



Review Article

VALIDATION OF SCREENING MODEL OF ANTI PSYCHOTIC DRUG: A REVIEW

Ankita Tripathi *, Utsav Gupta, Meenaskhi, Shallu Sharma, Bhakti Pandey, Pooja Chaurasiya, Nandini

IIMT College of Pharmacy, Greater Noida, India

*Corresponding Author Email: ankita.surendra@gmail.com

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ABSTRACT

Psychosis is a generalized term which used to describe the abnormal mental state. It is a common and functionally disruptive symptom of a variety of psychiatric, neurodevelopmental, neurologic, and medical conditions, as well as an important target for diagnosis and treatment in neurologic and psychiatric practice. Therefore, to treat the psychosis condition anti-psychotic medications are deployed these drugs in general work on different receptors of brain like the dopamine receptor to ease the psychotic conditions. Since these drugs work directly on the brain receptors the validation of screening models of anti-psychotic drug become really important and for that in broadly two ways are mainly approached i.e, the In-silico study where docking is deployed and the animal models' utilizations to study the effectiveness and toxic effect of drugs. Hence, in this article brief history of psychosis is discussed along with the approaches that validated the screening model of anti-psychotic drugs.

Keywords: validation, screening models, anti-psychosis, In-silico models, animal models

INTRODUCTION

The term "psychosis," which comes from the Greek word for "abnormal mental state," has been used in clinical medicine in a variety of ways.¹ Psychosis is a prevalent and functionally disruptive symptom of a wide range of psychiatric, neurodevelopmental, neurologic, and medical diseases, as well as an essential target for diagnosis and therapy in neurologic and psychiatric practice.²

Hence, to treat the psychotic conditions Antipsychotic medications are effective in the treatment of a variety of severe mental diseases. Short-term therapies of acute psychotic, manic, and psychotic-depressive disorders, as well as agitated states in delirium and dementia, and long-term treatment of chronic psychotic illnesses such as schizophrenia, schizoaffective disorder, and delusional disorders, are all possible applications. In clinical practice, newer "second-generation" antipsychotics have essentially supplanted earlier phenothiazine, thioxanthene, and butyrophenone neuroleptics.³⁻⁴ A key 1988 research demonstrated that clozapine was more effective than chlorpromazine in schizophrenia patients resistant to high doses of haloperidol and had none of the negative neurologic effects associated with previous antipsychotics.⁵ Clozapine was thought to be "atypical" in that it had a very low likelihood of extrapyramidal side effects. Despite their obvious chemical, pharmacologic, and clinical variability, this word has been used widely and indiscriminately to antipsychotic medicines launched in the last decade.⁶

Since the anti-psychotic drugs work directly on psychotic disorders. The validations of screening models of anti-psychotic drugs become really important. Hence, different screen models like In-silico and animal models are utilized to validate the anti-psychotic drugs. Therefore, in this article we will discuss about the history of psychosis and the validation of screening models of anti-psychotic's drugs in brief.

History of psychosis

Psychosis was described extensively in early editions of the American Psychiatric Association's (APA's) Diagnostic and Statistical Manual of Mental Disorders (DSM)⁷ as "gross impairment in reality testing" or "loss of ego boundaries" that interfered with the ability to satisfy routine living demands. This method of diagnosing psychosis focused on the presence of functional constraints rather than the symptoms that were thought to be the cause.⁶ and has muddled the line between psychotic and nonpsychotic mental diseases much too often. Simultaneously, the International Categorization of Diseases, Ninth Revision (ICD-9), released in 1975) used the then-standard distinction between "neurosis" and "psychosis" in its classification of mental diseases, although making no attempt to define these words.⁸ As a result, the early versions of the DSM and the ICD-9 included an unduly broad definition of psychotic illnesses, which proved impractical in clinical, research, and epidemiologic initiatives.⁸⁻⁹ Both the APA¹⁰ and the World Health Organization⁸ define psychosis narrowly in their present definitions, requiring the presence of hallucinations (without understanding of their pathologic character), delusions, or both hallucinations and delusions.⁹ Impaired reality testing remains important to psychosis in both of these current diagnostic categorization schemes. In contrast to previous diagnostic categorization methods, the current systems^{8,10} operationalize impaired reality testing by detecting the symptoms that indicate impairment. Delusions (i.e., fixed erroneous beliefs) are indicators of defective reality testing by definition: delusional beliefs are those that are held persistently in the face of incontrovertible evidence contradicting them. Similarly, hallucinations (perceptions that occur in the absence of external or somatic stimuli) are evidence of a distorted reality when the person experiencing them is unable to realize that they are hallucinatory. Both the current APA¹⁰ and World Health Organization⁸ classification systems recognize that "formal thought disorder" (i.e., disorganized thinking, including illogicality, tangentiality, perseveration, neologism, thought

