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Review

Targeting glutamate system for novel antipsychotic approaches: Relevance for residual psychotic symptoms and treatment resistant schizophrenia

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ABSTRACT

Antipsychotics are the mainstay of schizophrenia treatment. However, approximately one third of schizophrenic patients do not respond or respond poorly to antipsychotics. Therefore, there is a need for new approaches that can improve schizophrenia treatment significantly. Promising strategies arise from the modulation of glutamatergic system, according to its proposed involvement in schizophrenia pathogenesis. In this review, we critically updated preclinical and clinical data on the modulation of glutamate N-methyl-D-aspartate (NMDA) receptor activity by NMDA-Rs co-agonists, glycine transporters inhibitors, AMPAkines, mGluR5 agonists, NMDA-Rs partial agonists. We focused on: 1) preclinical results in animal models mimicking the pathophysiology of psychosis, mainly believed to be responsible of negative and cognitive symptoms, and predicting antipsychotic-like activity of these compounds; and 2) clinical efficacy in open-label and double-blind trials. Albeit promising preclinical findings for virtually all compounds, clinical efficacy has not been confirmed for D-cycloserine. Contrasting evidence has been reported for glycine and D-serine, that may however have a role as add-on agents. More promising results in humans have been found for glycine transporter inhibitors. AMPAkines appear to be beneficial as pro-cognitive agents, while positive allosteric modulators of mGluR5 have not been tested in humans. Memantine has been proposed in early stages of schizophrenia, as it may counteract the effects of glutamate excitotoxicity correlated to high glutamate levels, slowing the progression of negative symptoms associated to more advanced stages of the illness.

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1. Introduction

Despite relevant progresses in drug treatment of schizophrenia, cognitive and negative symptoms remain a major issue of the disease, often representing residual symptoms of resistant schizophrenia and being worsened by antipsychotics' side effects (Lindenmayer, 2000). Atypical antipsychotics have been predicted to exert superior

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Table 1
Overview of the most studied glutamate receptors' modulators.

Drugs	Mechanism of action	Doses	Therapeutic indication (FDA)	Clinical studies
Glycine	NMDA-Rs co-agonist	800 mg/kg/day	Solution for endoscopic irrigation and intravenous injection; antioxidant drugs	Potkin et al., 1999; Tsai et al., 1999; Javitt et al., 2001; Heresco-Levy and Javitt, 2004; Diaz et al., 2005; Tuominen et al., 2005; Buchanan et al., 2007.
D-serine	NMDA-Rs co-agonist	30 mg/kg/day	Food integrator	Tanii et al., 1994; Lanza et al., 1997; Tsai et al., 1998; Heresco-Levy and Javitt, 2004; Heresco-Levy et al., 2005; Tuominen et al., 2005; Lane et al., 2005; Olsen et al., 2006; Buchanan et al., 2007; Chiusaroli et al., 2010.
D-cycloserine	NMDA-Rs co-agonist	50 mg/day	Anti-tubercular drugs	Fletcher and MacDonald, 1993; Banerjee et al., 1995; McCoy and Richfield, 1996; Goff et al., 1999a,b; Heresco-Levy et al., 2002; Evins et al., 2002; Tuominen et al., 2005; Goff et al., 2008a,b;
Sarcosine	Gly-Transporter inhibitor	2 g/day	Manufacturing biodegradable surfactants and toothpastes	Tsai et al., 2004a,b; Lane et al., 2005,2006;
CX516	AMPAkine	–	–	Nishikawa et al., 1983; Deakin et al., 1989; Johnson et al., 1999; Gao et al., 2000; Goff et al., 2001.
ADX47273	mGluR5 agonist	–	–	Liu et al., 2008.
Memantine	NMDA-Rs partial trapping blocker	5 mg/kg/week	Alzheimer Disease (FDA)	Thomas et al., 2005; Carpenter et al., 2006; Krivoy et al., 2008; de Lucena et al., 2009.

therapeutic action on negative and cognitive symptoms and to reduce extrapyramidal side effects compared to typical antipsychotics (Kapur and Remington, 2001), although these data are still debated (Leucht et al., 2003). Atypical antipsychotics are suggested to mainly differ from typical antipsychotics for a low-to-moderate blockade of dopamine D_2 receptors and for antagonism or inverse agonism at serotonin 5-HT_2 receptor (Arnt et al., 1997).

However, both typical and atypical antipsychotics are not very effective on negative and cognitive symptoms of psychosis. This has prompted researchers to study novel pharmacological targets and different therapeutic strategies to treat resistant forms of schizophrenia. An attempt to improve antipsychotic therapies come from modulation of neurotransmission systems other than the dopaminergic and serotoninergic ones, in order to potentiate the action of traditional antipsychotic drugs, a strategy usually referred to as "augmentation" (Leucht et al., 2011).

Glutamate system has been hypothesized to be involved into psychosis pathophysiology and several neurochemical, neurodevelopmental and genetic data corroborate this view (Chumakov et al., 2002; Deakin and Simpson, 1997; Krystal et al., 2003; Meador-Woodruff and Healy, 2000; Stefansson et al., 2002). Due to its complex biochemistry, the glutamate system offers several possibilities of modulation and has become the target of recent search trends for augmentation strategies (Krystal et al., 2003), by means of two different pharmacological mechanisms: modulation of receptor activity or glutamate release inhibition.

Inhibition of glutamate release is aimed to reduce neurotoxic damage from increased glutamate release as a consequence of NMDA receptor hypofunction, a condition that has been implicated in psychosis pathophysiology (Olney and Farber, 1995). On the other hand, modulation of receptor activity is aimed to facilitate glutamatergic signaling, that is supposed to be impaired in psychosis, by different compounds and mechanisms: N-Methyl-D-Aspartate receptors (NMDA-Rs) co-agonists (i.e.: glycine or D-serine); glycine transporter inhibitors (i.e.: sarcosine); AMPAkines (i.e.: CX-516); agonists of subtype 5 metabotropic glutamate receptors (mGluRs5). Growing interest has also been aroused by the NMDA-R partial agonist memantine (Krystal et al., 2003). This review is focusing on an update of preclinical and clinical data on current strategies of augmentation therapies based on glutamate receptors' modulation strategy (Table 1).

