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Glutamate modulators for treatment of schizophrenia

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ABSTRACT

Over the past two decades, accumulating evidence has implicated the role of glutamatergic dysfunction in the pathophysiology of schizophrenia. There has been growing interest in glutamatergic system as a promising target for treatment of schizophrenia spectrum illness and several medications and compounds have been investigated to date. In the present study, we aim to provide a comprehensive review of clinical studies of glutamatergic agents in treatment of schizophrenia. We further discuss the heterogeneity of the results, the overall discouraging outcomes and future directions for investigating glutamatergic medications in schizophrenia.

1. Introduction

The glutamate hypothesis of schizophrenia emerged from observations in the 1960s that phencyclidine and similar psychotomimetic agents produce schizophrenia-like symptoms in humans [1]. The mechanism of action of these compounds, blockade of the *N*-methyl–aspartate receptor (NMDAR), was first described in the late 1980s [2–4], turning attention to abnormalities of the glutamate system in the pathophysiology of schizophrenia. Unique to PCP and ketamine induced psychosis, as opposed to amphetamine induced psychosis, is the presence of thought disorder, negative and cognitive symptoms similar to schizophrenia [4]. This makes the glutamate system even further appealing for the development of novel treatments for persisting and burdensome features of the illness [5].

Following the original description, several glutamatergic models of schizophrenia have been hypothesized [6]. Initial models focused on NMDA receptor hypofunction, which was centered on preclinical observations of neurodegeneration in certain brain areas following high-dose administration of NMDAR antagonist [7]. This model was eventually replaced by a more complex hypothesis of glutamatergic hyperactivity. Hyperglutamatergic models converged from pre-synaptic glutamate efflux in the prefrontal cortex induced by NMDA receptor antagonist injection in animal models, resulting in detrimental behavioral effects such as impaired working memory [8]. Hyperglutamatergic models suggest psychotomimetic effects of NMDA receptor blockers are due to enhanced glutamate release onto other receptors, rather than glutamate hypofunction at the NMDA site. GABAergic models propose that NMDA receptor antagonists contribute to downregulation of parvalbumin-containing γ-aminobutyric acid (GABA)–ergic interneurons, leading to excess glutamate release [9]. The Dopamine-Glutamate interaction model hypothesizes glutamate may impact dopamine activity in the substantia nigra (SN) and the ventral tegmental area (VTA). This model suggests that dysfunction of dopaminergic neurotransmitters in schizophrenia may be resultant of NMDA receptor hypofunction [10].

Nonetheless, over the past two decades several lines of evidence from preclinical and clinical studies have further supported the role of glutamate system dysfunction in the etiology and pathophysiology of schizophrenia [11]. Genome wide association studies (GWAS) of schizophrenia including The Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC), have also demonstrated several significant associations between the illness and genes involved in glutamatergic neurotransmission. Among the identified associations, the metabotropic glutamate receptor 3 (GRM3) contained the second most significant single-nucleotide polymorphism (SNP) after the dopamine receptor D2 (DRD2) [12]. A recent meta-analysis further supported the linkage between GRM3 and risk of schizophrenia [13]. Findings of proton magnetic resonance spectroscopy (H-MRS) studies implicated increased levels of glutamatergic indices in the medial prefrontal cortex (MPFC) and basal ganglia in medication-naïve patients. Furthermore, H-MRS studies have implicated a possible relationship between decreased hippocampal volume and elevated levels of glutamine and glutamate in the hippocampus of unmedicated patients [14].

We sought to review the extant literature on use of glutamatergic agents in patients with schizophrenia. Here we present a review of clinical studies involving pharmacological agents thought to act

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through glutamatergic mechanisms and to have a primary focus on schizophrenia symptomatology.

2. Methods

2.1. Search strategy

All English language, human studies published in peer reviewed journals were considered eligible for inclusion in the literature search. The final search was conducted on July 27, 2018 across four electronic databases including Pubmed, PsychINFO (1806-present), MEDLINE (1946-present), and Embase (1947-present). The search was conducted in two stages: first, to identify glutamatergic agents studied in Schizophrenia. The search strategy included using the keywords "glutamate or glutamatergic or glutamine" and "schizophrenia" and "treatment". Following identification of several glutamatergic agents, the second stage of the literature review included a separate search for each agent. Keywords at this stage included "schizophrenia" and the specific agent (e.g "serine", etc). Eligible articles were also searched to identify additional relevant studies.

