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# Glutamatergic drugs for schizophrenia treatment

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It is accepted that both positive and negative symptoms of schizophrenia may be due to hypofunction of glutamatergic pathways leading to altered dopaminergic neurotransmission activity. Specifically, there may be diminished glutamatergic signaling at the level of the NMDA receptors, but direct receptor agonists have no clinical utility due to their nonspecific actions and undesirable side effects.

Given the problems of ineffectiveness or side effects of drugs that act directly on ionotropic and metabotropic mGlu2-3 receptors, clinical trials have been conducted with other drugs that have other mechanisms of action, especially indirect mechanisms, such as the co-administration of NMDA agonists (glycine or D-serine), glycine transporter inhibitors (sarcosine bitopertin), ampakines (CX-516), and mGlu5 receptor agonists. However, despite repeated failures, the glutamatergic approach to the treatment of schizophrenia has not been exhausted and all theoretical aspects that relate these complex neurochemical mechanisms with symptoms of schizophrenia should be reviewed until we find truly effective molecules with an acceptable side effect profile.

**Keywords:** Glutamate, Schizophrenia, Metabotropic, D-serine, Glycine transporter inhibitor, Ampakines

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## Fármacos glutamatérgicos en tratamiento de la esquizofrenia

Actualmente se considera que tanto los síntomas positivos como en negativos de la esquizofrenia podrían deberse a una hipofunción glutamatérgica que tendría como consecuencia la alteración de la actividad de la neurotransmisión dopaminérgica. Concretamente, podría haber una disminución de la señalización glutamatérgica a nivel de los receptores NMDA, pero los agonistas directos de estos receptores no tienen utilidad clínica por ser inespecíficos y sus muchos efectos indeseables.

Dados los problemas de falta de eficacia o de efectos secundarios que presentan los fármacos que actúan directamente sobre los receptores ionotrópicos y mGlu2-3, se han ensayado otros que actúan por otros mecanismos, especialmente indirectos, como es la la administración co-agonistas de los receptores NMDA (glicina o D-serina), inhibidores del transportador de la glicina (sarcosina, Bitopertin), AMPAkinas (CX-516) y agonistas de los receptores mGlu5. Sin embargo, a pesar de los constantes fracasos, el enfoque glutamatérgico en el tratamiento de la esquizofrenia no está agotado y es necesario revisar todos los aspectos teóricos que relacionan estos mecanismos neuroquímicos con la compleja sintomatología esta patología hasta que logremos moléculas que sean realmente eficaces y que tengan un perfil de efectos secundarios aceptable.

**Palabras clave:** Glutámico, Esquizofrenia, Metabotrópico, Glicina, D-serina, Inhibidores del transporte de glicina, Ampakinas

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## INTRODUCTION

In recent years, there have been major advances in our knowledge of the role of glutamatergic neurotransmission in the pathophysiology of mental disorders, especially depression and schizophrenia.<sup>1</sup> For this reason, and given the limitations of dopaminergic drugs in terms of efficacy and side effects, the pharmaceutical industry has made an effort to synthesize and market drugs that may be effective with few side effects. However, it is unusual that none of the many molecules with glutamatergic action that have demonstrated antipsychotic effects in preclinical studies have been brought to market. Many of these molecules appear to have a promising profile and early clinical studies even suggested that they could be effective against a wide range of symptoms present in patients with schizophrenia. However, none of the clinical trials has shown that glutamatergic drugs offer real advantages over available drugs.

In this paper, we have attempted to address the reasons why we have not yet found any drugs with predominantly glutamatergic action that are truly effective for the treatment of schizophrenia or improve the efficacy and tolerability of currently available molecules. However, in order to understand the complicated mechanism of action of these drugs, we should first review some of the characteristics of glutamatergic neurotransmission, an extremely complex process. Only references that could be really useful to readers have been cited, particularly review articles, as there is an overwhelming volume of literature on the topic and it would be counterproductive to cite all the published articles.

