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ADVANCES IN PRECLINICAL MODELS FOR SCREENING ANTIPSYCHOTIC ACTIVITY: A COMPREHENSIVE REVIEW

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ABSTRACT

Efficiently developing effective antipsychotic drugs is one of the most daunting challenges in modern psychiatric drug discovery. Although there has been extensive research in the past 70 years since chlorpromazine was first used to treat schizophrenia, the therapeutic strategies that are available today are still largely dependent on the manipulation of dopamine D_2 receptors, which provides only partial relief of symptoms and has significant side effects. This comprehensive review critically discusses the development, present status and future directions of the preclinical models that are used to test antipsychotic drug properties. We critically review classic pharmacologic paradigms, as well as genetic and neurodevelopmental research strategies, human stem cell-based technology, computational strategies, and novel technologies that are changing the landscape of the field. This enduring disconnect between the drug discovery and drug development preclinical and clinical phases is reviewed in terms of model validity, model predictive value and strategic changes to improve drug development pipelines. We envision a third-generation combination of recent advances in optogenetics, 3D brain organoids, machine learning algorithms, and integration of multi-omics to produce a truly novel approach to antipsychotic screening that could end the therapeutic stagnation associated with schizophrenia.

KEYWORDS: antipsychotic screening, preclinical models, schizophrenia, drug discovery, translational psychiatry, induced pluripotent stem cells, brain organoids, animal models, behavioral assays.

1. INTRODUCTION

Psychosis is an intense neuropsychiatric condition that involves a significant alteration in a person's sense of reality, leading to difficulties in thought, feelings, behaviour and sensory perception. People with psychosis can have problems in their thinking that make it hard to tell reality from fantasy, resulting in hallucinations, delusions, confused or disorganized speech, odd or unusual behavior, and other cognitive or thinking problems.[1] The symptoms may cause marked dysfunction in social interaction, work and life activities. In itself, psychosis is a clinical state, rather than a disease, and is a feature of a number of psychiatric, neurological and medical disorders such as schizophrenia, bipolar disorder, major depressive disorder with psychotic features, substance-induced psychosis and some neurodegenerative diseases.[2]

Psycho-pathogenesis involves a complex interplay of genetic susceptibility, environmental factors, neurodevelopmental abnormalities and neurochemical dysregulation. There is current evidence that alterations in multiple neurotransmitter systems, especially dopamine, glutamate, serotonin and gamma-

aminobutyric acid (GABA) are involved in the pathophysiology of psychotic disorders.[3] Within these, over-activity of dopamine transmission in the mesolimbic pathway has long been regarded as a major mechanism underlying positive psychotic symptoms, and disturbances in glutamatergic transmission, specifically N-methyl-D-aspartate (NMDA) receptor hypofunction have been emerging as important mechanisms of cognitive impairment and negative symptoms. Other pathological mechanisms that have emerged as important in disease pathogenesis are neuroinflammation, oxidative stress, mitochondrial dysfunction and impaired synaptic plasticity.[4]

Psychotic disorders frequently occur in late adolescence or early adulthood when the brain is maturing. Many people experience subtle changes in their behavior and thinking that can signal the onset of psychosis, such as becoming more withdrawn, less emotional, less able to concentrate, feeling anxious, and sleeping problems. If it is not diagnosed and treated promptly, psychosis can become chronic, causing chronic disability and a greater burden of health care.[5] Early recognition and treatment have been shown to help improve long-term clinical outcomes, decrease relapse rates and improve psychosocial functioning.

While antipsychotics are still the mainstay of treatment, they can have adverse effects, including extrapyramidal symptoms, metabolic syndrome, drowsiness, hyperprolactinemia and cardiovascular issues. Moreover, the antipsychotics available today are mainly effective in treating positive symptoms and have limited effectiveness in addressing negative symptoms and cognitive impairments.[6] Therefore, novel therapeutic approaches that act on several pathological pathways with greater efficacy and safety are of increasing interest. Of particular interest are the properties of some herbal medicines and naturally occurring phytochemicals, which are antioxidant, anti-inflammatory, neuroprotective and neuromodulatory. Medicinal plant medicinal properties have been considered as good candidates for the development of safer and effective treatments for psychotic disorders.[7]