2.2. Study selection

For completeness, we included all randomized clinical trials (RCTs), open trials, case series and case reports. All relevant studies which reported on use of a glutamine modulating agent for treatment of any symptomatology in schizophrenia were included. We excluded investigational agents in early phases of development.

2.3. Data extraction and outcome measures

A data extraction table was developed by the authors for each glutamate modulating agent. It was pilot tested on eight randomly-selected studies and refined accordingly. The following data were extracted from each study: author/year of publication, study design, number of participants (completers) in each arm, baseline scores on psychometric scales, dose and duration of treatment, concomitant treatment with antipsychotics, follow up, outcome measures, and reviewer's comments which included significant side effects if present. We summarized the findings on a range of outcome measures as reported by the studies including impact of treatment on positive, negative, cognitive symptoms and general psychopathology.

3. Results

Table 1 provides a brief summary of the included studies for each gulatmate modulating agent and their reported outcome.

3.1. NMDA receptor coagonists

The NMDA receptor requires concurrent binding of agonists at both glutamate and glycine binding sites to function. Therefore, agonists of the glycine site, which enhance NMDAR function, have been also investigated for pharmacological development in schizophrenia considering the evidence linking NMDA dysfunction to schizophrenia. Glycine, D-Serine and D-Cycloserine are agonists at the NMDA glycine modulatory site and have been investigated for impact on positive and negative symptoms, global psychopathology and cognition in schizophrenia [15].

3.1.1. D-Cycloserine

D-cycloserine, an anti-tuberculosis medication, is a partial agonist at the glycine site of the NMDA receptor. One open label [16] and nineteen randomized clinical trials of D-cycloserine in schizophrenia, involving a total of 305 active cases, were identified [17–35]. Overall, D-cycloserine was well-tolerated across the studies.

Nine trials demonstrated statistically significant improvement of negative symptoms [17,18,21,23–25,30,32,35]. The number of cases that completed the active treatment with D-cyloserine ranged from 6 to 16 across these studies. Of these, three trials used an escalating dose from 5 to 250 mg/day for intervals of 4 days-2 weeks on each dose [17,18,30]. Goff et al (1995) [17] and Evins et al (2002) [18] showed improvement of negative symptoms only at the dose of 50 mg/day. Both of these studies used each dose for 2 weeks. Using the same method of escalating doses, Van Berckel et al (1996) [30] showed positive results only at a dose of 100 mg/day. Interestingly, the participants in the Van Berckel study were medication free (at least for 2 weeks prior to the trial). Three other trials used 50 mg/day for 6–8 weeks and showed improvement of negative symptoms. And the remaining three trials used 50 mg once per week prior to CBT or Cognitive remediation training. Of all the studies with positive results, only one [17] showed improvement of working memory and there was no other significant effect on cognitive symptoms.

Seven trials showed no effects on negative symptoms or other outcome measures. Rosse et al (1996) [28] used D-cycloserine 30 mg/day and concluded that lack of efficacy may be resultant of using a lower dose. Using adjunct D-cycloserine 50 mg/day for 4 weeks, Heresco-Levy et al (1998) [31] and Duncan et al (2004) [19] showed improvement of negative symptoms but their results fell short of statistical significance in comparison to placebo. Studies by Goff et al (2005) [20] and Buchanan et al (2007) [22] used D-cycloserine 50 mg for a longer duration, 6 months and 16 weeks, respectively. It is unclear as to why these studies failed to replicate previous findings. Of note, both of these trials aimed to recruit a large number of participants, and used different sources (i.e inpatient/outpatient, etc) for recruitment which resulted in a less homogeneous patient population than trials with positive results. Buchanan et al's study on adjunct D-cycloserine [22], the Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST), has the largest number of participants across all trials to date, with 46 cases and 45 controls who completed the studies. Studies have considered that adjunct D-cycloserine might be effective in a subset of patients, considering these mixed findings might be due to heterogeneity of the participants across studies. Potential predictors of positive response were reported younger age, lower neuroleptic dose and lower baseline levels of negative symptoms [32]. Results of a recent study by Takiguchi et al (2017) [27] revealed association between treatment response to D-cycloserine and white matter integrity. Furthermore, they demonstrated an inverse association between age of onset and treatment response.