## GLUTAMATE AS A NEUROTRANSMITTER

Glutamic acid (or glutamate for the English-speaking world), together with aspartate, is one of two primary central nervous system (CNS) excitatory amino acids, whose actions oppose those of GABA, the primary inhibitory neurotransmitter.

Glutamate is found in three different cellular compartments: presynaptic neurons, postsynaptic neurons, and glia, which have served to characterize the so-called "tripartite glutamate synapse." This integral neuronal-glia synapse is complex and consists of glutamate release, reuptake and deactivation by different glutamate receptors and amino acid transporters.<sup>2</sup>

Glutamate is synthesized by deamination of glutamine from glial cells by glutaminase, or by transamination of alpha ketoacids in the Krebs cycle, as alpha ketoglutarate, which is produced by aspartate amination before it becomes glutamate. The carbon skeleton of deaminated aspartate is

converted into oxaloacetate in a transaminase-mediated reaction. A third pathway of glutamate production is due to direct amination of alpha-ketoglutarate, a reaction catalyzed by glutamate dehydrogenase. Glutamic acid is stored in vesicles that are subsequently released into the intercellular space, where they act on specific receptors<sup>3</sup>:

There are two types of glutamate receptors: metabotropic receptors (mGluR) and ionotropic receptors. The mGluR are subdivided into three groups (I, II and III) that are distinguished by sequence homology, pharmacology, and second messenger systems. The group I metabotropic receptors (mGluR1 and mGluR5) are predominantly postsynaptic in somatodendritic zones, and they bind through Gq/G11 to phospholipase C, whereas group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, and mGluR8) metabotropic receptors bind through Gi/G0, inhibiting adenylate cyclase, and are mainly presynaptic in terminals and axons, where they modulate neurotransmitter release.<sup>4</sup>

There has been much speculation about the possible functions of metabotropic receptors, which may be the following:

- mGluR2 preferentially modulates the thalamo-cortical pathway related to attention and activation
- mGluR2 and mGluR3, which are located in the prefrontal cortex and hippocampus, may play an important role in the plasticity underlying learning and memory processes.
- mGluR5 modulates the ionic currents coupled to the NMDA receptor.

Ionotropic receptors are also divided into three groups: AMPA, kainate, and NMDA, corresponding to heteromeric ion channels formed by multiple protein subunits. When activated, ionotropic receptors produce increased cation conductance and differential permeability to Na<sup>+</sup> and Ca<sup>2+</sup> depending on the receptor type and subunit composition. The activation of NMDA receptors in the adult brain generally results in increased Ca<sup>2+</sup> conductance, whereas kainate receptor activation produces increased Na<sup>+</sup> conductance. AMPA receptors expressed in GABAergic interneurons of the hippocampus and amygdala seem to lack the GluR2 subunit and show preference for Ca<sup>2+</sup> conductance, while AMPA receptors in the pyramidal neurons are not permeable to Ca<sup>2+</sup>.<sup>3,5,6</sup>

After acting on the specific receptors, glutamate is taken up again by various types of transporters, even transporters situated in non-glutamatergic neurons, and can be released by monoaminergic neurons. Two types of reuptake have been identified:

- As a result of glial reuptake, glutamine forms again in the glia and is stored as a reserve in the mitochondria of the first neuron. From there, alpha ketoglutaric acid crosses the mitochondrial membrane and constitutes the glutamine cycle, which has a neuronal energy production function. Glutamate is metabolized in glial cells to glutamine, mediated by glutamine synthetase. Aspartate is formed by a transaminase that acts to aminate oxaloacetate by transamination of the amino group of glutamate (another form of glutamate breakdown). The carbon skeleton of glutamate becomes  $\alpha$ -ketoglutarate.
- By means of presynaptic reuptake, glutamate re-enters the cell through a Na/K pump, but a portion of what is captured leaves again through the cleft by a process of inverse reuptake and the action of a K/Na pump, with substantial release of free radicals.