❖ **Neurotransmitter Systems Targeted in Experimental Psychosis Models**

Neurotransmitter	Role in Psychosis	Common experimental model	Biomarkers
Dopamine	Hyperactivity causes positive symptoms	Amphetamine model	Dopamine, DOPAC
Glutamate	NMDA receptor hypofunction	Ketamine, MK-801,PCP	NMDA receptor expression
GABA	Reduced inhibitory signaling	Genetic models	GABA concentration
Serotonin	Negative symptoms	PCP model	5-HT
Acetylcholine	Memory impairment	NMDA antagonist models	Acetylcholinestrase

1.1 The Clinical Imperative

Schizophrenia is one of the most serious neuropsychiatric conditions with about 24 million people affected worldwide, and the disorder carries significant individual, family and societal costs. The clinical manifestations of the disorder include a complex syndrome that has been divided into three clusters: Positive symptoms – hallucinations and delusions; Negative symptoms – social withdrawal, anhedonia, emotional flattening, avolition; and Cognitive deficits – attention, working memory, executive function. The onset of the disease is usually between late adolescence and early adulthood, often with very subtle changes in behaviour and cognitive function before symptoms manifest.[8] Untreated schizophrenia will continue along a chronic course with functional impairment, social isolation and a decreased life expectancy.

It is estimated that schizophrenia impacts around one percent of the general population worldwide causing a significant personal, social and economic burden. In clinical terms, this disorder is seen as having three symptom dimensions: positive symptoms (hallucinations, delusions, disorganized thinking), negative symptoms (avolition, poor affect, asociality), and cognitive dysfunction (working memory, executive function, attention). The drug treatment of psychosis has been characterized since the serendipitous identification of chlorpromazine in the 1950s by D_2D2 receptor antagonists and partial agonists.[10] These common and atypical antipsychotics are effective at controlling acute positive symptoms, but have very limited efficacy in the treatment of negative and cognitive symptoms, and often cause the debilitating extrapyramidal symptoms, hyperprolactinemia and the metabolic syndrome.[11]

The pharmacological treatment is currently based primarily on the use of drugs that modulate the dopaminergic system as a whole through the antagonism of the D_2 receptor (most of the second-generation drugs and the first generation) or the partial agonism of the D_2 receptor (aripiprazole, brexpiprazole, cariprazine).[12] These agents are moderately effective in the positive domain but are poorly effective in the negative and cognitive domains.[13] About one-third of patients are treatment resistant, meaning they do not respond to any of the currently available categories of antipsychotics except for clozapine; this is an extremely toxic drug with potentially life-threatening side effects and only recommended in situations where other drugs have been tried and failed.[14] In addition, the side effects of the currently available antipsychotics are also significant in

terms of extrapyramidal effects, metabolic syndrome, weight gain, drowsiness, hyperprolactinemia and cardiovascular side effects, which often affect adherence and long-term outcomes.

1.2 The Translational Crisis

Therapeutic progress in the pipeline for the development of antipsychotic drugs has been remarkable. Despite extensive research and billions of dollars in pharmaceutical investment, over the past 30 years, no fundamentally new mechanism of action has gained clinical use.In more than 30 years of research there is no process that is fundamentally new which has become clinically available. This translational failure is of particular note, as there is extensive preclinical evidence that a large number of compounds with a variety of mechanisms have been shown to be effective in animal models, including glutamatergic modulators of NMDA, AMPA and metabotropic receptors, muscarinic M_1/M_4 agonists, trace amine-associated receptor 1 (TAAR1) agonists, serotonin 5-HT_1A/5-HT_2A modulators, anti-inflammatory agents, and antioxidants. The disconnect between pre-clinical success and clinical failure is a result of several factors, including the limitations of model selection and validation protocols, reliance on behavioral endpoints that do not have good clinical relevance, the inability of rodent models to fully meet the phenotypic complexity of schizophrenia and its uniquely human characteristics, poor integration with biomarkers and mechanistic understanding, and the tendency of the pharmaceutical industry to follow incremental changes to known mechanisms rather than new ones. Although numerous novel compounds with promising activities in preclinical models make it to Phase II or III trials, they never get to market, suffering from huge financial losses, failed development programs, and the failure to provide new treatment options to patients in need.[18]