2. Glutamatergic agonists

NMDA-R activation is positively modulated by glycine, that interacts with the strychnine-insensitive glycine-binding site. Glycine binding is necessary for opening the channel subunit, once the

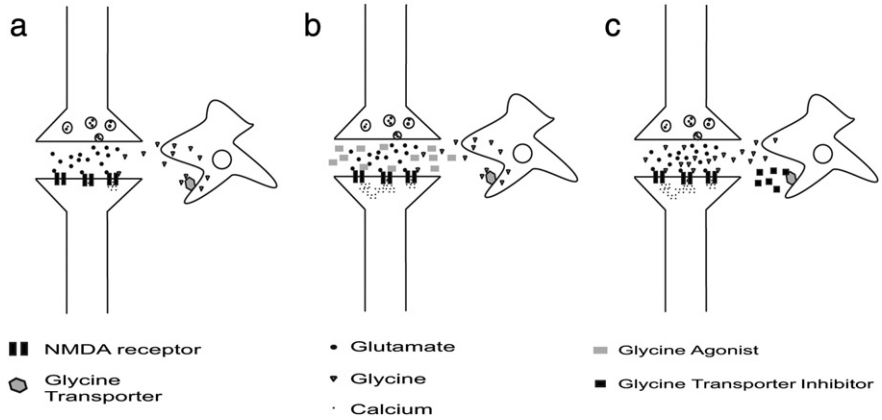

Fig. 1. Schematic depiction of the mechanisms of action of direct and indirect glutamatergic agonists. In the figure, we have graphically showed a schematic depiction of the mechanisms of action of glutamatergic drugs acting directly and indirectly as glutamate co-agonists. Panel a): low post-synaptic glutamate-mediated transmission may depend on NMDA receptor hypofunction due to pre-synaptic, receptorial, post-synaptic mechanisms or to low co-agonist (i.e. glycine, that is released by astrocytes) levels in the synaptic cleft. In the picture, only one NMDA receptor is activated by synaptic glutamate and glycine. Panel b): NMDA receptor hypofunction may be reverted by administration of glutamate co-agonists (i.e. glycine; D-serine; D-alanine; D-cycloserine). These compounds interact with the glycine binding site onto NMDA receptors and cooperate with endogenous glutamate to activate NMDA receptors. In the picture, administration of glutamate co-agonists allows to activate all NMDA receptors on post-synaptic neurons, thereby restoring physiologic post-synaptic glutamate transmission. Panel c): NMDA receptor hypofunction may be reverted by increasing the levels of synaptic glycine. This effect is obtained by blocking the glycine transporter located on astrocytes' membranes. In the picture, a glycine transporter inhibitor blocks glycine re-uptake within astrocytes and increases synaptic levels of glycine. As a consequence, heightened levels of glycine allows to activate all post-synaptic NMDA receptors, restoring physiologic post-synaptic glutamate transmission.

Table 2
Augmentation strategies involving glutamate receptors' modulators subdivided for the class of antipsychotics.

Drugs	Add-on to Clozapine	Add-on to Atypical Antipsychotics	Add-on to Typical Antipsychotics
Glycine	No augmentation effect	Improvement in negative and cognitive symptoms	Improvement in negative and cognitive symptoms
D-serine	No augmentation effect	Reduction of positive, negative symptoms. Improvement in depressive and cognitive symptoms	Reduction of positive, negative symptoms. Improvement of depressive and cognitive symptoms
D-cycloserine	Worsening of negative and positive symptoms	Reduction of negative symptom	Reduction of negative symptom; improvement in global performance
Sarcosine	No augmentation effect	Improvement in positive, negative and cognitive symptoms	Improvement in positive, negative and cognitive symptoms
CX516	Improvement in negative symptoms and in cognitive and memory tasks	Non specific improvement	Non specific improvement
Memantine	Clinical Improvement	Non specific improvement. Higher incidence of adverse effects	Non specific improvement

receptor has been activated by a glutamatergic agonist acting on the glutamate-binding site (Dannhardt and Kohl, 1998). Thereby, glycine and glycine agonists behave as glutamate co-agonists. Since direct stimulation of NMDA-R by glutamate may trigger neuronal excitotoxicity, the potentiation of NMDA-R-mediated neurotransmission may be obtained by stimulation of the glycine binding site without substantial risk of neuroexcitotoxicity (Danysz and Parsons, 1998). This action may be exerted by direct glycine agonists (glycine, D-serine, D-cycloserine) or by blocking glycine re-uptake and increasing synaptic glycine levels by means of glycine transporter inhibitors (N-methyl-glycine, called sarcosine) (Fig. 1).

2.1. Glycine

Abnormal glutamatergic signaling has been suggested to contribute to negative and cognitive symptoms of psychosis. Mutant mice with reduced NMDA-R glycine affinity and mice treated with a NMDA-R glycine site antagonist were shown to be impaired in a number of cognitive and social behavioral tasks (Labrie et al., 2008). Intriguingly, in most cases dysfunctions were reverted by exposure to

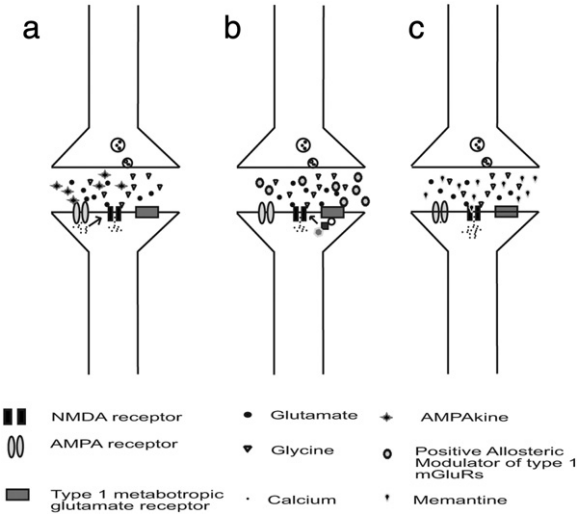

Fig. 2. Schematic depiction of the mechanisms of action of AMPAkines, positive allosteric modulators of type 1 metabotropic glutamate receptors, and memantine. Panel a): positive allosteric modulation of AMPA receptors by AMPAkine has been demonstrated to increase NMDA receptor-mediated neurotransmission, thus overcoming a condition of NMDA receptor hypofunction. Panel b): activation of type 1 metabotropic glutamate receptors (mGluRs) has been reported to increase the response of NMDA receptors to endogenous ligands. In the picture, a positive allosteric modulator of mGluRs cooperate with glutamate, the mGluRs endogenous agonist, to boost mGluRs activation and thus to increase the activity of NMDA receptors via the intracellular second messenger cascade. Panel c): memantine binds to a site within the NMDA receptor channel, ameliorating the NMDA receptor electrophysiology and restoring physiologic post-synaptic NMDA receptor-mediated neurotransmission.