Ionotropic and metabotropic receptors regulate excitatory neurotransmission at synapses and modulate diverse physiological brain functions, such as synaptic plasticity, learning, and memory. Various clinical studies support the involvement of the glutamatergic system in the pathophysiology of mood disorders. The glutamatergic system regulates mechanisms related with stress and neuroplasticity, which have an important relation with major depressive disorder.<sup>3</sup>

At excitatory synapses, the glutamate released by neurons is captured by glial cells and converted into glutamine, thus completing the cycle. Specifically, the physiological activity of the glio-neuronal glutamate-glutamine cycle terminates with deactivation once its specific neurotransmitter function is complete, which protects neurons and glial cells from the toxicity produced by high glutamate levels. These mechanisms include various receptors, second messengers, and other effectors; changes in this circuit could be involved in affective disorders.<sup>7,8</sup>

Although all the glutamate receptors are expressed in the cortex and thalamus, in addition to other brain regions like the hippocampus, five principal glutamatergic neurotransmission pathways have been described.<sup>3</sup>

1. The pathways that extend from the prefrontal cortex (PFC) to the brainstem (raphe, locus coeruleus [LC], ventral tegmental area [VTA], substantia nigra [SN]), where the release of various neurotransmitters (5-hydroxytryptamine [5-HT, or serotonin], norepinephrine, and dopamine) is regulated.
2. Pathways from the PFC to the striate (cortico-striatal glutamatergic pathway) and to the accumbens nucleus (cortico-accumbens pathway) constitute part of the cortico-striato-thalamic loop.

3. Thalamo-cortical pathways ascend from the thalamus and innervate the pyramidal neurons of the cortex.
4. Cortico-thalamic pathways descend from the PFC to the thalamus.
5. Cortico-cortical glutamatergic pathways.

It is important to emphasize the hippocampal glutamatergic neurotransmission. The hippocampus is formed by an abundant network of cholinergic and glutamatergic neurons and depends on glutamatergic action to produce long-term potentiation, which is a lasting synaptic connection.

The hippocampus and prefrontal cortex are the brain areas most directly involved in cognitive functions, such as working memory, which require proper hippocampal function; these functions are impaired in schizophrenia.

## GLUTAMATE AND SCHIZOPHRENIA

At present, the dopaminergic hypothesis of schizophrenia is encountering strong competition from the idea that schizophrenia is a consequence of diminished glutamate NMDA receptor function. This hypofunction could be the initial event responsible for changes in the activity of dopaminergic pathways, which are involved in both positive and negative symptoms.

It should be kept in mind that the dopaminergic hypothesis for decades has been the main hypothesis for explaining the pathophysiology of schizophrenia symptoms. It is unclear whether excess dopaminergic activity is the primary event in the pathophysiology of psychosis or excess dopamine is due to prior or subsequent neurodevelopmental alterations. It is now postulated that the glutamatergic system may be involved in the pathogenesis of schizophrenia, and that system dysfunction may result in increased mesolimbic dopaminergic activity and decreased mesocortical activity.<sup>3,6,9,10</sup>

The history of the relation between glutamate and schizophrenia is very old. According to the account by Javitt,<sup>11</sup> there were major advances in the field of psychopharmacology in the mid-twentieth century. Antipsychotic drugs were developed based on the clinical observations of Delay and Deniker and were related to D2 antagonism. Clozapine, the current "gold standard" for the treatment of schizophrenia, was eventually marketed in 1971. Antidepressants were developed in the 1950s using observational clinical data obtained with isoniazid. Benzodiazepines were developed based on studies of GABA receptor binding in the 1960s, and definitive studies demonstrating the efficacy of lithium were conducted in the early 1970s.

