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Understanding Existing Antipsychotics and Newer Drug Targets in Schizophrenia

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ABSTRACT

Schizophrenia is a chronic, debilitating, prototypic psychotic disorder, which has antipsychotics as the mainstay of treatment. Antipsychotics are broadly divided into two: typical and atypical. While typical drugs were popular in clinical practice until a few years ago, there are slowly being replaced by the atypical drugs, mainly because of improved efficacy and lesser incidence of extra-pyramidal symptoms. However, the newer drugs have their own demerits, in the form of other adverse effects, like metabolic syndrome, QT prolongation and sudden death. Several newer targets have been identified in the field, which might help in bringing about drugs with improved efficacy and safety parameters.

Keywords: Clozapine, Olanzapine, Risperidone, Quetiapine, Psychosis.

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INTRODUCTION

The history of pharmacotherapy in psychiatry is lit up by two significant milestones at two different time points, the first being the discovery of chlorpromazine's antipsychotic property and the second being the introduction of clozapine (and other newer drugs) into clinical practice. Antipsychotics came into existence when serendipity smiled at science, and revealed the antipsychotic effects of chlorpromazine, when the drug was actually being tested for its antihistaminic value [1,2]. Following this, several drugs came into popular practice under various names including "neuroplegics", "neuroleptics", "major tranquillizers", "ataractics", "anti-schizophrenics" and "antipsychotics" [3]. Antipsychotics are further divided into typical and atypical drugs. This review focuses on the existing pharmacotherapeutic concepts and various newer targets in the treatment of schizophrenia. Detailed information on individual antipsychotics is beyond the scope of this article.

Schizophrenia

Schizophrenia is the most common psychosis, making it the prototypic psychotic disorder. The worldwide prevalence of the disease is approximately 1%. The disease most commonly sets in during the adolescent period, and is multifactorial in aetiology, with genes and environment being the most influential factors [4]. As schizophrenia is a psychosis, it retains the basic highlight of any psychosis, i.e., there is a characteristic loss of insight (awareness of one's own illness) [5,6]. Schizophrenic patients present with various symptoms, which may be grouped under the following [7]:

- a. Positive symptoms like hallucinations, delusions, etc.
- b. Negative symptoms like apathy, anhedonia, social withdrawal, etc.
- c. Cognitive symptoms like learning difficulties, memory impairment, etc.
- d. Affective symptoms like depressed mood
- e. Aggressive symptoms like physical violence

All the above symptoms lead to functional impairment on the part of the schizophrenic patient, making it mandatory to initiate a wholesome approach towards management. Ideal management of schizophrenia includes administration of antipsychotics, psychotherapy and rehabilitation [7].

ANTIPSYCHOTICS: NOMENCLATURE

The modern term of "antipsychotics" has been preceded by various other terms, which are explained here [8].

- Neuroplegics – Since these drugs seemed to cause paralysis or weakness of the central nervous system (CNS), they were initially known as neuroplegics. At a later stage, it was discovered that these drugs do not actually depress the CNS.
- Neuroleptics – Neurolepsy is seen in animal models, and is said to be the equivalent of the extra-pyramidal symptoms (EPS) seen in humans. Since the early antipsychotic drugs were known to produce EPS, they were called neuroleptics. This term slowly faded out of common parlance once newer drugs (which do not produce this effect) were slowly creeping into the picture.
- Major tranquillizers – As these drugs produce a calming effect in patients with psychosis (i.e., calms the mind, without significantly altering the consciousness level), they were called as major tranquillizers (while the minor tranquillizers were drugs like benzodiazepines).
- Ataractics
- Anti-schizophrenics – The initial school of thought was that "all psychoses are schizophrenia", hence the name. Later, it was evident that schizophrenia is only one form of psychosis.

- Antipsychotics – After taking several forms, these drugs have finally been christened as “antipsychotics”.

The Role of Dopamine

Dopamine Pathways

Dopamine is believed to play a central role in the pathogenesis and management of schizophrenia. Before we delve into the pathogenesis of schizophrenia, we will have to decipher the various dopaminergic pathways in the CNS. There are at least six different pathways related to dopamine, as listed below [9,10].