D-serine or clozapine (Labrie et al., 2008), the prototype atypical antipsychotics that is believed to modulate glutamate signaling via its action on NMDA-R glycine site (Schwieler et al., 2008).

An early open-label study on six schizophrenics exposed to oral glycine (10.8 g/day t.i.d.) in adjunct to conventional antipsychotics showed mixed results. Beneficial effects were described in two patients, while other two worsened (Rosse et al., 1989). Challenging results were also observed in an open-label study where glycine was added to conventional antipsychotics in chronic treatment refractory patients (Costa et al., 1990). In the following years, glycine was tested at higher doses, focusing on the amelioration of negative symptoms (Heresco-Levy et al., 1996; Leiderman et al., 1996). High doses of glycine (i.e.: 0.8 mg/kg/day) were found to improve negative symptoms as measured by the Positive and Negative Symptoms Scale (PANSS) negative subscale and to improve Brief Psychiatric Rating Scale (BPRS) total score, without triggering extra-pyramidal side effects (EPS) or depressive symptoms (Heresco-Levy et al., 1999). In a subsequent trial, glycine (at a dose of 0.8 g/kg/day, i.e.: approximately 60 g/day) was reported to improve negative, positive and general psychopathology, with increasing efficacy during a treatment period of 6 weeks (Heresco-Levy and Javitt, 2004). The major effect size compared to placebo was reached for negative symptoms, while a moderate effect on positive symptoms and general psychopathology was described.

Despite these promising results, the usefulness of glycine as an add-on strategy has been challenged by a series of reports. Glycine at different doses was not shown to ameliorate symptoms or was even reported to worsen them when added to clozapine in treatment resistant patients (Diaz et al., 2005; Evins et al., 2002; Potkin et al., 1999). However, significant clinical efficacy has been described in a small open-label trial in patients receiving atypical antipsychotics (including clozapine) and high dose glycine (0.8 g/kg/day) (Javitt et al., 2001), although a separate analysis for clozapine-treated patients was not provided (Table 2). It has to be noted that clozapine augmentation resulted not successful also when associated to other NMDA-R co-agonists (Tsai et al., 1999) or to glycine re-uptake inhibitors (Lane et al., 2006), with a worsening of both negative and positive symptoms when combined to D-cycloserine (Goff et al., 1999a). This feature may depend on the suggested direct action of clozapine on the glycine binding site onto NMDA-Rs, that may induce clozapine and glycine agonists to behave as functional antagonists.

The efficacy of glycine on negative symptoms of schizophrenia has been confirmed by a meta-analysis, with a trend of effect for cognitive symptoms (Tuominen et al., 2005). However, the multi-centric CONSIST study (Buchanan et al., 2007), focused on the evaluation of negative and cognitive symptoms, reported no efficacy of glycine and D-cycloserine. A recent meta-analysis has confirmed that glycine treatment significantly improved multiple schizophrenia symptom domains (Tsai and Lin, 2010).

Overall, clinical data suggest that glycine may have efficacy, albeit limited, on negative, and perhaps cognitive, symptoms when added

to antipsychotics, with the exception of clozapine. Positive results, however, have been obtained in small samples size and have not been confirmed in a larger multi-center trial.

These observations warn against large clinical use of this compound. Glycine may represent a rationale augmentation strategy in refractory patients exhibiting prominent negative and cognitive symptoms. It is not clear, however, whether glycine (or other glycine agonists)-antipsychotic association may be more efficacious than clozapine alone on these symptom domains.

2.2. D-serine

D-serine is a full glycine agonist, synthesized and stored in astrocytes. Glutamate elicits the release of D-serine from astrocytes, allowing D-serine to act as a co-agonist on the glycine binding site of NMDA receptors (Schell et al., 1995). Recently, the serine-synthesizing enzyme, serine racemase, has been reported to be localized also within pyramidal neurons of the cortex and hippocampus and GABAergic neurons of the striatum (Miya et al., 2008).

Mutant mice lacking serine racemase were found to exhibit behaviors relevant to schizophrenia, that were reverted by D-serine and by clozapine (Labrie et al., 2009). In preclinical studies, D-serine has been found to improve antipsychotic drugs' effects in behavioral tasks (i.e.: inhibition of conditioned avoidance response) testing antipsychotic properties of compounds (Olsen et al., 2006). D-serine (50 mg/kg) and neboglamine (a glutamic acid derivative facilitating the effect of glycine without acting on the strychnine-insensitive glycine site (Lanza et al., 1997)) were described to inhibit phencyclidine (PCP)-induced hyperactivity (Chiusaroli et al., 2010), suggesting that a facilitation of glycinergic action may be effective *per se* in preclinical models used to predict antipsychotic efficacy.

D-serine has also been described to be effective in the amelioration of cognitive and social tasks in rodents. D-serine, as well as sarcosine and clozapine, has been described to enhance social memory in naïve rats (Shimazaki et al., 2010). Pretreatment with D-serine or clozapine, but not haloperidol, has been reported to prevent disruption of cognitive functions by MK-801 in rats (Karasawa et al., 2008). Prepulse inhibition (PPI) and latent inhibition model sensorimotor gating and attention processes in rodents. Both these tasks have been found to be potentiated by D-serine, as well as by clozapine, that also prevented their disruption by MK-801 (Lipina et al., 2005).

In humans, an early open-label study found that addition of D-serine (30 mg/day) to stable antipsychotics ameliorated positive, negative and cognitive symptoms without worsening side effects (Tsai et al., 1998). In schizophrenic patients with a history of drug resistance to typical antipsychotics, D-serine (30 mg/kg/day) in association to risperidone or olanzapine was demonstrated to improve negative, depressive and cognitive symptoms from week 2 of treatment, and positive symptoms from week 6 (Heresco-Levy et al., 2005). This trial also included patients with relevant depressive and extra-pyramidal symptoms. Notably, an impairment of negative symptoms was observed within 14 weeks after D-serine withdrawal. Patients treated with D-serine showed also an improvement of rating scales exploring abnormal involuntary movements, with a worsening following D-serine withdrawal (Heresco-Levy et al., 2005). Covariation analysis proved that negative symptoms improvement was not accounted for by changes in extra-pyramidal symptoms.

