

## Review Article

# Beyond Dopamine: Glutamate as a Target for Future Antipsychotics

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The dopamine hypothesis of schizophrenia remains the primary theoretical framework for the pharmacological treatment of the disorder. Despite various lines of evidence of dopaminergic abnormalities and reasonable efficacy of current antipsychotic medication, a significant proportion of patients show suboptimal treatment responses, poor tolerability, and a subsequent lack of treatment concordance. In recent decades, intriguing evidence for the critical involvement of other neurotransmitter systems in the pathophysiology of schizophrenia has emerged, most notably of dysfunctions within the glutamate pathways. Consequently, the glutamate synapse has arisen as a promising target for urgently needed novel antipsychotic compounds—particularly in regards to debilitating negative and cognitive symptoms poorly controlled by currently available drugs. In this paper, recent findings integrating glutamatergic and dopaminergic abnormalities in schizophrenia and their implications for novel pharmacological targets are discussed. An overview of compounds in various stages of development is given: drugs enhancing NMDA receptor function as well as metabotropic glutamate receptor (mGluR) agonist and positive allosteric modulators (PAMs) are emphasised. Together with other agents more indirectly affecting glutamatergic neurotransmission, their potential future role in the pharmacotherapy of schizophrenia is critically evaluated.

## 1. Introduction

Since the development of chlorpromazine in the 1950s antipsychotic drugs have been the primary treatment choice for schizophrenia [1]. The common pharmacological antagonism of dopamine (DA) D<sub>2</sub> receptors by all antipsychotics and direct link with clinical improvement led to the theory of excess dopaminergic neurotransmission precipitating psychotic states [2–4]. Later, advances in animal, postmortem, and neuroimaging studies led to refinements of the dopamine hypothesis and a regional specificity of abnormal DA signalling was proposed. Negative symptoms of schizophrenia (such as anhedonia, flat or blunted affect, alogia, and avolition) as well as cognitive impairments (including deficits in executive functions, attention, and working memory) were postulated to be caused

by deficiencies in DA transmission at D<sub>1</sub> receptors in mesocortical projections to the prefrontal cortex (PFC). This dysregulation in cortical DA pathways, through a reciprocal relationship with subcortical DA projections, was hypothesised to cause a hyperdopaminergic state at D<sub>2</sub> receptors in mesolimbic DA projections, resulting in positive symptoms of the disorder (such as hallucinations and delusions) [5–8]. Psychotomimetic effects of indirect DA agonists, such as amphetamines, in healthy individuals [9, 10] as well as more recent neuroimaging findings-linking increased DA synthesis at presynaptic striatal D<sub>2</sub> receptors to positive symptoms [11, 12] and DA deficiencies in PFC areas to cognitive deficits [13–15] have lent further support to the dopamine hypothesis. In addition, associations between specific candidate genes and dopaminergic dysfunction in schizophrenia have been identified [16–18].

Whilst first-generation antipsychotics (FGAs) are characterised by their principal blockade of D<sub>2</sub> receptors, second-generation “atypical” compounds comprise a more heterogeneous pharmacological profile involving actions on multiple neurotransmitter systems [19, 20]. Despite widespread anticipation of better tolerability of these newer agents (particularly in regards to extrapyramidal side effects associated with FGAs), metabolic complications such as weight gain, impaired glucose tolerance, and dyslipidaemia are commonly occurring side effects [21]. Further, it is estimated that one third of patients do not respond adequately to antipsychotic medication [22–24], with only clozapine showing better efficacy than FGAs in treatment-resistant schizophrenia [25, 26]. While positive symptoms are generally reasonably well controlled by antipsychotic treatment, negative and cognitive symptom clusters commonly fail to respond in a large proportion of patients [27–29], though their severity is associated with longer-term clinical outcomes [30–32].

These factors underline the urgent need for novel compounds with improved tolerability and efficacy, particularly for negative and cognitive symptoms. Research has identified other neurotransmitter systems in addition to dopamine in the pathology of schizophrenia [33–35]. Most prominently, work on the role of glutamate—the primary excitatory neurotransmitter in the central nervous system—forms the basis of efforts into developing the first nondopaminergic compounds in sixty years of pharmacotherapeutic treatment of schizophrenia [36–42].