- Mesolimbic pathway – This pathway arises from the ventral tegmental area (VTA) and ends in the limbic system. This pathway is said to be involved in normal reward system and various human emotions. Nucleus accumbens (which goes by the eponym of “reward centre”) is anatomically and functionally related to this pathway.
- Mesocortical pathway – This pathway starts in the VTA and ends in the cortex. The main branch gives two leaflets, one to the ventromedial prefrontal cortex, and the other to the dorsolateral prefrontal cortex.
- Nigrostriatal pathway – This dopaminergic pathway finds its birth in the substantia nigra and moves towards the corpus striatum. It is linked to preservation of normal movement of humans.
- Tuberoinfundibular pathway – It arises from the hypothalamus and ends in the pituitary gland. This pathway plays a key role in prolactin secretion.
- Medulloperiventricular pathway – The significance of this pathway is unclear, but scientists have elucidated that it may be associated with eating behavior.
- Incertohypothalamic pathway – The functional significance of this pathway is not well established in the human species. However, rodent studies have shown that this pathway is linked to copulation.

Dopamine Receptors

Till date, there have been five distinct types of dopamine receptors, identified in humans. They have been labeled as D₁ to D₅. They can be grouped into two broad categories: D₁-like and D₂-like receptors. D₁ and D₅ belong to the former, while D₂, D₃ and D₄ belong to the latter. This classification is chiefly based on the type of GPCR (G-protein coupled receptors) each receptor is. While D₁-like receptors are mainly G_s-coupled, the D₂-like receptors are G_{i/o}-coupled [11]. Every drug that is currently available as an antipsychotic is known to bind to dopamine receptors (with varied grades of affinity, majorly to the D₂ receptors), and hence alter dopaminergic transmission, which is abnormal in untreated schizophrenics [12].

Dopamine In Schizophrenia [2,4,7]

As mentioned earlier, dopamine plays a key role in the pathogenesis of schizophrenia. The “dopaminergic theory” of schizophrenia postulates that there is an increase in the dopaminergic transmission in the mesolimbic pathway, which leads to the development of positive symptoms. Also, there is a decrease in the dopaminergic transmission in the two mesocortical pathways, which lead to affective symptoms (chiefly due to ventromedial extension), cognitive symptoms (chiefly due to dorsolateral extension) and negative symptoms (both extensions). The nigrostriatal pathway and the tuberoinfundibular pathways are said to be untouched in untreated schizophrenic patients [13].

Table 1: Levels of dopamine in Schizophrenia

Dopamine pathway	Levels of dopamine in Schizophrenia
Mesolimbic	High
Mesocortical	Low
Nigrostriatal	Normal
Tuberoinfundibular	Normal
Medulloperiventricular	Unknown

This dopaminergic theory was framed based on the use of dopamine agonists (which increased the positive symptoms) and dopamine antagonists (which attenuated the positive symptoms) in animal and clinical models. Also, post mortem analysis of brain samples showed significant reduction in dopamine receptor numbers in the mesolimbic system following administration of dopamine antagonists. Similarly, in untreated schizophrenics, the level of dopamine and the number of receptors were both found to be high in the samples [10].

The chief demerits of this hypothesis are that it does not take into account the other chemicals involved in schizophrenia and does not explain the negative symptoms with as much clarity as it explains the positive symptoms. Further, atypical antipsychotics that act by non-dopamine-mediated mechanisms seem to have disproved this outdated hypothesis [14]. This led on to the development of alternate hypotheses for the development of schizophrenia, which are explained elsewhere in this review.

Antipsychotics & Dopamine [12]

As stated earlier, the chief abnormality in schizophrenia (that gives rise to positive symptoms) appears to be excessive dopaminergic activity in the mesolimbic pathway. Hence, antipsychotics are targeted against the dopamine (D₂) receptors, which are widely distributed in this pathway. This brings about a decrease in the abnormally high dopaminergic activity, thereby relieving the patient of positive symptoms [10]. But, since this pathway is involved in the normal reward mechanism (which requires ample quantity of dopamine), reduction in dopamine may lead to anhedonia in the subject, mimicking the negative symptoms of schizophrenia. Further, this may push the patient towards search of alternate sources of pleasure, like alcohol, nicotine and drugs with addiction liability [15].

However, in an untreated schizophrenic, there is a diminution in the dopaminergic activity in the mesocortical pathway (giving rise to negative, cognitive and affective symptoms), which is going to be further brought down by the antipsychotic agents (although this pathway has an abundance of D₁ receptors and minimal D₂ receptors). Hence, the use of antipsychotics (which act exclusively by D₂ antagonism) may actually worsen the clinical picture, and precipitate the negative symptoms [10].