D-serine treatment (2 g/day), in add-on to risperidone, has been also evaluated in patients suffering from acute psychotic relapse in a randomized double-blind placebo-controlled trial (Lane et al., 2005). However, the D-serine/risperidone co-therapy showed no significant advantage compared to risperidone monotherapy. In the same study, sarcosine/risperidone co-therapy reached greater clinical improvement than the association of D-serine with risperidone or than risperidone monotherapy (Lane et al., 2005). According to these data, D-serine appears to be less effective than sarcosine. Nonetheless, the short time window of the trial (i.e.: 6 weeks) and low D-serine dose may be responsible for the poor efficacy of the compound in comparison to risperidone alone or with the adjunct of sarcosine. Indeed, trials in chronic schizophrenic patients in which D-serine showed its efficacy were carried on for longer time-windows, with the effect on positive symptoms occurring after 6 weeks. Moreover, the 2 g/day D-serine dose, that was reported to improve negative symptoms in chronic phase of schizophrenia, may be ineffective in acute relapse of the disease. However, a recent randomized double-blind placebo-controlled trial of add-on strategies has described no significant differences between the D-serine and the placebo group in any psychometric measure (Lane et al., 2010). Further support to the use of D-serine in schizophrenia come from a recent meta-analysis including approximately 800 subjects from 26 studies investigating effects and tolerability of glutamate enhancers. In this meta-analysis, D-serine has been found to be safe and effective in multiple schizophrenia symptom domains, most of all for negative and cognitive ones, as add-on to antipsychotics, with the exclusion of clozapine (Tsai and Lin, 2010).

The efficacy of D-serine on negative symptoms, when added to antipsychotics, has been confirmed by a meta-analysis, while only a trend for cognitive improvement has been found (Tuominen et al., 2005). Nonetheless, as in the case of glycine and D-cycloserine, D-serine association to clozapine has been reported to not ameliorate schizophrenic symptoms (Tsai et al., 1999) (Table 2).

One explanation of low consistency in clinical results may be the dose used in clinical trials. Indeed, it has been recently demonstrated that D-serine doses of 60 mg/kg/day or higher (up to 120 mg/kg/day) are significantly more efficacious in reducing PANSS scores and improving neuropsychological measures than the classical 30 mg/kg/day dose, with an obvious dose-dependent effect (Kantrowitz and Javitt, 2010).

This finding stimulates further research about the clinical usefulness of high dose D-serine as an augmentation therapy. To date, evidence appears to be not exhaustive to recommend the use of D-serine as an augmentation therapy, although prescription may be beneficial in refractory patients.

D-alanine is an analogous of D-serine, also acting as a glycine site agonist. D-alanine has also been proven in association to antipsychotics as an augmentation strategy, resulting efficacious in several psychopathological domains and well-tolerated (Tsai et al., 2006). The elevation of synaptic D-serine levels has also been attempted by means of inhibitors of D-aminoacid oxidase (DAAO), the enzyme catalyzing D-serine oxidation. However, this strategy has provided inconsistent results in preclinical settings (Adage et al., 2008; Smith et al., 2009) and has not been tested in clinics to the best of our knowledge.

One major issue challenging the possibility to use D-serine and D-alanine in clinics is their low oral bioavailability. When orally administered, both compounds are substantially catabolized by D-amino acid oxidase (DAAO). However, recent preclinical studies have reported that the association of D-serine or D-alanine to 5-chloro-benzo[d]isoxazol-3-ol (CBIO), a DAAO inhibitor, may revert dizocilpine-induced PPI deficits in rats, while D-serine and D-alanine alone were ineffective in this task (Hashimoto et al., 2009; Horio et al., 2009). Moreover, co-administration of CBIO and D-serine or D-alanine was associated with an increase in frontal cortex extracellular levels of D-serine or D-alanine, respectively (Hashimoto et al., 2009; Horio et al., 2009). This strategy could improve clinical efficacy of both D-serine and D-alanine.

2.3. D-cycloserine

The antitubercolar agent D-cycloserine is a glycine partial agonist, acting on the strychnine-insensitive glycine-binding site of NMDA-Rs, and whose activity ranges within 40-60% of glycine activity (Dravid et al., 2010; Sheinin et al., 2001).

In preclinical studies, D-cycloserine was described to counteract apomorphine-induced stereotypy when given with a dopamine D_2 receptor antagonist (Dall'Olio and Gandolfi, 1993). D-cycloserine reinforced olanzapine in reverting behaviors elicited by stimulation of serotonin 5-HT_{2A} and dopamine D_2 receptors, potentially resembling psychotic behaviors (Dall'Olio et al., 2005). Adjunct of D-cycloserine to haloperidol was found to decrease haloperidol- and clozapine-induced expression of Homer1a (Polese et al., 2002), an inducible gene whose expression has been associated to increased glutamatergic and dopaminergic signaling (Iasevoli et al., 2007, 2009, 2010).

The first trial with D-cycloserine in humans, however, was negative (Cascella et al., 1994). D-cycloserine at a dose of 250 mg o.a.d. in association to conventional antipsychotics caused a worsening of patients' clinical conditions. A subsequent study established that a 50 mg/day dose may be more suitable to observe an amelioration at least in negative symptoms and cognitive deficits when added to conventional antipsychotics in schizophrenic patients (Goff et al., 1995). Moreover, 5 or 15 mg/day D-cycloserine added to molindone was well-tolerated but not efficacious on psychometric measures (Rosse et al., 1996). These early studies suggested that doses of D-cycloserine may follow an inverted U shape in terms of clinical efficacy.

D-cycloserine (50 mg/day) in association to typical antipsychotic drugs has been described to induce a significant reduction of negative symptoms and an improvement of global performance at the Sternberg Item Recognition Paradigm (Goff et al., 1995, 1999b), without significant changes in cognitive symptoms.

D-cycloserine has also been demonstrated to increase the efficacy of the atypical antipsychotics olanzapine and risperidone, leading to a reduction of negative symptoms after six weeks of combined treatment (Heresco-Levy et al., 2002). Although a direct comparison has not been carried out, D-cycloserine seems to induce a higher reduction of negative symptoms when added to typical antipsychotics (Goff et al., 1999b) than to risperidone (Evins et al., 2002). Nonetheless, as in the case of glycine, the positive action on antipsychotic efficacy is completely abolished when D-cycloserine is added to clozapine. D-cycloserine (50 mg/day) has been observed to worsen both negative and positive symptoms when added to clozapine (Goff et al., 1999a).