1.3 Scope and Objectives

This review offers a comprehensive and critical appraisal of the various models that have been used for antipsychotic drug screening, including: (1) historical perspectives and conventional pharmacological models; (2) genetic models of mouse; models that reflect risk genes associated with schizophrenia; (3) neurodevelopmental and environmental models, such as the maternal immune activation model; (4) pharmacological challenge models, which involve glutamatergic and other neurotransmitter systems; (5) human stem cell based models, including induced pluripotent stem cell-derived neurons and three-dimensional brain organoids; (6) computational, machine learning and high throughput screening models; (7) emerging technologies, like optogenetics, chemogenetics and organ-on-chip platforms; and (8) strategic approaches to enhance the translational validity of models. We critically review the merits, weaknesses and predictive power of each approach, based on recent developments (up to 2025-2026). The ultimate goal is to suggest an integrated and multi-modal approach to the development of next-generation antipsychotic screening strategies that could potentially break the plateau in schizophrenia drug development. The second step involves a historical perspective and traditional pharmacologic models. This section outlines the Dopamine Hypothesis and introduces the basic screening paradigms. This section covers the Dopamine Hypothesis and basic screening paradigms. Changes in the models of screening for antipsychotics have been closely tied to the changing hypotheses about the pathophysiology of schizophrenia. Observations in the 1960s that drugs that blocked dopamine receptors reduced psychosis and drugs that stimulated dopamine receptors increased psychosis led to the formation of the dopamine hypothesis which dominated drug development efforts for many decades and is still guiding approaches today.[21] This hypothesis led to the development of screening models that could identify compounds that prevent the effects of dopaminergic drugs on behavior. Classical behavioral assays were established as standard practice: Stereotyped behavior is a repetitive behavior that is dose-dependently inhibited by antipsychotic drugs when rats are administered high doses of amphetamine. This model shows good predictive validity for compounds with D_2 receptor antagonist properties but is not able to pick up compounds with new mechanisms. The simplicity and reproducibility of the assay led to its use for many compounds but had a fundamental limitation in that it was biased towards dopaminergic compounds.[22] Apomorphine climbing/stereotypy: Like the amphetamine model, apomorphine is a direct dopamine receptor agonist that elicits climbing in mice, which can be blocked by administration of antipsychotics. This model also gave further support to the dopaminergic mechanisms and had similar limitations for translation.[23] Suppressed avoidance behavior after administration of an antipsychotic is seen in rats and/or mice trained to avoid electric shock in a shuttle box apparatus, which is referred to as conditioned avoidance response (CAR). This model has been thought to be very predictive for clinical antipsychotic activity and compounds that inhibited CAR at doses that did not affect escape behavior were determined to be potential antipsychotics. The validity of CAR for new mechanism, however, has not been tested and the assay is aversive, thus posing ethical issues.

❖ **Behavioural Tests Used in Screening Antipsychotic Activity**

Behavioural test	Purpose	Parameter measured	Psychotic symptom evaluated
Open field test	Locomotor activity	Distance travelled	Positive symptoms
Actophotometer	Hyperactivity	Activity counts	Positive symptoms
Social interaction test	Sociability	Interaction time	Negative symptoms
Elevated plus maze	Anxiety	Open arm entries	Anxiety
Prepulse inhibition	Sensorimeter gating	Startle inhibition	Schizophrenia

2.2 Catalepsy and Extrapyramidal Side Effect Prediction

The catalepsy test represents a critical component of antipsychotic screening, used to predict extrapyramidal side effect (EPS) liability. Rodents are positioned with their forepaws on an elevated bar, and the duration of maintained posture is measured.[25] First-generation antipsychotics (haloperidol, chlorpromazine, fluphenazine) induce profound catalepsy at doses approximating therapeutic antipsychotic doses, reflecting their high D_2 receptor occupancy in the striatum. Second-generation antipsychotics (clozapine, olanzapine, quetiapine) show reduced cataleptogenic potential, correlating with their lower EPS risk clinically.