The nigrostriatal pathway, which is virtually unaffected in untreated schizophrenics, is also subjected to the dopamine-antagonizing action of antipsychotic agents, thus resulting in a decrease in dopaminergic activity in the pathway. Dopamine normally keeps the acetylcholine levels in check (i.e., increase in dopamine causes a decrease in acetylcholine levels). But now, since the levels of dopamine are cut down (by antipsychotics that act exclusively by D₂ antagonism), there is going to a relative increase in the levels of acetylcholine. This gives rise to several movement disorders, which are grouped under a single roof called “extra-pyramidal symptoms” (EPS). EPS may either be acute (acute dystonia, Parkinsonism, akathisia) or delayed (tardive dyskinesia) [10,14]. EPS is treated using central anticholinergic agents. Also, a change in the antipsychotic treatment protocol has to be initiated.

The tuberoinfundibular pathway of dopamine, which is also unaffected in untreated schizophrenic patients, faces a similar reduction in the dopaminergic activity, on exposure to antipsychotics with exclusive D₂ blockade. Dopamine, which plays a role in inhibition of prolactin secretion, is reduced. This leads to hyperprolactinemia, which presents clinically as galactorrhoea (both in females and males), gynaecomastia and amenorrhoea, ultimately resulting in infertility [10,14].

Table 2: Levels of dopamine after administration of a typical antipsychotic agent

Dopamine pathway	Levels of dopamine after a typical antipsychotic administration
Mesolimbic	Normal / Low
Mesocortical	Low
Nigrostriatal	Low
Tuberoinfundibular	Low
Medulloperiventricular	Unknown

Atypicality

The drugs that have been stated so far as those with exclusive D₂ antagonism are the older antipsychotics, also called as the typical antipsychotics or first generation antipsychotics. Examples include chlorpromazine, haloperidol, etc. Conventionally, any antipsychotic that acts by mechanisms other than just dopamine antagonism is known as an atypical antipsychotic or second generation antipsychotic (sometimes, newer antipsychotic) [16]. The definition (or criteria) for this “atypicality” has not been put forth by experts in the field. However, from intense review of literature revealed four different ill-defined criteria for an antipsychotic to be labeled as “atypical” [12].

- A mechanism in addition to dopamine antagonism (most commonly, serotonin antagonism)
- Reduced risk of EPS and hyperprolactinemia
- Production of relief from both positive and negative symptoms
- Ability to treat drug-resistant schizophrenia

However, these are not established criteria, and till date, any drug that has been introduced after clozapine (the first atypical antipsychotic) has been assigned under the title of “atypical antipsychotics”.

The Role of Serotonin

Serotonin in Schizophrenia

The serotonin hypothesis of schizophrenia was the earliest of the various theories put forward by experts¹⁰. Although it was thought that there was some degree of disruption in the serotonergic activity, it was unclear about the location and the specificity of the abnormality. Then came the most widely accepted “dopaminergic overactivity hypothesis”.

Following this wide acceptance of the dopamine hypothesis, another theory for schizophrenia combining these two existing hypotheses was brought into the picture, and this was the “serotonin-dopamine” hypothesis of schizophrenia. This hypothesis gave an explanation to the various negative symptoms, as opposed to the simple dopamine hypothesis. Serotonin normally keeps the levels of dopamine in check, in the mesocortical and nigrostriatal pathways (mediated through the 5HT_{2A}). Hence, serotonin blockade here will cause an increase in the levels of dopamine. This increase in dopamine in the mesocortical areas will lead to relief of negative symptoms (which are seen due to deficiency of dopamine). Further, 5HT_{1A} receptors function as auto-receptors, thereby decreasing the release of serotonin from the presynaptic membrane, reflexly leading to an increase in dopamine levels [10,12,14].

Antipsychotics and Serotonin [10,12]

As mentioned earlier, serotonin blockade by the atypical antipsychotics will bring about relief in both positive and negative symptoms of schizophrenia.

Since serotonin antagonism causes an increase (or rather, prevents the decrease) in dopamine levels in the nigrostriatal pathway, the risk of developing EPS with the use of atypical agents is very low (since increased levels of dopamine equate to decreased levels of acetylcholine).

Once again, serotonin blockade in the tuberoinfundibular dopamine pathway causes inhibition of prolactin secretion, thus preventing the incidence of hyperprolactinemia.

