDZ HDC 912) also have been in clinical development, though they either were not as effective as the current standard of care or they did not have sustained action at therapeutic doses.^{93,94}

Other major investigational approaches

Modulation of NMDA receptor neurotransmission.

One of the most frequently studied approaches to improving cognitive function and reducing negative symptoms of schizophrenic patients is enhancing NMDA receptor function by acting on the glycine modulatory site (GMS).^{95,96} A recent review of a series of relatively small placebo-controlled studies have suggested that either high-dose glycine, D-serine, or the partial agonist D-cycloserine improve negative symptoms, cognitive dysfunction, and depression when added to antipsychotic drugs other than clozapine.⁹⁷ In contrast, either symptom exacerbation or lack of symptomatic improvement has been observed with agonists or partial agonists when the GMS are added to ongoing treatment with clozapine. A recent meta-analysis of glutamatergic drugs (e.g., glycine, D-serine, D-cycloserine, and the AMPAkinase CX516) added to antipsychotic drug treatment found a moderate effect size for glycine or D-serine added to antipsychotics with respect to negative symptoms.⁹⁸ Only a trend was present for cognitive dysfunction. Little evidence for a beneficial effect was found with D-cycloserine augmentation. A recent study of adjunctive D-cycloserine in patients predominantly with negative symptoms failed to demonstrate efficacy.⁹⁹ It should also be noted that a relatively large multicenter, double-blind, placebo-controlled study of D-cycloserine and glycine drugs failed to observe symptomatic improvement for negative or cognitive symptoms.¹⁰⁰

Serotonin 5-HT_{2A} antagonists. One example of an extensively explored approach for selectively targeting a single receptor thought to play a key role in pathophysiology of schizophrenia is the investigation of selective 5-HT_{2A} receptor antagonists as putative antipsychotic drugs. The development of the highly selective 5-HT_{2A} receptor antagonist, M100907,¹⁰¹ was discontinued after two phase 3 studies in the U.S. found M100907, although superior to placebo, to be inferior to haloperidol and a European phase 3 study in schizophrenic patients with predominant negative symptoms failed to observe separation of the M100907 from placebo.¹⁰² The termination decision was derived in large part from objective recep-

tor occupancy studies in healthy humans that confirmed that M100907 was tested at doses that saturate prefrontal cortical 5-HT_{2A} receptors.¹⁰³ Furthermore, a phase 2 study of SR46349B (eplivanserin), another 5-HT₂ receptor antagonist with approximately 20-fold selectivity for 5-HT_{2A} over 5-HT_{2C} receptors, also showed antipsychotic efficacy intermediate between that of placebo and haloperidol.¹⁰⁴ An unresolved challenge is how a modestly effective therapeutic with a presumed superior side effect profile can be used in the clinic either as a monotherapy or in combination with other agents during different stages of the schizophrenia syndrome.

Neurokinin 3 NK3 receptor antagonist. Another mechanism of action that may be associated with a relatively modest degree of efficacy is blockade of neurokinin 3 (NK3) receptors. The same meta-trial that found modest efficacy for the Sanofi-Aventis (Paris France) 5-HT₂ receptor antagonist also reported antipsychotic efficacy for the NK3 receptor antagonist, SR142801, that was intermediate between placebo and haloperidol.¹⁰⁴ This NK3 receptor antagonist is reportedly in a phase 2b trial. GlaxoSmithKline (UK, USA) also appears to have a NK3 receptor antagonist, talnetant (SB-223412), that undergoing phase 2b testing (ClinicalTrials.gov identifier NCT00103727) involving both a placebo and an active comparator (risperidone).