blocking, derailment, or some combination of these thought disturbances) is one of several commonly co-occurring features of psychotic disorders.²

Validation of screening models of anti-psychotic drugs

In-silico models

Virtual screening is a common approach in drug development that is used to find new compounds that target a certain protein of interest.¹¹ Computational screening technologies have acquired widespread adoption because, when compared to high-throughput screening procedures, they may save time and money by reducing the number of chemicals that must be examined experimentally.¹² Virtual screening may be divided into two types: ligand-based and structure-based virtual screening.¹³ If the 3D structure of a therapeutic target is available via experimental research (e.g., X-ray crystallography) or molecular modelling, the latter can be utilized (homology modeling).¹³ High-throughput docking is the method of choice if a 3D structure of the target is known via experimental or molecular modelling research.¹⁴

By employing a homology model of the dopamine D2 receptor based on the dopamine D3 receptor template, a successful structure-based virtual screen for competitive antagonists of the dopamine D2 receptor. Ten of the twenty-one substances examined were shown to exhibit affinity for the dopamine D2 receptor as well as other antipsychotic receptors (5-HT_{1A}, 5-HT_{2A}, D₁, and D₃). Even though a protonatable nitrogen atom is a critical component of the standard pharmacophore model, one of the most potent molecules is an orthosteric dopamine D2 receptor ligand without it. When compared to known ligands from ChEMBL, all the molecules exhibit significant chemical originality.¹⁵

Animal models

Antipsychotic medication effectiveness tests on animal models

Antipsychotic activity in laboratory animals is determined by determining if a medicine can prevent or reverse behavioural changes that can be generated by the pharmacological drugs outlined above. The conditioned avoidance response (CAR), stereotypies, hyperlocomotion, and disruption in the startle reflex's prepulse inhibition are all important (PPI).¹⁶

Conditioned avoidance response

To cause a behavioural anomaly in the CAR, no additional pharmaceutical intervention is required (i.e., it is not a pharmacological model). This is one of the earliest and most well-known tests for predicting antipsychotics' therapeutic effectiveness.¹⁷ Animals in the CAR are taught to avoid unpleasant stimulus, such as an electric shock, by performing a precise behavioural response in a shuttle box, such as going to the opposite side of the box.¹⁸⁻¹⁹

Antipsychotics block the CAR in levels that don't interfere with escape after stimulus onset and have a good correlation with clinical doses.¹⁷ Surprisingly, the proportion of striatal D2 receptor occupancy necessary to block the CAR is approximately 70%, which is comparable to the threshold required for antipsychotics to have a therapeutic impact in people.^{17, 20-23} Furthermore, because sedative medicines (e.g., benzodiazepines) generally decrease both the avoidance and escape reactions, this paradigm does not provide false-positive results. This methodology is reliable for discovering novel medications in terms of predictive validity, as well as being simple, rapid, and low-cost.¹⁷ Its face legitimacy, on the other hand, is poor.¹⁶

Stereotypies

Stereotypy is defined by repeated, unvarying, and functionless behaviour, which is a unique hallmark of schizophrenia. Stereotypy has lately been characterised as a set of strictly repeating motor acts, separating it from perseveration, a cognitive habit.²⁴ It may be generated in rats and manifests as licking of the paws, sniffing, and biting the cage bars, all of which are normal behaviours for this species. Direct (apomorphine) and indirect (amphetamine) dopaminergic agonists can cause these reactions. They appear to be caused by the activation of D2 receptors in the dorsal striatum rather than the nucleus accumbens, which is thought to be the location of antipsychotic medication therapeutic action.²⁵