Table 3: Levels of dopamine after administration of an atypical antipsychotic agent

Dopamine pathway	Levels of dopamine after an atypical antipsychotic administration
Mesolimbic	Normal / Low
Mesocortical	Normal
Nigrostriatal	Normal
Tuberoinfundibular	Normal
Medulloperiventricular	Unknown

Superiority of Atypical Antipsychotics

From the above deductions, it should be clear that atypical antipsychotics are (not entirely) devoid of EPS and hyperprolactinemia. In addition to this better adverse effect profile, these drugs also provide relief of both positive and negative symptoms (while the typical agents can conventionally eliminate only the positive symptoms). This has paved way for the preference of atypical agents over the typical ones, in the clinical setup [10,12,14].

Several studies have been conducted to compare the efficacy of the atypical agents with that of the conventional agents. Although the results obtained contradict one another, there seems to be at least a marginally better efficacy with the atypical drugs. Particularly, clozapine seems to be zooming well past the other drugs, in terms of efficacy end points in most studies. Clozapine is the “go-to” drug when there is a case of refractory schizophrenia, and also the only antipsychotic drug that can reduce suicidal ideations in schizophrenics. Thus, clozapine has a clear edge over all other antipsychotics [17]. But, it also appears to be a double-edged sword, as there are life threatening adverse effects like agranulocytosis and myocarditis, with its usage [18,19].

Olanzapine is another drug that has shown significant promise. It has been shown to be more efficacious compared to other antipsychotics (excluding clozapine), but there is lack of concrete evidence to support this statement [20]. Also, there are not many efficacy studies comparing the newer antipsychotics with the older ones, making it difficult to arrive at a definite conclusion.

The Downside of Atypical Antipsychotics

We have highlighted the advantages of using the atypical antipsychotics over the conventional drugs. But, this improved efficacy comes at a price. The atypical drugs are not entirely devoid of adverse effects. They have their own battery of adverse effects, as listed below.

EPS

The widespread general notion is that the atypical drugs are totally devoid of EPS. However, this is not entirely true, and is considered as a myth. Any antipsychotic (typical or atypical) has the potential to produce EPS. As evident from various studies, the incidence is lower with the atypical agents [21]. Risperidone (when given at a dose of >6mg/day) and olanzapine seem to exhibit a greater propensity to cause EPS, among the atypical drugs [14,22]; whereas, clozapine and quetiapine seem to be the safest among the atypical agents [17,23].

Table 4: Risk status of EPS among atypical antipsychotics

Drugs with high risk of EPS	Drugs with low risk of EPS
Risperidone Olanzapine	Clozapine Quetiapine

Hence, if a patient has to be switched over from a typical antipsychotic to an atypical antipsychotic because he/she has developed EPS, the drugs of choice would be quetiapine (preferred, as it is safer) and clozapine [17,23].

Hyperprolactinemia

Once again, the atypical antipsychotics are not completely free from prolactin disturbances. But, like with EPS, the risk is lower with the use of these drugs. Risperidone (when given at a dose of >6mg/day) and its derivative, paliperidone are the most commonly implicated atypical drugs in the development of hyperprolactinemia [22,24,25].

Table 5: Risk status of hyperprolactinemia among atypical antipsychotics

Drugs with high risk of hyperprolactinemia	Drugs with low risk of hyperprolactinemia
Risperidone Paliperidone	Clozapine Quetiapine Aripiprazole

Yet again, clozapine and quetiapine are said to “virtually lack” this adverse effect. Also, aripiprazole has not been accused of producing hyperprolactinemia²⁵.

Weight Disturbances

One of the most distressing problems with the atypical agents is their ability to cause clinically significant weight gain (although typical antipsychotics may also cause weight gain). Based on a 10-week study comparing the weight gain induced by various atypical drugs, we can conclude that clozapine and olanzapine are the drugs that cause maximal weight gain, followed by quetiapine and risperidone (even at low doses). The newer agents like aripiprazole, ziprasidone and asenapine seem to have the least effect on body weight [12,26].

Table 6: Risk status of weight gain among atypical antipsychotics

Drugs with high risk of weight gain	Drugs with low risk of weight gain
Clozapine Olanzapine	Aripiprazole Ziprasidone

Although the exact mechanism of antipsychotic-induced weight gain is unclear, it has been attributed to imbalance between energy intake and expenditure, probably due to action at two central receptors, H₁ and 5HT_{2c}. Both these receptors play significant roles in hunger and satiety in humans. Blockade at these sites may hence enhance appetite or decrease satiety, ultimately resulting in weight gain. Further, H₁ blockade also leads to sedation and decrease in activity, which could play a supportive role [27,28].