Dopamine D4 receptor antagonist. Dopamine D4 antagonists appear to lack appreciable efficacy in the treatment of acute schizophrenia. A relatively small phase 2 study reported a slight worsening of patients relative to the placebo group following treatment with L-745,870.¹⁰⁵ These results were confirmed in a recent, large multicenter, placebo- and active comparator (olanzapine)-controlled, study involving a 40-fold dose range for a Pfizer (USA) dopamine D4 receptor antagonist (sonopiprazole).¹⁰⁶ Given these results, it is not surprising that a dopamine D₄/5-HT_{2A}/α-1 adrenergic receptor antagonist also did not exhibit antipsychotic efficacy in a relatively small (97 patients with approximately 2:1 active:placebo randomization) phase 2 study in the treatment of schizophrenia patients.¹⁰⁷

Neurotensin NTS1 antagonist. The placebo-controlled meta-trial using haloperidol as a positive comparator that demonstrated moderate efficacy for the Sanofi-Aventis NK3 receptor antagonist and 5-HT₂ receptor antagonist failed to see any efficacy for a neurotensin NTS1 antagonist (SR48692).

Cannabinoid CB1 receptor antagonist. In the trial listed above,¹⁰⁴ the cannabinoid-1 (CB1) receptor antagonist, SR141716 (rimonabant), at the dose (20 mg) efficacious at reducing weight showed no antipsychotic efficacy. This report did not disclose whether positive effects were seen for any of the treatments on cognitive dysfunction or whether there was an effect of rimonabant on weight. Regarding the relationship of CB1 receptors

to psychosis, it is interesting to note that a recent report found patients abusing cannabis appeared to have a higher degree of psychopathology and longer duration of hospitalization in British psychiatric intensive care units.¹⁰⁸

Other miscellaneous targets. A number of additional investigational therapies are in progress at the present time. A small phase 2 study is underway for the α7 nicotinic agonist (3–2, 4 dimethoxy benylidene) for improving cognitive dysfunction in schizophrenia patients employing the MATRICS battery (ClinicalTrials.gov identifier NCT00100165). The NIMH is sponsoring a study examining whether pharmacogenomic status may be informative for the effects of the COMT inhibitor, tolcapone. Other investigational putative antipsychotic agents currently in phase 3 include bifeprunox (Wyeth & Solvay Pharmaceuticals, USA; DU-127090, a partial agonist at dopamine D2 and 5-HT_{1A} receptors), paliperidone extended release (Johnson & Johnson, an active risperidone metabolite), asenapine (Organon, Netherlands, USA; Pfizer; ORG 5222; a 5-HT₂ antagonist/dopamine D2 partial agonist). Other phase 2 investigational compounds include ORG 24448 (Organon, Cortex, USA; an AMPA potentiator), ACP-103 (Acadia, USA, a 5-HT_{2A} inverse agonist, ClinicalTrials.gov identifier NCT00087542), lonasen [blonanserin, Dainippon Pharmaceuticals, Japan] a D2/5-HT_{2A} receptor antagonist), talnetant (the GlaxoSmithKline NK3 receptor antagonist discussed above, SB-223412), secretin (Repligen RG1068 endogenous pancreatic hormone for psychosis and autism).

CHALLENGES OF DRUG DISCOVERY

Target identification and validation

Until recently, new therapies emerged from the serendipitous discovery of chlorpromazine as an antipsychotic and a quest to discover new drugs that lack the extrapyramidal motor side effects of the older, so-called, typical antipsychotics. It is true that the atypical antipsychotics have provided a significant benefit to the patient via not only better therapeutic margin but also somewhat better efficacy at treating the negative symptoms of schizophrenia. However, future drug discovery approaches have to be truly revolutionary, and this will require target identification and validation methods based on a better understanding of the pathogenesis of the disease. Clearly, an understanding of the genetic etiology of the disease is critical to be able to identify new targets in a pathogenic biochemical pathway. In fact, the success of the disease modifying therapy approaches for Alzheimer's disease is a testament to the ability to convert genetic breakthroughs into druggable approaches. Thus, the identification of familial mutations in amyloid precursor protein and presenilins in a small fraction of patients led to the

identification of a pathogenic biochemical pathway regulating A- β production or clearance and thereby identification of β and γ secretases as drug discovery targets (although none have reached registration status today). However, two factors are likely to hamper a similar breakthrough in schizophrenia research: 1) lack of a stable, objective phenotype associated with the disease pathophysiology (e.g., A- β deposition in Alzheimer's disease) and 2) absence of the Mendelian form of the disease. Nonetheless, the success of the recent molecular genetic studies suggests that a better understanding of the etiopathology of schizophrenia will likely be achieved in the recent future.