Overall, the putative positive effects of D-cycloserine as an augmentation therapy were not consistently found in all trials and were of small size, explaining the lack of statistical significance favouring D-cycloserine-antipsychotics association in a recent meta-analysis (Tuominen et al., 2005). D-cycloserine efficacy in schizophrenia has been recently challenged in a large meta-analysis that did not find improvements in any symptom domain of patients treated by antipsychotics plus D-cycloserine compared to those treated by antipsychotics alone (Tsai and Lin, 2010).

Given the described occurrence of tachyphylaxis and based on good results after single-dose administration in anxiety disorder therapy and to enhance learning in animal models, a recent trial has studied the efficacy of D-cycloserine administration once-weekly for 8 weeks as an augmentation therapy to antipsychotics (Goff et al., 2008a). Even in this paradigm, D-cycloserine showed only a small size improvement of negative symptoms (without any effect on cognitive symptoms). Indeed, results were not conclusive because of a worsening of negative symptoms in the placebo group and a significance level close to the threshold (Table 2).

To date, D-cycloserine use as an augmentation therapy should be cautiously based on the available evidence. The partial agonist action of D-cycloserine may explain the dose-dependent effect: it may be presumed that high doses may exert a functional antagonism rather than agonism on the glycine binding site and thus on NMDA receptor activity. This feature renders D-cycloserine of very complex use and clinical results almost unpredictable.

3. Glycine transporter (Gly-T) inhibitors

Gly-T inhibitors impair glycine re-uptake by blocking glycine transporters localized on astrocytes, thus increasing glycine synaptic levels with a consequent facilitation of NMDA-R-mediated neurotransmission (Fig. 1).

Reduction of Gly-T activity has been associated to antipsychotic-like and pro-cognitive effects in animal paradigms and in genetic models. The Gly-T inhibitor sarcosine has been described to ameliorate PPI deficits in mGluR5 knock-out mice, a putative animal model of psychotic disease (Chen et al., 2010). Social memory in rats was found enhanced by sarcosine and disruption of cognitive tasks by MK-801 was reverted by pre-treatment with this compound (Shimazaki et al., 2010). In another study, sarcosine and clozapine were reported to reverse ketamine-induced PPI deficits and hyperlocomotion in rats (Yang et al., 2010). Sarcosine has also been described to revert cognitive deficits in mice exposed to repeated PCP administration (Hashimoto et al., 2008). Amelioration of PCP-induced cognitive deficits was obtained by subchronic (i.e.: 2 weeks) but not by acute sarcosine administration (Hashimoto et al., 2008).

Gly-T inhibitors have been reported to prevent PCP-induced hyperactivity, with a potency correlated to their activity in reducing glycine reuptake *in vitro* (Javitt et al., 1999). Moreover, Gly-T1 heterozygous knock-out mice exhibited partial resistance to PCP-induced disruption of PPI (Tsai et al., 2004b). Sarcosine analogous, albeit acting primarily on glutamatergic system, were also described to prevent PCP-induced dopaminergic dysregulation in rodents (Javitt et al., 2004), reinforcing the hypothesis of a functional interplay between these two neurotransmitter systems. The recently described Gly-T inhibitor RG1678 has been reported to attenuate hyperlocomotion induced by d-amphetamine or by a glycine site antagonist in mice and to prevent the enhanced response to d-amphetamine in rats exposed chronically to PCP (Alberati et al., 2012; Hashimoto, 2011), suggesting that Gly-T inhibitors may modulate both glutamatergic and dopaminergic transmission.

However, the Gly-T inhibitor SSR103800 exhibited a selective antipsychotic-like profile, as it was able to revert hyperactivity in transgenic mice carrying a loss-of-function mutation in the NMDA receptor and in MK-801-treated mice. Unlike traditional antipsychotics, the same compound was unable to revert hyperactivity in DAT(−/−) mice and in mice treated with amphetamine (Boulay et al., 2010). These findings suggest that the putative antipsychotic action of Gly-T inhibitors is different from antipsychotic action of compounds targeting primarily the dopaminergic system. Consistent with these findings, the Gly-T inhibitor SSR504734 has been found to attenuate PCP-induced hyperlocomotion but to potentiate the motor stimulant and motor depressant effects of amphetamine and apomorphine, respectively (Singer et al., 2009). However, in another study, SSR103800 has been reported to revert latent inhibition disruption after administration of amphetamine (Black et al., 2009). Thus, Gly-T inhibitors appear to be effective in animal models of psychosis based on glutamatergic impairment but only partially, and possibly limited to cognitive tasks, in models provided by perturbation of dopaminergic transmission. These preclinical features may challenge the clinical utility of Gly-T inhibitors as antipsychotics in monotherapy but may corroborate their use as add-on agents to ameliorate core symptoms of schizophrenia.

Despite promising preclinical data, the antipsychotic efficacy of glycine reuptake inhibitors has been poorly evaluated in clinics, although this mechanism of action may be safer than enhancing NMDA-R transmission by glycine agonists in terms of excitotoxicity risk (Farber et al., 1999). In association with antipsychotics, glycine re-uptake inhibitors have been reported to potentiate antipsychotic effect. In a double-blind placebo-controlled trial, sarcosine (2 g/day) in add-on to typical or atypical antipsychotics has been demonstrated to improve positive, negative and cognitive symptoms in clinical

stable schizophrenic patients (Tsai et al., 2004a), with also efficacy on depressive symptoms. Sarcosine potential efficacy in schizophrenia has been recently corroborated by a meta-analysis showing improvement in different symptom domains in patients taking sarcosine plus antipsychotics (Tsai and Lin, 2010).

Sarcosine has been tested in a double-blind placebo-controlled study in clozapine-treated, clinically stable schizophrenic patients who achieved no satisfactory response to clozapine (Table 2). However, when added to clozapine, sarcosine (2 g/day) failed to improve clinical outcomes in any symptom domain compared to placebo plus clozapine (Lane et al., 2006), confirming the results obtained with glycine and glycine agonists. Indeed, clozapine has been shown to reduce the expression of the glutamate transporter GLUT-1 in rat cortical glial cells (Melone et al., 2001) and to inhibit glycine uptake into rat brain synaptosomes (Javitt et al., 2005). The ultimate results may be an increase of glutamate and glycine levels in the synaptic cleft and thus an augmentation of NMDA-R mediated neurotransmission, that may render ineffective a further enhancement by glycinergic compounds or Gly-Ts inhibitors.