More recently, the roles of leptin and adiponectin are being studied in antipsychotic-induced weight gain. Leptin resistance has been found to be associated with schizophrenics on treatment with atypical drugs. Further research is needed to ascertain the relevance of the same [27,29].

Hyperglycaemia

Another significant adverse effect seen with the atypical agents is an increase in the blood glucose levels, either leading to diabetes mellitus, or worsening of already-present diabetic status. Again, clozapine and olanzapine are the drugs that are most likely to cause hyperglycaemia [17,20], whereas risperidone, ziprasidone and aripiprazole are relatively safer options [12,22].

Table 7: Risk status of hyperglycaemia among atypical antipsychotics

Drugs with high risk of hyperglycaemia	Drugs with low risk of hyperglycaemia
Clozapine Olanzapine	Risperidone Aripiprazole Ziprasidone

The exact cause of hyperglycaemia is not known, although it is widely believed to be due to insulin resistance, secondary to the weight changes. An alternate hypothesis is that M₃ blockade (seen with several atypical antipsychotics) might be responsible. M₃ receptors are present on the pancreatic beta cells. Blockade at this site will cause inhibition of insulin release, ultimately resulting in hyperglycaemia [29,30]. The limitation of this explanation is that it does not explain the hyperglycaemia seen with agents which have no / limited M₃ blockade. Also, antipsychotic-induced hyperglycaemia is known to be associated with increased levels of insulin in the blood, as evident from several studies. So, this hypothesis does not account for this hyperinsulinemia.

The most widely accepted hypothesis currently is that this adverse effect is mediated by an unknown receptor (labeled as “X”), which is believed to be present in the liver, adipose tissue and peripheral tissues as well. Due to an unclear mechanism, atypical antipsychotics act on this mysterious receptor, causing hyperglycaemia and hyperinsulinemia [12].

Hyperlipidemia

Hyperlipidemia is also more likely to set in with the use of clozapine and olanzapine, and least likely with risperidone, ziprasidone and aripiprazole [12,31].

Table 8: Risk status of hyperlipidemia among atypical antipsychotics

Drugs with high risk of hyperlipidemia	Drugs with low risk of hyperlipidemia
Clozapine Olanzapine	Risperidone Aripiprazole Ziprasidone

The major component that is elevated is the triglyceride quotient. Hypertriglyceridemia, with or without an elevation in the total cholesterol level, is the hallmark of antipsychotic-induced hyperlipidemia [32]. The reason for this elevation is unknown. However, it might again be secondary to the weight gain induced by atypical antipsychotics. A gene-mediated mechanism has also been elucidated, but not with much success. The sterol regulatory element binding protein (SREBP) is believed to be activated by the antipsychotic agent (on long term use), which results in an enhancement in the biosynthesis of cholesterol, fatty acids and triglycerides [33]. Also, leptin normally reduces biosynthesis of lipids. Antipsychotics, by unknown mechanism, can cause leptin resistance, resulting in hyperlipidemia [29].

Changes in Blood Pressure

Acute hypotension is commonly encountered with all antipsychotics, especially those that exhibit potent α -blockade [34]. But, paradoxically, increase in BP has also been reported, mainly with clozapine and olanzapine. As discussed earlier, these two agents are notorious in producing metabolic changes. Hence, this elevation in BP could be attributed to be secondary to the metabolic dysfunction [12].

The constellation of symptoms (obesity, hyperglycaemia, hyperlipidemia and hypertension) is collectively called as the metabolic syndrome, Syndrome X or Raven’s syndrome. Management of metabolic syndrome involves a multimodal approach, which includes exercise, dietary changes, insulin or oral hypoglycaemic agents, antihypertensives and lipid-lowering drugs. Also, the antipsychotic regimen has to be modified, based on the drug’s propensity to cause metabolic syndrome. Further, routine monitoring of the patients’ parameters is mandatory, as it is possible to detect metabolic syndrome at a very early phase [35,36]. If left untreated, the patient slips further down the “metabolic highway” [12].

Sedation

Sedation is another frequently seen adverse effect of antipsychotics. Agents with intense H_1 antagonism have a greater propensity to induce sedation. The degree of sedation varies from patient to patient. 5HT blockade may also have a role in the development of sedation, especially in drugs with weak antihistaminic action. Clozapine and quetiapine are well known sedative-antipsychotics [10,12,37].