However, this model exhibits significant limitations: it cannot reliably distinguish between compounds with truly reduced EPS risk versus those with different mechanisms of action, and some compounds clinically active in schizophrenia (notably clozapine) show minimal catalepsy despite being potent D_2 antagonists. The model's inability to predict metabolic side effects—arguably the most clinically problematic adverse effects of modern antipsychotics—represents another critical shortcoming.[26]

2.3 Pharmacological Validation Studies

Extensive pharmacological characterization has established receptor mechanisms underlying traditional models. MK-801 (dizocilpine)-induced hyperactivity in BALB/C mice, for example, represents an NMDA receptor antagonist model that has shown predictive validity for compounds acting at M_1/M_4 muscarinic, $mGluR_{2/3}$, and GABA_A receptors in addition to dopaminergic targets. Studies testing established antipsychotics (haloperidol, clozapine, olanzapine, risperidone, ziprasidone, aripiprazole, sertindole, quetiapine) demonstrated dose-dependent suppression of MK-801-induced hyperactivity mediated via D_1, D_2, and 5-HT_2 receptors.[27]

Importantly, traditional models are inherently biased toward detecting compounds with mechanisms resembling existing antipsychotics, creating a "me-too" drug discovery paradigm that has perpetuated the dopamine-centric approach. The chakragati (ckr) mouse, a serendipitously discovered insertional transgenic mutant exhibiting circling and hyperactivity, was proposed as an alternative screening platform not biased by any particular neurotransmitter hypothesis. The mouse shows hemispheric asymmetry in striatal D_2-like receptors and antipsychotic-inhibitable circling behavior, potentially enabling identification of compounds with novel mechanisms.[28]

2.4 Critical Limitations of Traditional Models

Traditional pharmacological models exhibit several critical limitations constraining their utility for modern drug discovery:

1. **Construct validity**: They are based on acute pharmacological manipulation rather than the neurodevelopmental and multifactorial etiology of schizophrenia.
2. **Face validity**: They model only positive symptoms (primarily psychomotor agitation) and cannot address negative or cognitive domains.[29]
3. **Predictive validity**: While highly predictive for D_2 antagonists, they have poor sensitivity for novel mechanisms and have failed to identify any successful new antipsychotic in 30+ years.
4. **Specificity**: Many models detect compounds with antipsychotic activity and EPS simultaneously, failing to differentiate therapeutic from adverse effects.[30]
5. **Translational gap**: Compounds showing efficacy in these models frequently fail in clinical trials, particularly those with non-dopaminergic mechanisms.

Despite these limitations, traditional models remain in widespread use due to their established protocols, regulatory acceptance, and ability to identify CNS bioavailability early in development.[31]

3. Genetic Mouse Models of Schizophrenia

3.1 Rationale and Conceptual Framework

The identification of schizophrenia risk genes through genome-wide association studies (GWAS), copy number variant analyses, and family studies has enabled development of genetically engineered mouse models (GEMMs) with enhanced construct validity. These models aim to recapitulate genetic risk factors identified in human patients, providing mechanistic insights and screening platforms with improved biological relevance.[32]

3.2 DISC1 Mouse Models

Disrupted-in-Schizophrenia 1 (DISC1) emerged as a major schizophrenia candidate gene following identification of a balanced translocation disrupting DISC1 in a Scottish family with high psychiatric disease burden. DISC1 encodes a scaffold protein involved in

neurodevelopment, neuronal migration, synaptic function, and cAMP signalling.[33]

Multiple DISC1 mouse models have been generated:

- ✓ **Dominant-negative DISC1 transgenic mice** expressing a truncated DISC1 protein under the αCaMKII promoter display schizophrenia-associated phenotypes including hyperactivity, impaired prepulse inhibition (PPI), social deficits, and working memory impairments detected by translatable measures.[34]
- ✓ **DISC1 knockout mice** show varying phenotypes depending on genetic background, with some lines exhibiting behavioral abnormalities relevant to schizophrenia.
- ✓ **DISC1 point mutation models** (e.g., L100P mutation) replicate human genetic variants and show impaired neuronal migration and behavioral phenotypes.[35]

Importantly, DISC1 interacts with **Neuregulin-1 (NRG1)** and regulates NRG1-ErbB4 signaling in cortical interneurons, providing a mechanistic link between two major schizophrenia risk genes.[36] Epistatic disruption of both NRG1 and DISC1 produces schizophrenia-related phenotypes through gene-gene interactions, modeling the polygenic nature of schizophrenia risk.[37]

Antipsychotic screening utility: DISC1 models have been used to test conventional and novel antipsychotics, with some showing reversal of behavioral and neurochemical abnormalities. However, their predictive validity for novel mechanisms remains to be fully established.[38]