Based on the efficacy of sarcosine in add-on to antipsychotic therapy in chronic schizophrenic patients, sarcosine monotherapy has been tested in a double-blind placebo-controlled trial in drug-naïve and non-naïve schizophrenics suffering from acute psychotic relapse, in doses of 1 or 2 g/day for 6 weeks (Lane et al., 2008). Despite the small sample size, 20% of patients dropped out because of unsatisfactory response. The higher sarcosine dose and drug-naïve groups were more likely to respond to treatment compared to lower dose and non-naïve groups, albeit no significant dose-dependent effect may be recognized. The major frequency of response in drug-naïve patients raised the question about the utility of early treatment. Indeed, it has been proposed that NMDA-R hypofunction may have a critical role in the early phases of disease development, and might be more responsive to NMDA-R-enhancing treatments. These considerations may provide a rationale for sarcosine use, at least in the early stages of psychotic disease.

In acute patients, sarcosine has been evaluated compared to D-serine and placebo as an add-on to risperidone. Sarcosine (2 g/day) plus risperidone showed to be more effective in reducing PANSS-total and Scale for the Assessment of Negative Symptoms (SANS) score from day 14 of treatment compared to both risperidone plus placebo or plus D-serine (Lane et al., 2005). Outcomes on PANSS subscales suggested that sarcosine may be effective on general psychiatric symptoms, depression, and possibly on negative symptoms, while efficacy against positive symptoms during acute phases was not substantiated. As reported above, glycine reuptake inhibitors may be more efficacious in their antipsychotic effect than glycine agonists, because of their increase of glycine phasic wave, while glycine agonists are demonstrated to act through a tonic stimulation of NMDA receptors.

Nonetheless, since sarcosine is demethylated to glycine by sarcosine dehydrogenase, it has been suggested that the mechanism of action of sarcosine may implicate the conversion to glycine within the central nervous system (CNS), together with the inhibition of glycine transporter in the brain. However, expression of sarcosine dehydrogenase has been found to be high in liver, but minimal in the brain (Bergeron et al., 1998; Tsai et al., 2004a). Moreover, the therapeutic dose of sarcosine, as described in clinical trials, is significantly lower than that of glycine (30 mg/kg/day *vs.* 800 mg/kg/day), suggesting that the therapeutic effect of sarcosine is unlikely to depend on its conversion to glycine in the CNS.

In a recent phase II, randomized double-blind trial, the novel Gly-T inhibitor RG1678 has been found to ameliorate negative symptoms in schizophrenic patients when administered in association to second-generation antipsychotics compared to antipsychotics plus placebo (Hashimoto, 2010). Further evaluations are ongoing and a phase III trial with the compound is currently in the patient enrolling stage.

4. AMPAkines

2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid (AMPA) ionotropic receptors of glutamate may represent candidate targets for future antipsychotic therapy for schizophrenia. AMPA receptors involvement in schizophrenia pathogenesis is supported by several studies in post-mortem brains of schizophrenic patients revealing increase in AMPA receptor binding in prefrontal cortex and decrease in AMPA receptor binding in hippocampus (Deakin et al., 1989; Gao et al., 2000; Nishikawa et al., 1983).

AMPAkines are AMPA channel receptors allosteric modulators that increase the peak and the duration of open-channel phase (Suppiramaniam et al., 2001). AMPA receptors play a role in starting the events responsible for synaptic plasticity, as long-term potentiation mediated by NMDA-Rs activation (Dozmorov et al., 2006). At the membrane resting potential, NMDA-Rs are blocked by a Mg^{2+} ion pushed by the electrochemical gradient from the outside into the channel pore of the receptor. Relief from Mg^{2+} block occurs by means of the membrane depolarization consequent to AMPA receptors activation. Consistent with this physiologic mechanism, positive modulation of AMPA receptors by AMPAkines is predicted to strengthen glutamatergic transmission, to enhance long term potentiation and synaptic plasticity mediated by NMDA-Rs (Johnson et al., 1999; Wezenberg et al., 2007), and ultimately to improve cognitive functions (Fig. 2).

In preclinical studies, AMPAkines have been demonstrated to enhance cognitive tasks, including memory and attention. The AMPAkine CX-516 has been reported to facilitate short-term memory in rats (Hampson et al., 1998), while the AMPAkine CX-717 has been described to facilitate task performance and to remove the effects of sustained sleep deprivation in non-human primates (Porrino et al., 2005). Moreover, AMPAkines reduced submissive behaviors in rats, a preclinical model of depression (Knapp et al., 2002). CX-516 has been found to synergistically potentiate the activity of typical and atypical antipsychotics in blocking methamphetamine-induced locomotor activity and behavioral modifications in rats (Johnson et al., 1999). CX-516 potentiated the suppression of conditioned avoidance response, a behavioral test believed to have high predictive validity for antipsychotic efficacy, of threshold doses of several antipsychotics, including clozapine (Olsen et al., 2006).

In human trials, AMPAkines have been demonstrated to improve memory encoding (Ingvar et al., 1997). The AMPAkine CX-516 has been tested as a monotherapy in a small sample of schizophrenic patients. However, no obvious improvement in psychosis' and in cognitive measures was observed (Marenco et al., 2002). In a double-blind trial on 19 schizophrenic patients (Goff et al., 2001), CX-516 in add-on to the atypical antipsychotic clozapine was reported to produce an improvement in cognitive and memory tasks and in negative symptoms compared to patients treated with clozapine only (Table 2). Nonetheless, in a successive trial CX-516 addition to olanzapine, risperidone, or clozapine in stable schizophrenics was not effective on cognitive measures (Goff et al., 2008b).

In conclusion, it appears that studies on humans for AMPAkines are still very limited and do not allow to trace reliable conclusion on this class of compounds. AMPAkines seem to be not an effective antipsychotics when given in monotherapy, while they may have a moderate efficacy on negative and cognitive symptoms in addition to conventional antipsychotics. Of note, this class of compounds appears to preserve its efficacy even when given with clozapine.