Sexual Dysfunction

Sexual dysfunction seen with antipsychotics may be attributed to several reasons: α -blockade and anticholinergic properties, leading to erectile dysfunction; dopamine antagonism, leading to lack of pleasure and sexual drive; and hyperprolactinemia, leading to lack of orgasms and infertility [12,38].

QT Prolongation

QT prolongation and sudden death are major concerns with ziprasidone, quetiapine and risperidone among the atypical antipsychotics. However, thioridazine (a conventional antipsychotic) has the greatest propensity to cause QT prolongation [38].

Cataract

Quetiapine is the atypical drug that is most often linked with the development of cataracts [12,38]. This might be augmented by other risk factors for cataract development, like diabetes mellitus and hypertension. Olanzapine-induced cases of cataract formation are also available in the literature, although the causal relationship is not clear [38].

Agranulocytosis

Agranulocytosis is a serious adverse effect, as it can result in fatality. As of today, clozapine is the only antipsychotic that has been reported to have caused this adverse effect. It is because of this adverse effect that clozapine is not being used routinely, despite the drug's ability to treat drug-resistant schizophrenia [16-18].

Myocarditis

Myocarditis is another adverse that has been reported with the use of clozapine. However, the incidence seems to be low [16,17].

Newer Targets in Schizophrenia

All existing antipsychotic agents exert their antipsychotic action by interacting with dopamine D₂ receptors, with or without effect on additional receptors [39]. Most of the drugs under development at present seem to interact with receptors other than D₂. Hence, before delving further into the newer targets, we should focus on the "glutamate hypothesis of schizophrenia".

Glutamate Receptors

Glutamate receptors can be divided into two broad divisions based on the type of receptors present, i.e., GPCR or ligand-gated ionotropic. The GPCR glutamate receptors are known as the metabotropic receptors (further divided into at least 8 subtypes), whereas the ionotropic receptors may be of three types: NMDA type, AMPA type and kainite type (named after the ligand that binds to the receptor to activate it). The metabotropic receptors are found on both the presynaptic as well as the postsynaptic regions, whereas the others are located postsynaptically. Glutamate binds to all these receptors to bring about the action. NMDA receptors are special in that they need an additional chemical (to be bound at an allosteric site) to get activated. This additional chemical molecule is usually glycine, D-serine or D-cycloserine [40-42].

The Role of Glutamate

NMDA (a type of glutamate receptor) antagonists like ketamine and phencyclidine have been known to produce a state similar to that seen in schizophrenics. Positive, negative and cognitive symptoms were seen in experimental and clinical tests conducted with NMDA antagonists. Hence, it has been believed for ages that NMDA hypofunction (as evidenced by antagonism at NMDA) can result in schizophrenia. The NMDA receptors are linked to GABA interneurons, which are inhibitory in nature. Hence, when NMDA hypofunction is present, there is disinhibition of these GABA interneurons, resulting in an increase in the levels of dopamine (as well as glutamate and acetylcholine), thus precipitating schizophrenia [39, 40, 43-45]. Also, this hypofunction leads to accumulation of glutamate, resulting in excitotoxicity [40].

AMPA-Kines

As mentioned earlier, AMPA glutamate receptors are located on the postsynaptic membrane. Various target molecules are being tried as positive allosteric modulators (PAMs) at the AMPA receptors (as seen in Figure 1). Targeting and activating the AMPA receptor with these AMPA-kines increase the conduction, leading to stronger inhibition by the GABA interneurons. Hence, AMPA-kines will compensate for the NMDA hypofunction seen in schizophrenics [12,46,47].

Direct Glycine Site Agonists

NMDA receptors are also being targeted directly, but not on the glutamate site. The allosteric glycine site is the target of interest. Several agonists are under study for occupation of these sites, which will ultimately increase NMDA receptor signaling, hence relieving the hypofunctional state seen in schizophrenia (as seen in Figure 1) [12,43,47,48].