## 2. Glutamate and Schizophrenia

*2.1. The Glutamate Hypothesis of Schizophrenia.* Two main types of receptors underlie glutamatergic neurotransmission: the ligand-gated ionotropic receptor family, divided into  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA) and kainate receptors, and the G-protein coupled metabotropic receptor (mGluR) family comprising groups I to III with a total of eight identified subtypes [43]. While ionotropic receptors, in particular AMPA and NMDA, mediate fast excitatory transmission at the glutamate synapse, ligand binding at metabotropic receptors leads to conformational changes directly or indirectly affecting neurotransmission via second messenger pathways [44]. A number of shortcomings of the historically prevailing dopamine hypothesis—most prominently the suboptimal or lacking clinical response of negative and cognitive symptoms to D<sub>2</sub> antagonism and findings of structural brain changes associated with the schizophrenia—inspired the integration of glutamate into a theoretical framework of the disorder [45–47]. The observation that administration of noncompetitive NMDA receptor (NMDAR) antagonists like phencyclidine (PCP) and ketamine could mimic symptoms of schizophrenia in healthy individuals gave rise to the hypothesis of impaired NMDAR functioning contributing to its pathophysiology [48–50]. Importantly, it was found that PCP and ketamine immediately and reliably induced symptom patterns identical to the cognitive impairments and

negative symptoms of schizophrenia not observed under amphetamine challenge [51]. In recent years, several lines of evidence have suggested that reduced glutamatergic excitation of subcortical gamma-aminobutyric acid (GABA) interneurons, through an initial hypofunction of NMDAR, results in disinhibition of glutamate (as well as dopamine and acetylcholine) neurotransmission to the cortex [49, 52–54]. In addition, increased glutamate signalling mainly at AMPA receptors has been found to be a possible downstream effect of NMDAR blockade [38, 55]. Hence, refinements of the glutamate hypothesis postulate that behavioural and cognitive symptoms of schizophrenia appear to be caused by a dysregulation of glutamatergic neurotransmission, characterised by NMDAR hypofunction and subsequent excess glutamatergic activity.

### *2.2. Evidence for the Glutamate Hypothesis of Schizophrenia.*

Evidence for glutamatergic abnormalities in schizophrenia comprises findings from a range of animal models and human methodologies. In rodents, higher cortical glutamate levels after NMDAR antagonist injections into thalamic structures have been linked to cortical neurotoxic changes reminiscent of grey matter volume reductions in patients with schizophrenia [49, 56, 57]. In addition, persistent, long-term cognitive impairments similar to cognitive dysfunction in schizophrenia have been observed in rodents as a result of NMDAR antagonist-induced neurotoxicity in prefrontal cortical areas [58]. Despite lacking evidence for abnormal cerebrospinal fluid glutamate levels in patients with schizophrenia [48, 59], recent advances in neuroimaging have given rise to more consistent support for glutamatergic abnormalities. Pilowsky et al. [60] employed single photon emission tomography (SPET) in unmedicated patients with schizophrenia and demonstrated a reduction in NMDA receptor binding compared to healthy controls in hippocampal areas. A number of proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) studies have found increased levels of prefrontal glutamatergic neurotransmission in unmedicated patients during early disease stages, which appeared to be normalised in chronic patients [41, 61–63], reflecting a possible influence of antipsychotic treatment and/or disease progression on glutamate signalling. Structural abnormalities of NMDA receptors in schizophrenia [40] as well as reduced levels of the endogenous neurotransmitter D-serine have further been documented [64, 65]. As either glycine or D-serine is required as a coagonist with glutamate for channel opening at the NMDAR glycine site, D-serine levels appear to reflect glutamatergic neurotransmission [66]. Finally, a number of possible candidate risk genes for schizophrenia involved in glutamate signalling have been proposed, including polymorphisms of several NMDAR subunits and allelic variations of mGlu receptors [67–70].

*2.3. Integration with the Dopamine Hypothesis.* Several unifying approaches have been made in recent years to integrate the evidence for glutamatergic abnormalities and dopamine in the pathogenesis and current treatment of schizophrenia [34, 42, 71, 72]. A current, widely supported theory states that dopaminergic imbalances in striatal and cortical areas

are preceded and modulated by NMDAR hypofunction in the PFC. In turn, the arising dopaminergic dysregulation might further disrupt glutamatergic signalling at NMDA receptors [39, 73, 74]. Dopaminergic dysregulation might thus be the result of primary impairments of glutamate neurotransmission and a subsequent reinforcing factor in maintaining these impairments [75]. In fact, lower glutamate levels in hippocampal areas of individuals in the prodromal states of schizophrenia, but not in healthy controls, have been found to be linked to increased dopaminergic neurotransmission [76].