5. Metabotropic glutamate receptor 5 agonists

Metabotropic glutamate receptors (mGluRs) are expressed in several brain regions, including basal ganglia and subthalamic nucleus (Awad et al., 2000). mGluRs are G-protein coupled receptors (GPCRs) and are divided in three groups: group I (type 1 and 5) is coupled to

Gq proteins; group II (type 2 and 3) and group III (type 4, 6, 7 and 8) to Gi proteins (Conn and Pin, 1997). mGluRs have an important role in regulating neuronal excitability induced by glutamate activation of channel receptors. Particularly, mGluR5 are postsynaptic receptors involved in neuron activation, facilitating depolarization, NMDA-R currents, firing frequency and burst-firing activity (Awad et al., 2000). mGluR5 amplification of NMDA-R mediated responses provides the basis to suggest that mGluR5 activation may rescue putative NMDA-R hypofunction hypothesized in psychosis pathogenesis (Fig. 2).

However, direct activation of mGluR5 has been observed to cause rapid desensitization of the receptor and is not a viable strategy to augment NMDA-R function (Shipe et al., 2005). mGluR5 positive allosteric modulators (also known as PAMs) are compounds that do not exert direct agonism on mGluRs, yet facilitating receptor activation by its endogenous agonist. PAMs have been postulated to achieve a substantial augmentation of NMDA-R function, without inducing receptor desensitization (Shipe et al., 2005).

Preclinical studies in animal models appear to suggest an antipsychotic effect for several and structurally different mGluR5 PAMs (Rodriguez et al., 2010). The recently described PAM CPPZ has been observed to revert MK-801-induced hyperlocomotion and to reduce conditioned avoidance responses to electric shock in rats (Spear et al., 2011). CDPPB has been shown to be effective in reverting the impairment by MK-801 of sucrose preference in animals, a putative model of negative symptoms of schizophrenia (Vardigan et al., 2010). This compound has also been described to reverse amphetamine-induced hyperlocomotion and deficits in PPI in rats (Kinney et al., 2005). ADX47273, one of the most widely studied PAM, exhibited relevant antipsychotic-like propensity in models sensitive to antipsychotic drug treatment. ADX47273 reduced conditioned avoidance response in rats, decreased apomorphine-induced climbing in mice, reverted phencyclidine, apomorphine, and amphetamine-induced hyperlocomotion and ameliorated cognitive functions in rats (Liu et al., 2008; Schlumberger et al., 2010). ADX47273, as well as typical and atypical antipsychotics, has been shown to revert amphetamine-induced hyperlocomotion and apomorphine-induced deficits in PPI in rats (Schlumberger et al., 2009). Remarkably, the compound did not reduce spontaneous locomotion and rearing, thereby suggesting the lack of sedative side effects. ADX47273 has been reported to not affect striatal dopamine levels but to decrease dopamine levels in nucleus accumbens (Liu et al., 2008). This regional selectivity for the mesolimbic system rather than the nigrostriatal pathway resembles that of atypical antipsychotics, predicting a lower liability for extrapyramidal side effects.

To date, however, there are no published reports on mGluR5 PAMs efficacy as antipsychotics from human studies. Based on preclinical findings, PAMs may represent a valuable tool to complement antipsychotic action against both positive and negative symptoms. More challenging is the possibility that PAMs may *per se* exert a substantial antipsychotic activity.

6. Glutamatergic antagonists: memantine

Memantine (1-amino-3, 5-dimethyladamanantate) is a partial uncompetitive trapping blocker of NMDA channel receptors. It is an analogue of Mg^{2+}, the endogenous NMDA-R antagonist, but it bears only one positive charge, therefore showing an even stronger functional voltage-dependence compared to Mg^{2+}. Memantine restores normal synaptic plasticity reducing Mg^{2+} concentration and prolongs duration of NMDA-R-dependent post-synaptic Long-Term Potentiation (LTP), that is considered crucial for neuronal memory formation (Johnson and Kotermanski, 2006; Parsons and Gilling, 2007). The pharmacological action of memantine is apparently similar to that of phencyclidine and ketamine, two other non-competitive NMDA receptor antagonists that have been described to exacerbate psychotic symptoms and to cause cognitive impairment (Lahti et al., 2001). Memantine has been reported to ameliorate cognitive dysfunctions in both preclinical and clinical settings and has been proposed in the therapy of schizophrenia as add-on to antipsychotics. Thus, albeit apparently similar in their pharmacological action, memantine and psychotogenic non-competitive NMDA receptor antagonists strikingly differ in their clinical effects. A large number of subtle differences in the pharmacological action of these compounds have been proposed to account for such a dramatic clinical divergence, including memantine action onto two NMDA receptor sites (Kotermanski et al., 2009) and memantine propensity to behave as a partial trapping channel blocker, unlike psychotogenic NMDA receptor antagonists (for a review, see: Johnson and Kotermanski, 2006). These subtle pharmacological differences may underlie significant differences in terms of NMDA receptor electrophysiological activity. Because of its propensity to act as a partial rather than a “full” antagonist, memantine has been regarded to induce a decrease in synaptic ‘noise’ due to excessive NMDA receptor activation (Parsons et al., 1999) and to balance inhibition and excitation of neural networks regulated by NMDA receptors (Schmitt, 2005). Due to the complexity of both NMDA receptor physiology and neural networks modulated by this receptor, it is reasonable to assume that subtle variations in the action of NMDA receptor inhibitors may induce great variations in NMDA receptor network effects (Fig. 2). Thus, inhibitors with limited pharmacologically differences can exhibit dramatically divergent therapeutic potential. The hypothesis underlying memantine clinical use, indeed, is that the drug allows physiological activation and inhibits pathological over-activation of NMDA-Rs (Johnson and Kotermanski, 2006; Parsons and Gilling, 2007).

In preclinical studies, memantine has not been tested in animal paradigms predicting antipsychotic liability of compounds and has been described to have complex actions on PPI in both rats and humans (Swerdlow et al., 2009). However, memantine has been described to possess high pro-cognitive activity. Memantine administration has been reported to reverse reference memory errors induced by lesions of the entorhinal cortex in rats (Zajaczkowski et al., 1996), to strengthen hippocampal LTP and spatial memory in freely moving rats (Barnes et al., 1996), and to prevent cognitive impairment by methamphetamine in rats (Camarasa et al., 2008).

On the contrary, however, memantine was also shown to impair other cognitive tasks, as accuracy in a delayed nonmatch-to-sample task in rats (Willmore et al., 2001), while its ability to ameliorate cognitive impairment in a transgenic mice model of cognitive deficits was limited and possibly dose-dependent (Van Dam et al., 2005) (Van Dam and De Deyn, 2006).