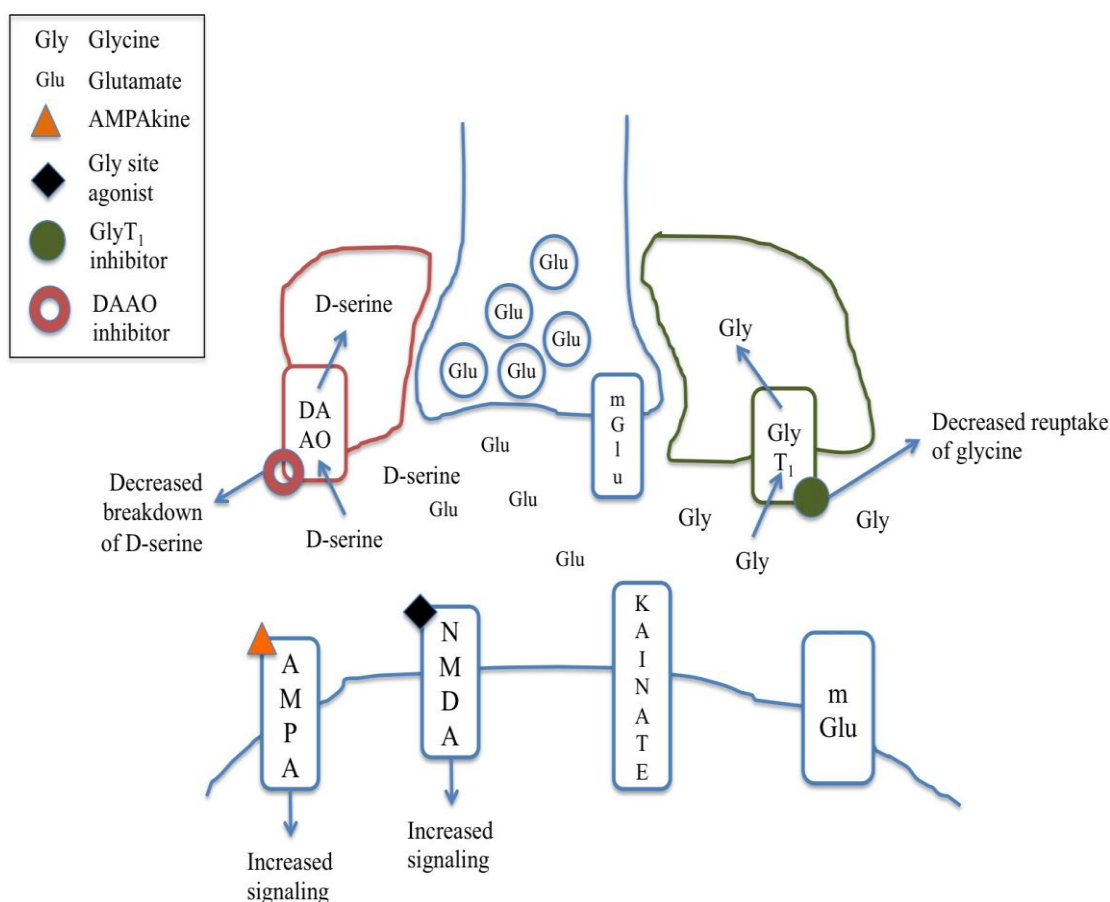


Figure 1: Schematic representation of newer targets in schizophrenia, based on NMDA hypofunction hypothesis

Inhibitors of Glycine Transporters

Excess of glycine from the synapse is normally removed by the glycine transporters (GlyT₁). Hence, inhibitors of this transport process will ensure the availability of more glycine in the synapse and postsynaptic membrane. Hence, more NMDA receptor activation occurs, nullifying the schizophrenic symptoms (as seen in Figure 1). This is one of the most promising approaches towards better pharmacotherapy of schizophrenia. Bitopertin and sarcosine are examples of drug molecules under trial^{12,40,47,48}.