Limitations of animal models

The most commonly used animal models for antipsychotic drug discovery are based on pharmacological manipulation (typically psychostimulant-induced behaviors). These models traditionally have helped identify antagonists at dopamine D₂ or serotonin 5-HT_{2A} receptors, core pharmacological activity of FGA and SGA, respectively. A number of models are founded also on the neurodevelopmental hypothesis of schizophrenia.^{109,110}

Of these, the neonatal hippocampal lesioned rat represents a widely used model and is characterized extensively by Lipska et al.¹¹¹ However, this model, too, suffers from poor construct validity to be applied for new target discovery. Additionally, it is highly labor intensive and does not lend itself readily to drug screening. The end-points applied to these animal models vary from locomotor activity to pre-pulse inhibition of the startle response, the latter reflecting sensory gating deficits associated with schizophrenia.¹¹² However, the clinical translation of these end-points, with the exception of the pre-pulse inhibition, is poor. Thus, the biggest limitation for target identification and validation for novel drug therapies targeting unmet medical needs or disease modification is the lack of a disease etiology or pathology-based animal model. This is especially true for models of negative symptoms because in rodents these have to rely on anthropomorphized and nonspecific outcome measures such as social behaviors between rodents. The vast literature on animal constructs of cognitive behaviors have led generally to the expectation that models of cognitive deficits of schizophrenia should be relatively easier to simulate in rodent and nonhuman primates, thereby facilitating discovery of procognitive drugs. However, a number of animal tests have poor translatability to the clinical constructs, are not specific to a disease, have a small dynamic range, and are too complex to be reliably replicated between laboratories. Additionally, few have the requisite throughput for screening novel drug candidates. Thus, overall the progress for novel therapeutics for schizophrenia has been severely

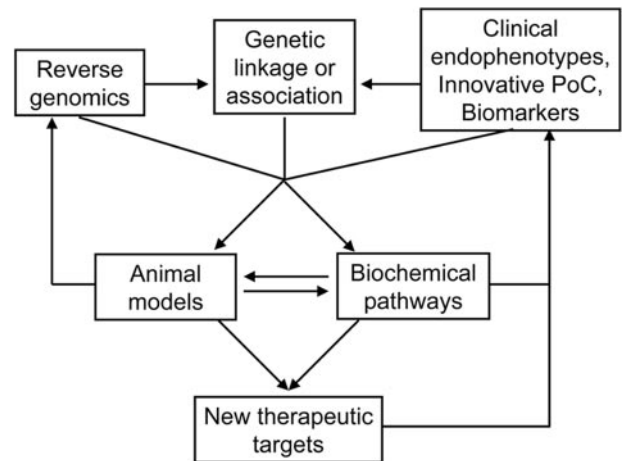


FIG. 1. A schematic diagram depicts a drug discovery and development approach based on emerging understanding of schizophrenia etiopathology.

hampered by the lack of predictive, reliable, and efficient animal models.