This body of evidence suggests that memantine use may reveal beneficial on selective cognitive tasks and that this effect may strongly depend on the dose used, possibly implying a switch from functional antagonism to functional agonism at NMDA-Rs with varying doses. These features render memantine an high promising tool for human therapies but also warrant caution for its use.

In humans, memantine is currently used for the treatment of moderate to severe Alzheimer's disease, being well tolerated without psychotomimetic adverse effects. Besides this application, in few case reports memantine has been used off-label for psychiatric disorders, above all for schizophrenia (Krivoy et al., 2008), on the basis of the putative glutamatergic dysfunction underlying schizophrenia pathogenesis (Olney and Farber, 1995). Memantine has been hypothesized to have a neuroprotective action in schizophrenia (Rands, 2005). The use of memantine in the early stages of schizophrenia may block the glutamate excitotoxicity correlated to high glutamate levels, slowing the progression of negative symptoms associated to more advanced stages of the illness.

In early case reports, memantine has been tested in add-on with the atypical antipsychotic clozapine in patients with catatonic schizophrenia, resulting in rapid clinical improvement (Carpenter et al., 2006; Thomas et al., 2005). The rationale for using memantine in

this cases was ascribed to the counteraction of striatal glutamatergic hyperactivity that has been hypothesized in catatonia. In another case-report, memantine adjunction to antipsychotics allowed reducing ongoing antipsychotic doses in a patient with Alzheimer's disease and aggressive behaviors (Sleeper, 2005).

Memantine augmentation to stable antipsychotic regimen has been tested in a small open-label trial including seven paranoid schizophrenia patients with residual symptoms (Krivoy et al., 2008). Antipsychotic plus memantine association was found to significantly improve PANSS total score compared to antipsychotics alone. The most prominent results regarded negative symptoms, while cognitive status showed no appreciable improvements (Krivoy et al., 2008). However, in a subsequent randomized double-blind placebo-controlled study adding memantine to on-going atypical antipsychotics in stable schizophrenics with residual symptoms, outcome measures (including PANSS, Clinical Global Impression, CGI, and Brief Assessment of Cognition in Schizophrenia, BACS) were not significantly different in the group receiving memantine add-on compared to the group receiving placebo add-on (Lieberman et al., 2009).

Notably, in another double-blind placebo-controlled trial on refractory schizophrenics treated by clozapine, memantine add-on to clozapine resulted in significant clinical improvement compared to placebo as assessed by score reduction in several psychopathological scales, including BPRS, CGI, and Mini-Mental State Examination (MMSE) for cognitive symptoms (de Lucena et al., 2009). A possible explanation of the discrepancy in memantine efficacy when added to clozapine compared to other antipsychotics may rely in the peculiar clozapine action at glutamatergic synapses (Gray et al., 2009). Nonetheless, differences in selection criteria for type of schizophrenia and severity of resistance, sample size and even in the duration of the trial may also be taken in account when trying to explain the different results.

Overall, clinical data on memantine use in schizophrenia are limited and only suggest a potential benefit in resistant patients and in add-on to clozapine (Table 2). More structured placebo-controlled studies with more selective assessment of cognitive symptoms, selection criteria for schizophrenia type, and with sample homogeneity between groups are needed.

7. Conclusions

Targeting glutamate signaling is a promising strategy to improve the efficacy of antipsychotic compounds, above all in those conditions characterized by residual symptoms that are refractory to antipsychotics. In the great part of cases, residual symptoms belong to negative and cognitive domains of psychopathology and no reliable pharmacological approaches have yet been proposed for their care, while psychosocial interventions have assured a considerable, but still limited, level of efficacy. One possible explanation for the occurrence of residual negative and cognitive symptoms may rely on their peculiar neurobiology, presumably depending on dysfunctions in the glutamatergic rather than in the dopaminergic system, which is the primary target of currently available antipsychotics. Therefore, research has been focusing in the last years on the characterization of strategies and compounds that may revert putative glutamatergic dysfunctions, ameliorate some core psychotic symptoms, and putatively be beneficial in a part of refractory schizophrenics. These strategies mainly started from the hypothesis that the key lesion involving glutamatergic system consists of a hypofunction of NMDA-Rs. Consistent with this view, therapeutic approaches pointed to restore adequate NMDA-R signaling with a variety of mechanisms of actions, including prominently, albeit not only: direct or indirect agonism at the glycine-binding site onto NMDA-Rs; positive allosteric modulation of metabotropic or ionotropic glutamate receptors; modulation of NMDA-R functioning by partial agonists. These approaches are highly promising in preclinical models, resulting effective in animal models testing efficacy on negative and cognitive symptoms and predicting antipsychotic-like activity. Nonetheless, data in human studies are still very limited and do not allow tracing conclusive recommendations.

The possibility of D-cycloserine use has been at least in part disappointed by the results of human studies. Glycine may ameliorate negative and perhaps cognitive symptoms when added to conventional antipsychotics, with the exclusion of clozapine. Studies on D-serine resulted in inconsistent findings, however these may have been biased by using too low doses of the compounds. A recent trial with high doses of D-serine has renewed the interest in this agent.

More attractive findings have been reported for glycine transporter inhibitors, suggesting that these compounds may be effective both in monotherapy and as augmentation agents. However, these data need further confirms and again association to clozapine has been found to not improve or even to worsen psychotic symptoms.

AMPAkines appear to be not suitable as antipsychotics, also in association to conventional agents. These compounds may have a role as cognitive enhancers, also in adjunct to clozapine, while their efficacy as add-on agents to ongoing antipsychotics appears questionable.

Positive allosteric modulators of mGluR5 have not been tested in humans but hold promising potential and may represent a novel therapeutic strategy for schizophrenia with a different mechanism of action.

Memantine use in schizophrenia has given inconsistent results. However, it appears that memantine may act synergistically with clozapine and improve clinical outcomes with this antipsychotic, a feature divergent from that observed with direct and indirect agonist at NMDA-Rs and that may represent a substantial advance in the treatment of schizophrenia resistant forms.

In conclusion, despite several failures, the glutamate approach in schizophrenia therapy deserves further consideration and more studies are warranted. At this point, it will be important to consider critically all the available preclinical and clinical results and move quickly to larger clinical trials, considering adaptive clinical studies with the strategies that have yield more significant positive results.

Disclosure/Conflict of Interest

Authors declare they have no conflict of interest.

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