In this period, molecules called "dissociative anesthet-

ics" appeared and include phencyclidine (PCP, or "angel dust") and ketamine. In monkeys, these substances produce behaviors and symptoms very similar to those of schizophrenia. Although many studies of PCP were conducted in the 1960s and extensive data on clinical effects were obtained, it took another 20 years to characterize these effects at the molecular level. As Coyle<sup>12</sup> describes it, several important milestones were reached, such as the pharmacologic identification of the PCP receptor in 1979, demonstration of the electrophysiological interactions between PCP and the NMDA receptor in the 1980s, followed shortly thereafter by its pharmacologic confirmation, identification of the glycine modulatory site of the NMDA receptor in 1987, and confirmation of the psychotomimetic effects of ketamine in the 1990s. Although some researchers have not yet conceded the relation between NMDA receptor antagonism and psychotic symptoms, few now dispute the idea that the NMDA receptor can be considered the molecular target of PCP, ketamine, dizocilpine (MK-801), and other psychotomimetics.

Knowledge of the mechanism of action of PCP has served as a pharmacologic tool for advancing the study of the pathophysiology of schizophrenia and potentially useful new molecules for the treatment of schizophrenia<sup>13</sup> but, unfortunately, none of these molecules has been brought to market so far.

If the glutamatergic hypothesis of schizophrenia is based primarily on NMDA receptor hypofunction, it is important to understand the mechanisms related to this receptor.<sup>12</sup> The NMDA receptor was identified and differentiated from the AMPA and kainate receptors 30 years ago. Glycine has been observed to reinforce NMDA receptor responses in such a way that glycine/D-serine must be present for the associated ion channel to open. Extracellular glycine levels in the brain are approximately 7  $\mu$ M, almost saturating the glycine modulatory site (GMS). This site once seemed irrelevant as a target for NMDA receptor modulators until it was demonstrated that the glycine transporter GlyT1 maintains subsaturation glycine concentrations in the synaptic cleft. We will return to the importance of this transporter in the design of possible antipsychotic drugs later.

Viewed in a simplified manner, glutamatergic paradigms predict that NMDA receptor agonist molecules could be effective in the treatment of schizophrenia. Possible mechanisms of action of drugs are at the level of the glycine/d-serine receptor and redox zones of the NMDA receptor, as well as pathways regulating glutamate or the synthesis and/or release of glycine/d-serine and glutathione. D-cycloserine, a partial agonist of the glycine receptor, can enhance learning and neuronal plasticity in various disorders, including schizophrenia.

The conceptual term "NMDA receptor hypofunction" was

introduced after observing vacuolization and neurodegeneration in specific brain regions following administration of high doses of NMDA receptor antagonists. In experimental animal paradigms, the neurotoxic effects of PCP are antagonized by the administration, among others, of benzodiazepines and  $\alpha$ 2 adrenergic agonists, but these substances were not effective when tested in humans. Nonetheless, this model can explain the persistent fronto-temporal neurocognitive deficits observed in some patients addicted to ketamine. Subsequent models of hyperglutamatergic effects have focused on excessive glutamate release induced by NMDA antagonists, particularly in the prefrontal cortex. Studies were conducted with lamotrigine or agonists of metabotropic receptors 2/3, which inhibit glutamate release. Most importantly, NMDA antagonists like ketamine may be therapeutically beneficial for treatment-resistant depression or autism.<sup>11</sup>

On the other hand, changes observed in glutamatergic neurotransmission in the hippocampus and entorhinal, cingulate, orbital, and prefrontal cortex in patients with schizophrenia, together with the fact that glutamate plays a key role in learning and memory processes and that excess glutamate has a neurotoxic effect, support the involvement of this neurotransmitter in schizophrenia.

Due to a glutamate deficit in schizophrenia, failure of the cortico-striatal inhibitory pathway would intervene in positive symptoms (NMDA antagonists produce psychotic symptoms and exacerbate schizophrenia), and failure of the excitatory pathway (efficacy of D-cycloserine, indirect NMDA agonist) would contribute to negative symptoms and cognitive processes.