Clinical proof of concept studies

At a clinical level, cognitive dysfunction remains one of the most challenging areas for developing antipsychotic drugs. For the near term and given our poor understanding of the etiology of schizophrenia, it would appear unlikely that a single treatment would target psychotic, negative, and cognitive symptoms. The more likely path toward success would be the development of novel drugs, that when added to SGAs, would result in significant cognitive improvement. A recent review from the MATRICS initiative described seven cognitive domains (working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, information processing speed, and social cognition) that should be targeted by a cognitive test battery.¹¹³ Keefe and colleagues¹¹⁴ have recently described a newly developed instrument, the Brief Assessment of Cognition in Schizophrenia, which appears to meet a number of criteria for a practical, reliable test with construct validity. It remains to be seen how well this instrument will predict outcome for SGAs or novel therapeutic agents.

EMERGING OPPORTUNITIES FOR DRUG DISCOVERY AND DEVELOPMENT

Figure 1 schematically represents an approach of antipsychotic drug discovery and development that utilizes emerging understanding of the disease pathophysiology from genetic, genomic, and clinical research. As discussed above and depicted in the figure, these studies have led to and in the near future could provide further

refined, testable hypothesis for the biochemical pathways associated with the disease etiology and/or progression. Two emerging areas most likely to be affected by these new discoveries as well as most critically needed to revolutionize antipsychotic drug development are animal models and clinical proof of concept studies as discussed below.

Genetic etiology-based animal models

Generation of genetic etiology-based rodent models (e.g., neuregulin knockout) and their careful phenotypic characterization by a combination of behavioral, physiological, and functional neuroanatomical end-points chosen on the basis of clinical studies of schizophrenic patients will help establish a model with construct and face validity to facilitate novel target validation and drug screening. In choosing the end-points, it would be critical to include those with a reasonable clinical counterpart (e.g., pre-pulse inhibition for sensory gating deficits). Additionally, such models may be used to identify new targets by the application of global, unbiased techniques such as gene chip microarrays to identify target pathways associated with genetic vulnerability factors. Here again, the field is ripe to take advantage of the recent advances in the technology and its successful application to studies of genomic alterations in postmortem schizophrenic brains^{115,116} to assess or establish the validity of the various animal models. Finally, the validated animal models are critically needed to discover biomarkers of disease progression. Applying lessons from progressive neurological disease such as Alzheimer's disease, it may be possible, some day, to use the animal model(s) to identify a biochemical marker in the CSF that correlates with the disease phenotype. A targeted or unbiased proteomic and/or metabolomics approach may yield valuable information on disease-associated biochemical alterations in an accessible, relevant compartment.

Clinical proof of concept studies—endophenotypes and pharmacogenomics

The heterogeneity of schizophrenia raises serious question as to whether simply identifying endophenotypes for schizophrenia (e.g., neuropsychological instruments, pursuit eye movements, P50 auditory event-related potentials) will be a sufficient strategy to lead to therapeutic breakthroughs.¹¹⁷ A recent example involving a functional polymorphism [Val (108/158)Met] in the COMT gene addresses how genomic stratification may provide links to prefrontal physiology, cognitive function, and clinical improvement.¹¹⁸ A successful study in a genomically stratified population would lead to further widespread clinical phase 2 testing using genotyping strategies along with functional imaging to confirm and extend the initial proof of concept study.

CONCLUSIONS

In conclusion, the second-generation antipsychotic drugs represent a significant advance in the psychotherapeutics of schizophrenia. However, a major focus for future drug discovery and development efforts is on the unmet medical need of cognitive deficits and disease modification. Several recent advances in the field indicate that the latter objective may be attainable in the not too distant a future; some of the key advances include 1) identification of replicated genetic susceptibility factors; 2) better understanding of endophenotype-genotype correlations; and 3) accumulated experience in the use of unbiased techniques to assess changes in disease-associated transcriptome, proteome, and metabolome. Additionally, application of learnings from the successful and failed clinical trials to refine the disease model is critical to ensure success of future efforts. An area that needs further improvement to facilitate target and drug discovery is the development of animal models based on etiology and using clinically translatable end-points.

Acknowledgments: The authors thank Drs. Kjell Svensson and Kurt Rasmussen for critical reading of the review.

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