### 3. Glutamatergic Drugs for Schizophrenia

**3.1. Currently Available Compounds.** No drug targeting glutamate neurotransmission has yet been licensed for schizophrenia. Several compounds approved for other indications, however, have been identified as additionally affecting glutamate neurotransmission. Lamotrigine, an anticonvulsant, inhibits glutamate release by acting on presynaptic sodium channels [77] and has been experimentally used as an adjunct treatment in schizophrenia. Although a Cochrane review concluded with a lack of robust evidence for its efficacy [78], a more recent meta-analysis suggests moderate effects for use in patients with suboptimal response to clozapine [79]. Another anticonvulsant, topiramate, exhibits antagonistic actions at AMPA and kainate receptors [80] and has been used to augment standard antipsychotic treatment [81], though its efficacy is modest [82, 83]. There is similarly some evidence for the tetracycline antibiotic minocycline, which exhibits neuroprotective actions by depressing glutamate-induced excitotoxicity [84–87]. Nevertheless, current data is underwhelming, and further large-scale randomised controlled trials into all these agents are required.

**3.2. NMDAR Enhancing Agents.** The development of novel drugs with antipsychotic properties through direct binding on the glutamate site of the NMDA receptor has proven challenging. Its wide distribution in the central nervous system—associated with decreased tolerability—and the potentially neurotoxic effects of receptor overactivation have stimulated the search for compounds more indirectly affecting glutamatergic signalling [36, 88]. Attempts to develop NMDA receptor enhancing treatments have most notably focused on full agonists of the glycine modulatory site of the NMDAR—glycine and D-serine—as well as sarcosine, a glycine transporter type 1 (GlyT1) inhibitor.

Discouragingly, the Cognitive and Negative Symptoms in Schizophrenia trial (CONSIST) found no beneficial effect of using glycine as an add-on treatment in chronic schizophrenia [89]. A recent meta-analysis by Tsai and Lin [90] found a consistently good tolerability of both glycine and D-serine as adjunct treatments but failed to demonstrate more convincing evidence for their efficacy than moderate effect sizes for negative symptoms and small effect sizes for positive and cognitive symptoms. Interestingly, no additional benefits could be observed for patients receiving clozapine treatment, possibly due to clozapine's action as a partial

NMDAR agonist and the generally later disease stage in this group of patients [91, 92]. Whilst evidence to date for adjunctive D-serine has been weak, there is some data to indicate this might be due to inadequate dosing [93]. Trials of indirectly increasing D-serine by inhibiting the metabolising enzyme D-amino acid oxidase (DAAO) have not yet advanced to clinical phases [94, 95].

An alternative approach to enhancing glycine levels is the inhibition of glycine reuptake via type 1 glycine transporters (GlyT1). Sarcosine, the endogenous GlyT1 inhibitor, has demonstrated efficacy in alleviating positive, negative, and general symptoms of schizophrenia as an adjunct treatment to nonclozapine antipsychotics [96], both in the acute phase [97] and in chronically ill patients [98, 99]. Lane et al. [100] investigated sarcosine as monotherapy for schizophrenia and found some efficacy, with 2 g/day producing stronger symptom reduction than 1 g/day, but lacked placebo as well as active control groups. While no published results are available for the selective GlyT1 inhibitor ORG25935 developed by Merck (phase II completed), Roche's compound RG1678/RO4917838 has entered phase III testing after moderately beneficial results in reducing positive and negative symptoms as an adjunct treatment were reported [101, 102].

**3.3. Metabotropic Glutamate Receptor Compounds.** A multitude of potential new antipsychotic drugs target the less widely distributed metabotropic glutamate receptors (mGluRs) as agonists or positive allosteric modulators (PAMs). Selective agonists at mGlu2/3 receptors are thought to exert their antipsychotic actions by limiting glutamate release presynaptically and have been shown to attenuate the effects of NMDAR antagonists in humans [38, 103]. Animal models have suggested reduced PCP-induced dopamine signalling in striatal areas and increased dopaminergic neurotransmission in the PFC after administration of mGlu2/3 agonists [56, 104, 105]. As a result, compounds of this type have been predicted to alleviate negative, cognitive, and positive symptoms [106]. Monotherapy with pomaglumetad methionil (LY2140023, an oral prodrug of LY404039) developed by Eli Lilly demonstrated superior efficacy to placebo and equal results to olanzapine in reducing positive and negative symptoms of schizophrenia in a phase II trial while being well-tolerated [107]. These findings could not be replicated in a follow-up trial as neither pomaglumetad nor olanzapine showed greater efficacy than placebo while the incidence of a number of adverse events limited the drug's tolerability. Nevertheless, the compound has recently entered phase III for long-term testing and head-to-head comparisons with atypical antipsychotics (<http://www.clinicaltrials.gov/>). In contrast to mGlu2/3 agonists, selective agonists at mGlu5 receptors—which are located mainly postsynaptically and are thought to modulate NMDAR function by increasing NMDAR-mediated current—have not yet reached clinical stages [106].