These mechanisms merit more detailed explanation. The glutamatergic pathway projecting from the cerebral cortex to the brainstem communicates with the mesolimbic dopamine pathway by means of GABAergic interneurons in the VTA. When this pathway is activated, GABA release occurs, which in turn inhibits dopamine release in the mesolimbic pathway; consequently, the glutamatergic ascending pathway acts as a brake on the mesolimbic pathway. If the glutamatergic activity of the descending pathway is diminished or the GABAergic brake fails, mesolimbic dopamine hyperactivity occurs, causing the positive symptoms of the psychosis.<sup>3</sup>

Moreover, this descending glutamatergic pathway also regulates the dopamine activity of the mesocortical pathway in VTA by tonic stimulation. If failure occurs in this pathway, it results in hypoactivity of the mesocortical pathway, which could explain the cognitive, negative and affective symptoms of schizophrenia.<sup>3</sup>

However, things are less than clear because there may be excitotoxic glutamatergic mechanisms in neurodevelopmental stages, possibly due to oxidative stress processes,

that result in interruption of long-term potentiation and glutamate-regulated synaptic plasticity.

## THERAPEUTIC POSSIBILITIES OF DRUGS ACTING THROUGH GLUTAMATE

Lately, much attention has been paid to metabotropic receptors and the therapeutic possibilities of their agonists. Of all the metabotropic receptors, those pertaining to group II, the mGlu2 and mGlu3 receptors, seem to be most involved in the pathogenesis of schizophrenia.

What would be the role of these metabotropic receptors in schizophrenia? The results of postmortem studies are contradictory since some studies have found increases, others have found decreases and others, no change in specific areas of the right lobe prefrontal cortex (Brodmann area 46, AB46). The only noteworthy differences are in the laminar distribution of receptor mRNA in the white matter of zone BA46 in schizophrenics, in which an increase of approximately 53% in mGlu2 receptor mRNA is observed in the right lobe PFC. Other studies indicate that the density of mGlu3 receptors in AB10 does not differ from normal subjects.

No differences in the distribution of mGlu3 receptor mRNA are found in the hippocampus. However, in the anterior hippocampus of schizophrenics there is no positive correlation between the RNA of glutamate carboxypeptidase II (GCPII), which metabolizes NAAG, an endogenous agonist of mGlu3 receptors, and the mRNA of the mGlu3 receptor observed in the brains of control subjects.

For these reasons, although there may be diminished glutamatergic signaling at the level of NMDA receptors in schizophrenia, direct agonists of these receptors have no clinical utility because they are nonspecific and have many undesirable effects. However, indirect agonists, which modulate the NMDA receptor, could be effective in theory.

The mGlu2 and mGlu3 receptor agonists reverse the effects of stress and have anxiolytic actions and antipsychotic effects in various experimental paradigms in rodents *in vivo*. Administration of various mGlu3 receptor agonists antagonizes the effects of PCP and amphetamine, which suggests their therapeutic potential for schizophrenia. The mechanism underlying all these actions is the following:

- Regulation of glutamate release: increased glutamate release in the PFC (hyperfrontality) caused by NMDA receptor dysfunction affects working memory, and poor transmission through these receptors in the right PFC affects executive function. Another explanation is that NMDA receptor hypofunction in the mesencephalic GABAergic neuronal projections results in the disinhibition

of thalamo-cortical glutamatergic inputs in the pyramidal neurons of the PFC, which increases glutamate release in this area.

- Regulation of dopamine release: one of the underpinnings of the dopaminergic hypothesis of schizophrenia is dopaminergic hyperactivity of the nucleus accumbens (the cortex of this nucleus receives most of the glutamatergic terminations from the PFC, hippocampus, and amygdala). Therefore, the selective effect on dopamine release in this region may explain the antipsychotic effects of mGlu2/3 receptor agonists. Also, if limbic projections to the nucleus accumbens cortex exercise facilitating control over dopamine terminals, stimulation of the mGlu2/3 receptors could reduce both baseline dopamine release and dopamine release evoked by a self-regulating effect on glutamatergic transmission. Conversely, and in contrast to dopaminergic hyperactivity in the nucleus accumbens, diminished dopamine activity in the PFC has been linked to impaired working memory and negative symptoms of schizophrenia.
- Interaction with 5-HT<sub>2A</sub> receptors: 5-HT<sub>2A</sub> receptor antagonism is one of the possible mechanisms responsible for the clinical effect of new antipsychotic agents. Data suggests that this receptor interacts functionally and anatomically with the mGlu2 receptor in the frontal cortex. Metabotropic Glu2/3 receptors act to negatively regulate responses mediated by 5-HT<sub>2A</sub> receptors to stimulate glutamate release, presumably from thalamo-cortical afferents to the PFC.