mGlu Agonists

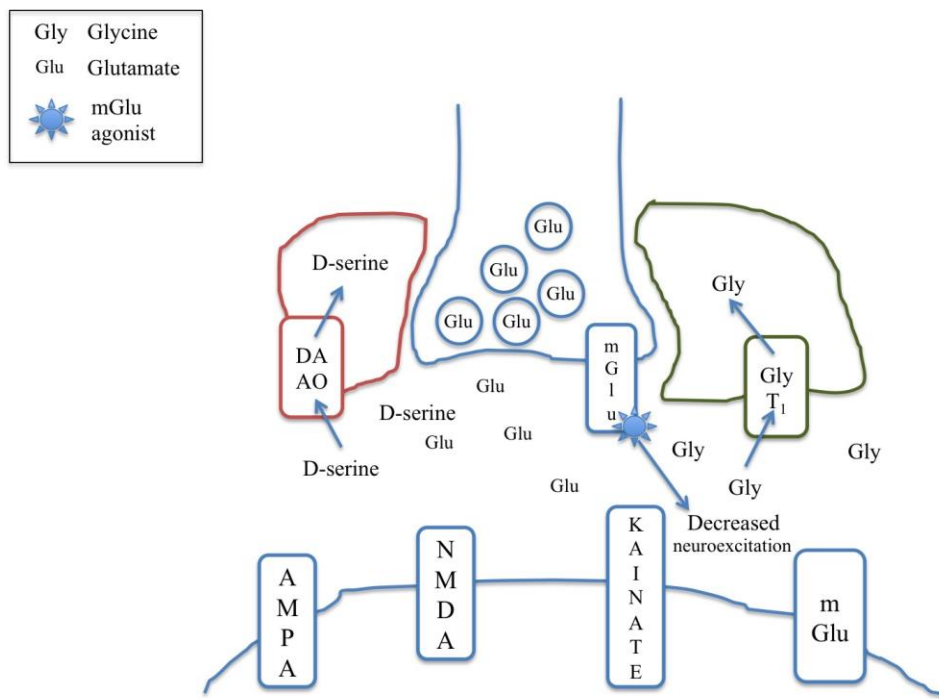


Figure 2: Schematic representation of the site of action of presynaptic mGlu agonists

We had mentioned earlier that NMDA hypofunction (evidenced by the use of ketamine or phencyclidine) leads to glutamate excito-toxicity in the CNS. Hence, the use of presynaptic mGlu agonists can decrease the amount of glutamate pushed out (as seen in Figure 2), decreasing the effects of neuro-excitation [12,40,44,47,48].

D-Amino Acid Oxidase Inhibitors

D-Amino Acid oxidase (DAAO) is an enzyme responsible for breakdown of D-serine and other D-amino acids. By blocking the actions of this enzyme, the amount of freely available D-serine is augmented (as seen in Figure 1), resulting in more activation of NMDA receptors [40,48].

Alpha 7 nACh Receptor Agonists

Nicotine has been known to delay the cognitive deficit seen with schizophrenic patients. Hence, there is ongoing research to develop agonists at the nicotinic receptor (alpha-7 nACh), as there is no drug that is currently available to prevent or treat the cognitive component [47-49].

M₁ Agonists

M₁ agonists are also under development for treating the cognitive features in schizophrenia, although not with much success [43,47-49].

Neuropeptides

Neurokinins (especially NK-3) have been implicated in schizophrenia, probably due to their ability to modulate dopamine levels in the CNS. Hence, NK-3 antagonists are under development. Talnetant is one such

molecule that has shown promising results in preclinical and early clinical trials [47,50]. Also, neurotensin agonists are under trials, and they show lack of EPS [47].

Omega-3 Fatty Acids

There have been a few reports that the levels of omega-3 fatty acids are reduced in schizophrenic patients, mostly on a long-term basis. Hence, supplementation of the same may have a beneficial effect [47,51].

Melatonin

Melatonin has been in use for treatment of schizophrenic spectrum for ages now. But the FDA does not approve it for the same. The major applications in a schizophrenic patient include the sleep-oriented symptoms and also to prevent tardive dyskinesia (mechanism is unknown). Also, recently, melatonin has been shown to have a protective effect against development of metabolic syndrome, secondary to the use of antipsychotics. However, further studies are required to ascertain the relevance of the same [52-54].

Cannabinoids

Another system that has been implicated in schizophrenia is the cannabinoid system, as evidenced by the presence of increased levels of endogenous cannabinoids in the brain and CSF samples of patients with schizophrenia. Hence, cannabinoid receptor antagonists are being evaluated [47,55].

Other Agents under the Microscope

Other molecules that have been tried or are being tried include GABA-A modulators [56] (chiefly for the cognitive component enhancement), adenosine 2A receptor agonists [57] (for positive and negative symptoms) and alpha 2 agonists [58] (for positive and negative symptoms), to list a few.

CONCLUSION

Although the pathophysiology and aetiology of schizophrenia are poorly understood, we have several drugs that are able to effectively exert therapeutic effect. The future of schizophrenic pharmacotherapy looks even more encouraging, considering the umpteen molecules currently undergoing preclinical and clinical studies. However, a better understanding of the disease process is essential to make sure the patient is given a holistic treatment.

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