While the potential of alleviating cognitive symptoms in schizophrenia via mGlu5R agonism has stimulated interest in this target [108], full agonistic action at orthosteric

sites of mGluRs (that is, primary sites of endogenous ligand binding) has generally been associated with receptor downregulation and an increased risk of neurotoxic effects [109–111]. Consequently, a number of compounds targeting the allosteric site of mGluRs have been developed, some of which have reached clinical testing phases. As binding to an allosteric site only modulates the receptor in the presence of an endogenous ligand—therefore causing transient and activity-dependent changes—unfavourable effects of orthosteric agonists could potentially be avoided [112, 113]. Several generations of selective positive allosteric modulators at mGlu5 receptors (mGlu5R PAMs) have shown potential in animal models for their antipsychotic properties [114, 115]. Most notably, potential reductions in all symptom areas of schizophrenia have been suggested for the compound ADX-47273 currently in preclinical development by Addex [116, 117] and transition into clinical testing is awaited. Although an mGlu2/3 receptor PAM compound (AZD8529), developed by AstraZeneca, has recently completed a phase II trial, no reports have been published to date and it is unclear if further development of this drug can be expected [88]. Encouraging results from preclinical studies, however, have suggested antipsychotic potential for selective positive allosteric modulators at the mGlu2 receptor. As growing evidence from animal studies has emphasised the critical role of the mGlu2 receptor in mediating the clinical effects of this group of compounds [118, 119], potent selectivity for this subtype might yield increased efficacy. Notably, strong potential for antipsychotic action has been demonstrated for the two major prototypes, LY487379 and Biphenylindanone A (BINA), resembling results of the aforementioned orthosteric mGlu2/3 agonists [120–122].

**3.4. Other Potential Targets.** In addition to targeting NMDAR and metabotropic glutamate receptors, several research efforts have focused on PAMs for the ionotropic AMPA receptor, so-called “ampakines”. Based on animal models of improved memory, attention and learning through enhanced glutamatergic signalling [123, 124], the AMPA PAM prototype CX516, developed by Shire and Servier and Cortex, showed preliminary evidence in clinical trials for enhancing cognitive function as an adjuvant treatment in schizophrenia [125]. In line with the failure to reproduce these results in a larger trial [126], phase II trials of the related compound Farampator (ORG24448) developed by Cortex were terminated and results have not been published [127]. While it remains unclear whether research into these agents for the treatment of schizophrenia will be continued, a number of nonglutamatergic targets indirectly modulating the glutamate system have shown promise. In particular, potential antipsychotic properties have been preliminary demonstrated for the nonhallucinogenic cannabinoid cannabidiol (CBD) [128–130] as well as the selective muscarinic M1/M4 receptor agonist xanomeline in development by Lilly [131, 132]. Further preclinical work is required, however, to evaluate their suitability for use as antipsychotic treatment.

## 4. Conclusion

Although supported by a large body of evidence and dominating decades of research into aetiology and treatment, the dopamine hypothesis of schizophrenia insufficiently accounts for the complexities of the disorder. Both generations of dopaminergic antipsychotics leave a substantial proportion of patients suboptimally treated, particularly regarding negative and cognitive symptoms, as well as having significant side effects that limit patient concordance with treatment. The clinical and financial costs of psychosis are enormous and the need for novel antipsychotic compounds is acute. Better understanding of the neuropathology of schizophrenia has highlighted the involvement of alternative neurotransmitter systems and, in particular, the potential of the glutamate synapse for providing new pharmacological targets has arisen. Abnormal glutamate neurotransmission has been linked to the prodromal phase of schizophrenia and early psychotic episodes and with the frequently treatment refractory processes of negative and cognitive symptoms. Consequently, compounds aiming at restoring glutamatergic dysregulation could provide relief for symptoms not optimally treated by current antipsychotic drugs, intervene in a potentially critical disease stage and have downstream effects on dopaminergic neurotransmission. A variety of glutamatergic agents in development are currently undergoing preclinical and clinical testing. A number of compounds licensed for medical conditions, several NMDAR enhancing drugs as well as different mGlu agonists and PAMs have accumulated preclinical and, in part, early clinical evidence for use in antipsychotic treatment. Most notably, a GlyT1 inhibitor and an agent modulating glutamate signalling through selective agonistic action at mGlu2/3 receptors have shown promising antipsychotic efficacy as well as favourable side effect profiles and have recently been entered into phase III trials. While these encouraging advances, together with the emergence of new potential agents, instil confidence in a timely identification of novel antipsychotic drugs, moderate or inconclusive results of several compounds emphasise the need for further large-scale, high-quality research efforts. In particular, efficacy of promising candidate drugs, their role in antipsychotic monotherapy or adjunct treatment as well as their long-term safety and tolerability require confirmation and clarification.

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