On the other hand, the effect of mGluR5 amplifies NMDA receptor-mediated responses, suggesting that their activation may be useful in compensating for putative NMDA hypofunction in schizophrenia. However, direct activation of mGluR5 produces rapid desensitization of the receptor.

Positive allosteric modulators (also known as PAMs) of mGluR5 are not direct agonists; they facilitate receptor activation by an endogenous agonist. PAMs enhance NMDA receptor function without inducing receptor desensitization (ADX47273).

Of all the metabotropic receptor agonists, several are being examined for clinical use and one of them, LY2140023, is a prodrug that improves the low oral biosensitivity of LY404039, an mGlu2/3 receptor agonist. Recent phase 2 studies show improvement in both positive and negative symptoms of schizophrenia, suggesting that antipsychotic drugs may target glutamate receptors and bypass the dopamine system. It is important to note that patients taking LY2140023 do not show the typical side effects of current antipsychotics (such as extrapyramidal syndromes, high prolactin levels, and/or weight gain). Therefore, mGlu2/3 receptor agonists may be superior to existing

antipsychotic agents for treating schizophrenia. However, more studies are needed because, on the one hand, LY2140023 was not as effective as olanzapine for the treatment of positive and negative symptoms, and the cognitive functions that are essential for the treatment of schizophrenia were not examined in this study.

### CLINICAL REALITY OF GLUTAMATERGIC DRUGS: TOO STRONG OR INEFFECTIVE

Despite all these advances in the search for new drugs that act through glutamatergic mechanisms, the results obtained in different clinical studies are inconclusive, since it has been observed that agonists or antagonists of glutamatergic NMDA or AMPA receptors produce an effect that is too abrupt (psychotic symptoms occur with a single dose of NMDA antagonists such as phencyclidine or ketamine). Moreover, the effect of agonists or antagonists of glutamatergic metabotropic receptors is insufficient.

Given all of the above, it could be asked if glutamatergic mechanisms can be clinically effective in schizophrenia or not.

### INDIRECT MECHANISMS: GLYCINE MEDIATED MECHANISMS

According to the glutamatergic hypothesis of schizophrenia, the decrease in NMDA receptor function is associated with the pathophysiology of schizophrenia, so receptor function enhancers have become a therapeutic strategy for this disease.

The opening of the NMDA ionophore complex requires the binding of glutamate or an agonist to its respective receptor and of glycine or D-serine to their respective receptors. The glycine receptor is a more attractive target for increasing NMDA receptor function than the glutamate receptor because the risk of neurotoxicity and seizures is lower. Sarcosine and other GlyT1 transporter inhibitors can increase the glycine concentration available for activating these receptors.

This transporter is found mainly in glial cells and helps to modulate the amplitude and kinetics of postsynaptic receptor-mediated currents as well as long-term NMDA-dependent potentiation. The antipsychotic effects of sarcosine can be due to both GlyT1 inhibition and its structural similarity with glycine; the possibility that sarcosine per se is a co-agonist of the NMDA receptor is being considered. Various inhibitors of this transporter, such as bitopertin, are being studied for the possible indication of schizophrenia with predominantly negative symptoms.<sup>15</sup>

### AMPAKINES: POSSIBLE TARGET FOR SCHIZOPHRENIA THERAPY

Ampakines are allosteric modulators of AMPA receptors that increase the peak and duration of the ionophore opening phase.<sup>14</sup> It has been postulated that AMPA receptors play a role in initiating the processes responsible for synaptic plasticity, including long-term potentiation mediated by NMDA receptor activation.<sup>16</sup> During the resting membrane potential, NMDA receptors are blocked by  $Mg^{2+}$ , which penetrates the receptor channel as a result of the electrochemical gradient from outside. The exit of  $Mg^{2+}$  is produced by membrane depolarization following AMPA receptor activation. For that reason, it could be that positive modulation of AMPA receptors by ampakines (CX-516) increases glutamatergic transmission, improves long-term potentiation and synaptic plasticity mediated by NMDA, and ultimately enhances cognitive functions.<sup>17</sup>