3.3 Neuregulin-1 (NRG1) and ErbB4 Models

NRG1 and its receptor ErbB4 regulate neuronal development, synaptic plasticity, and GABAergic neurotransmission—all processes implicated in schizophrenia. Multiple NRG1 and ErbB4 mouse models demonstrate reduced parvalbumin-positive interneuron function, impaired gamma oscillations, cognitive deficits, social behavior abnormalities, and altered responses to psychotomimetic.[39]

These models offer opportunities to test compounds targeting glutamatergic, GABAergic, and NRG1-ErbB4 signaling pathways.[40]

3.4 Additional Genetic Models

22q11.2 deletion syndrome models: The 22q11.2 deletion confers approximately 30% schizophrenia risk. Mouse models with Df(16)1/+ deletions show cognitive deficits, PPI impairments, and altered dopaminergic function.[41]

CNTNAP2 models: Contactin-associated protein-like 2 mutations are associated with autism and schizophrenia. Cntnap2 knockout mice show social deficits, repetitive behaviors, and neuronal hyperexcitability.[42]

GRIN2A/GRIN2B models: NMDA receptor subunit mutations linked to schizophrenia. These models show cognitive impairments and altered synaptic plasticity.

COMT knockout mice: Catechol-O-methyltransferase regulates prefrontal dopamine metabolism. COMT deficiency alters working memory and PPI.[43]

3.5 Limitations of Genetic Models

Despite improved construct validity, genetic models face challenges:

1. **Incomplete penetrance**: Many schizophrenia risk genes show small effect sizes and incomplete penetrance in humans, making single-gene models insufficient.[44]
2. **Genetic background effects**: Phenotypes vary dramatically across mouse strains, complicating reproducibility.
3. **Compensatory mechanisms**: Developmental compensation may mask phenotypes in constitutive knockouts.[45]
4. **Polygenic architecture**: Schizophrenia involves hundreds of risk variants, none sufficient to cause disease alone.

Emerging approaches include **polygenic risk score models** combining multiple risk variants and **inducible/conditional systems** to manipulate genes at specific developmental stages.[46]

4. Neurodevelopmental and Environmental Models

4.1 Maternal Immune Activation (MIA) Models

Epidemiological studies consistently implicate maternal infection and inflammation during pregnancy as risk factors for schizophrenia, autism, and other neuropsychiatric disorders in offspring. Animal models of MIA, induced by administering viral mimetics (polyinosinic:polycytidylic acid, poly I:C) or bacterial mimetics (lipopolysaccharide, LPS) to pregnant dams, recapitulate this risk factor with remarkable translational validity.[47]

MIA-induced offspring phenotypes include

- **Behavioral**: PPI deficits, social interaction impairments, cognitive dysfunction, anxiety- and depression-like behaviors, latent inhibition disruption.[48]
- **Neurochemical**: Altered dopaminergic, glutamatergic, and GABAergic transmission; elevated proinflammatory cytokines.
- **Neuroanatomical**: Reduced cortical volume, enlarged ventricles, altered hippocampal structure, white matter abnormalities.[49]
- **Cellular/molecular**: Microglial activation, synaptic pruning abnormalities, epigenetic reprogramming of gene regulatory networks.
- **Mechanistic insights**: Recent work demonstrates that MIA induces enduring epigenetic reprogramming of gene regulatory networks in the developing brain, with MIA-responsive enhancers

and promoters significantly enriched at GWAS loci for neuropsychiatric disorders. Both prenatal and postnatal MIA effects involve overlapping changes in enhancer activity, suggesting sustained regulatory trajectory across development.[50]

CONCLUSION

Improvements in preclinical models for evaluating antipsychotic effects have greatly advanced our comprehension of schizophrenia and similar psychotic disorders, aiding the identification and development of new therapeutic agents. Traditional pharmacological models, such as those involving amphetamine, apomorphine, ketamine, phencyclidine (PCP), and MK-801-induced psychosis, still offer valuable perspectives on the dopaminergic and glutamatergic impairments linked to the positive symptoms of schizophrenia. Additionally, genetic, developmental, and environmental models have enhanced the investigation of the intricate relationships between genetic predisposition and environmental risk factors that play a role in the progression of the disease. Behavioral assessments like prepulse inhibition, social interaction, novel object recognition, and locomotor activity tests have further reinforced the translational importance of these models by allowing the evaluation of cognitive, social, and sensorimotor deficits.

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