The benefit of this test is that stereotypies may be easily measured by a skilled observer at a low cost and with quick findings. The ability of antipsychotic medicines to reverse this behaviour proves its predictive value. Nonetheless, the fact that this behaviour appears to be dependent on dopaminergic activity in the dorsal striatum rather than the nucleus accumbens (the alleged location of antipsychotic medication action) suggests that it has limited construct validity.²⁵

Hyper locomotion

Certain medicines may cause an increase in locomotion in experimental animals, which might be typical of positive symptoms of schizophrenia. Increased dopaminergic activity in the mesolimbic pathway leading to the nucleus accumbens causes this reaction.¹¹ Direct and indirect dopaminergic agonists^{19,25} as well as NMDA receptor antagonists,²⁶⁻²⁷ can elicit it.

Treatment with both conventional and atypical antipsychotics effectively prevents hyperlocomotion, proving its predictive value.^{18, 25, 28} However, substances that have sedative effects may produce false positives. As a result, assessing the effects of potential medications on baseline spontaneous locomotion is a required control to confirm that the reversal of hyperlocomotion is not due to the drug's sedative properties. Another issue is the lack of consistency for test length, room light intensity, and arena size, among other things.

Despite these flaws, this test is inexpensive and easy to repeat. Furthermore, because this reaction is simple to measure, it is suitable for early screening of novel candidate antipsychotic medications in rats and mice.²⁹ Locomotion can be measured in a round or square arena or in an open field, where automated tracking devices allow for quick and accurate medication effects analysis. This can be done by recording a standard arena with a camera and computer software, or by using an arena with laser beams that measure the animals' horizontal and vertical movement.

Disruption of the startle response's pre-pulse inhibition

The PPI aims to investigate the information processing abnormalities that are common in schizophrenia patients. In most cases, loud, unexpected stimuli trigger a common reaction known as the startle reflex. The startle reaction is suppressed if the quick, strong startling stimulus (pulse) is followed by a lesser, nonstartling sensory signal (prepulse) (hence, prepulse inhibition). Patients with schizophrenia have a PPI deficit, which means they respond to the startle even when the pulse is preceded by a mild stimulus.^{19, 30, 31}

A contraction of the skeletal and facial muscles, similar to an eye-blink reaction, can be used to evaluate the startle reflex in

humans. This effect may be measured in laboratory mice and rats using comparable stimuli (tone presentations) and quantifying the startle by placing the animal on a platform that monitors its movement.^{30, 32} Because of its face validity, this exam has gotten a lot of attention. Nonetheless, it necessitates the purchase of a more expensive device (the startle box), as well as the monitoring of pharmacological effects on the startle response. When a medicine restores PPI (in the prepulse-pulse sequence) without interfering with the response to the pulse alone, it is said to have a particular antipsychotic effect (which would be indicative of a motor impairing effect).

Tests that are related to schizophrenia's negative and cognitive symptoms

While not explicitly connected to schizophrenia or antipsychotic action, several behavioral measures may be beneficial in predicting effectiveness against negative symptoms. Most of them involve detecting the reversal of impairments caused by sub-anesthetic NMDA antagonist dosages. The social interaction test is one such example. Treatment with ketamine, phencyclidine, and dizocilpine reduces social contact in rats, but antipsychotics restore it. Surprisingly, the results with atypical antipsychotics have been more consistent.^{25, 33-35} Anxiolytic medications also boost social interaction in rats, therefore this function isn't exclusive to this family of pharmaceuticals. In any event, this test is important since existing antipsychotic medications only have a limited effect on negative symptoms.