### NEW ANTIPSYCHOTICS ACTING THROUGH GLUTAMATERGIC MECHANISMS

Despite progress in the treatment of schizophrenia, negative and cognitive symptoms are still a major problem, often becoming residual symptoms that may worsen after administration of antipsychotic agents due to the side effects of these drugs.<sup>18</sup> Atypical antipsychotics seem to be more effective in reducing these symptoms and extrapyramidal effects compared to classical antipsychotic agents, although their efficacy in counteracting the negative symptoms of any of the antipsychotics that we have today is much debated.<sup>19</sup> One way to increase the effectiveness of antipsychotic treatment is to reinforce the action of antipsychotic agents with so-called "augmentation" strategies.<sup>20</sup>

As mentioned, the glutamatergic system seems to be involved in the pathophysiology of psychosis. Due to the complexity of its neurochemistry, this system offers various possibilities for neuromodulation and has become the target of recent augmentation strategies<sup>21</sup> by means of two different pharmacologic mechanisms: modulation of receptor activation and inhibition of glutamate release. The inhibition of glutamate release is assumed to reduce neurotoxic damage due to an increase in release as a consequence of NMDA hypofunction, a mechanism involved in the pathophysiology of psychosis. On the other hand, the modulation of receptor activity facilitates glutamatergic signaling, which is assumed to be altered in psychosis through different mechanisms and substances, such as NMDA receptor co-agonists (glycine or D-serine), glycine transporter inhibitors (sarcosine), ampakines (CX-516), and mGlu5 receptor agonists. Memantine, a partial agonist of the NMDA receptor, has also attracted interest.<sup>22</sup>

The results obtained in clinical trials with D-cycloserine have not been very encouraging. Meanwhile, glycine may improve negative symptoms and, perhaps, cognitive symptoms when associated with antipsychotic agents, both classic and atypical, except clozapine. Inconsistent results have been obtained with D-serine, although these results could be biased by the use of too low of doses of the components of the association. A recent study in which high doses of D-serine were used has renewed interest in this substance. The association of D-cycloserine with clozapine exacerbated both the positive and negative symptoms; conversely, the association with other antipsychotic agents produced a reduction in negative symptoms, whereas the association with classical antipsychotics improved overall performance.<sup>22</sup>

Promising studies have been made with glycine transporter inhibitors, which suggests that these molecules may be effective both as monotherapy and associated with other potentiating substances. However, these preliminary data need to be confirmed by further studies, and the association with clozapine again has not resulted in any clinical improvement and has even worsened psychotic symptoms. It does not seem possible to use as ampakines as antipsychotic agents, even in combination with conventional drugs. These molecules may have a role as cognitive potentiators, including when used in combination with clozapine, whereas their effectiveness as molecules to associate with other antipsychotics seems questionable.

Positive allosteric modulators of the mGluR5 receptor have not been tested in humans, but show promise and may be a new therapeutic strategy for the treatment of schizophrenia with different mechanisms of action.

The use of memantine in schizophrenia has produced discordant results. However, memantine seems to act in synergy with clozapine and improve the clinical results obtained with these antipsychotics. This divergence of the effects observed with direct and indirect NMDA receptor agonists could be an important advance for the treatment of resistant forms of schizophrenia.

## CONCLUSIONS

Despite repeated failures, the glutamatergic approach to the treatment of schizophrenia has not been exhausted. All the theoretical aspects that relate these neurochemical mechanisms with the complex symptomatology of schizophrenia should be reviewed until we obtain molecules that are truly effective in clinical practice and have acceptable side effects.

## CONFLICTS OF INTERESTS

None.

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