Similarly, existing medications do not enhance cognitive impairment, which is a major sign of schizophrenia. As a result, medicines that can alleviate learning and memory deficiencies in this disease are desperately needed. Several methods may be used

to cause memory deficiencies, which can then be assessed using the object recognition test and the Morris water maze. These tests aren't particular for antipsychotic medicines, which don't always correct memory problems. Other tests include the 5-Choice Serial Reaction Time Task, which is useful for investigating the attention process.^{29, 33-35}

Animal models to study cardiotoxicity caused by anti-psychotic drug

There are different animal models to study the toxicity caused by anti-psychotic drugs like rats, mice, zebrafish larvae and zebrafish.³⁶⁻³⁸ However, the reason for more focus on the zebrafish model is because of its short life cycle, small size, and high fecundity.³⁹ The zebrafish needs a small amount of habitat, little upkeep, and little manpower.⁴⁰

Antipsychotics are a family of drugs used to treat psychosis (delusions, hallucinations, or disordered thought), especially in schizophrenia and bipolar disorders, by reducing symptoms like hallucinations (both visual and auditory) and paranoid thoughts.⁴¹ However, the initial generation of antipsychotics has been linked to an increased risk of cardiovascular death owing to QTc interval lengthening, which can lead to TdP. Many antipsychotic medications have had to be pulled from the market, and the ICH E14 advice has advocated undertaking a "thorough QT/QTc research" to see if the drug affects the QT interval since 2005.⁴²⁻⁴⁴ Early antipsychotic treatments had serious side effects, prompting researchers to continue their hunt for new therapies that would prevent serious ventricular arrhythmias and premature cardiac death. Functional and medication-related factors, rather than structural alterations, may be linked to cardioregulatory system dysfunction.⁴⁵

Table 1: Existing research on antipsychotic medication's cardiotoxicity

Models	Rats	Mice	Rats and mice	Zebrafish larvae
Antipsychotic study	Clozapine induces myocarditis, showing inflammatory responses, myocyte vacuolar degradation and myofiber necrosis	7- or 14-days clozapine daily treatment causes myocarditis as well as inflammatory lesions after	Histological determination of cardiotoxicological effect of antipsychotic as aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone	Cardiotoxicological effects of first-generation antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone) on heart rate, morphology and motility
Reference	36	37	37	38

Certain antipsychotics have been studied in mammalian models for cardiotoxicity [Table 1]. Clozapine, for example, was discovered to cause myocarditis in rats, resulting in an inflammatory response, myocyte vacuolar degradation, myofiber necrosis, and interstitial fibrosis.³⁶⁻³⁷ similarly, clozapine has been shown to have a cardiotoxic impact in rats, with myocarditis and inflammatory lesions being detected after 7 or 14 days of daily treatment with 5, 10, or 25 mg/kg dosage.

Despite these findings, there is a paucity of comprehensive evidence of antipsychotic medications' cardiotoxicological effects. Antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, on the other hand, have not been studied for cardiotoxicity in rats, owing to the high expense of such studies. As a result, most investigations on the cardiotoxicity of these medicines in rats have focused on histological analysis, which has resulted in a limited knowledge of their cardiotoxic effects.⁴⁶⁻⁴⁷ this emphasizes the need for more cost-effective models for these investigations.

For these reasons, the zebrafish appears as a particularly suitable model for antipsychotic toxicity investigations. Despite the fact that mammalian toxicity studies are still the gold standard for risk assessment, the zebrafish has emerged as a viable model due to

the toxic reactions that appear to be quite similar in mammalian and zebrafish. Aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone have all been shown to have cardiotoxicological effects.⁴¹

As a result, using the zebrafish as a model in this research will allow for a more thorough, simple, and complete understanding of drug cardiotoxicity, resulting in a deeper comprehension of the process. Similarly, the zebrafish is an appealing screening tool for assessing cardiovascular risk following treatment with atypical antipsychotic medications since it allows for the measurement of heart rate.⁴⁸⁻⁴⁹

CONCLUSION

The psychosis is a very serious conditions where the patients in generalized term suffer a lot of mental stress. Hence, the main of the antipsychotic drugs is to target the dopamine receptors in such a way that patients feel relieved. However, with time it was observed that new drugs are becoming the need of the hour. Hence, to accelerate the research process In-silico model study was utilized which gave some promising results. Along with that the animal model studies also reveal a lot of finding like from drug action studies to their toxic effects. Hence, these models are

widely utilized, and their results help in the validation of screening models of anti-psychotic drugs.

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