Four trials of D-cycloserine resulted in worsening of symptoms. Two of these trials used adjunct D-cycloserine 50 mg/d in patients on clozapine, and were associated with worsening of negative symptoms. The two other trials showed worsening of positive symptoms, using doses of 250 mg/day for 6 weeks and 100 mg daily for 8 weeks, respectively. The conclusion drawn from these studies indicated high dose D-cycloserine or augmentation with clozapine is associated with exacerbation of symptoms.

In summary, the efficacy of D-cycloserine for treatment of negative symptoms is highly questionable and it failed to show superior effects for cognitive symptoms. As mentioned above, studies with positive results were mainly conducted with a small number of participants or had a short duration.

3.1.2. D-Serine

D-serine is a selective full agonist at the glycine site of the NMDA complex and is not known to affect other neurotransmitter systems [36]. D-serine has been studied as a potential agent in patients with schizophrenia in light of the hypo-NMDA hypothesis. D-serine has been shown to block phencyclidine induced hyperactivity and stereotypy in preclinical studies [37,38]. We found ten clinical trials of D-serine [36,39–48], one open label trial [49] and one case report [50] in patients with schizophrenia representing a total of 309 completers in the

Table 1
Summary of findings.

Agent	Mechanism of action	Number/type of studies	N*	findings
NMDA receptor co-agonists				
D-cycloserine	partial agonist at the glycine site of the NMDA receptor	19 clinical trials 1 open label	305	9 trials showed improvement of negative symptoms 7 trials with no effects 4 studies showed worsening; 2/4 studies were in patients on clozapine
D-serine	selective full agonist at the glycine site of the NMDA complex	10 clinical trials 1 open label 1 case report	309	10 trials reported on clinical outcome 5 trials had positive outcome, on a range of positive, negative, total PANSS 5 trials with no efficacy
Glycine	obligatory co-agonist at the glycine modulatory site of the NMDA receptor	10 clinical trials 3 open label 1 case series	171	Early studies had mixed outcome (number of improvement, & worsening with a small n) 7 trials with positive outcome, mostly on negative symptoms 4 trials including CONSORT trial showed no efficacy; 3/4 trials patients were on clozapine
GlyT1 inhibitors				
Sarcosine	a potent endogenous non-selective GlyT1 inhibitor	7 clinical trials 1 open label 2 case reports	141	6 trials showed improvement in a wide range, positive, negative, cognitive, general psychopathology 2 trials without efficacy; one showed benefit with sarcosine + benzoate but not sarcosine alone 2 case reports of activation/hypomania
Bitopertin	selective and potent inhibitor of GlyT1	9 clinical trials	1936	3 trials had improvement in negative or positive symptoms 6 trials without efficacy
DDAO inhibitors				
Sodium Benzoate	competitive inhibitor of DDAO	3 clinical trials	81	All studies showed improvement in a range of outcome measures including negative, cognitive, positive symptoms and GAF
mGlu agonists				
LY2140023 pomaglumetad methionil	mGlu2/3			Terminated at phase III trial development after one of the trials failed to meet its primary endpoint
Other Glutamate modulating agents				
Memantine	non-competitive (partial) NMDA antagonist	9 clinical trials 2 open label 1 case series 5 case reports	277	10 studies showed improvement of negative symptoms, plus a range of other symptoms (positive, cognitive, GAF) 2 studies showed no effects
Lamotrigine	inhibition of presynaptic glutamate release by blockade of sodium channels	9 clinical trials 6 (small) case series 6 case report	292	5 of 9 trials showed improvement over a range of outcome measures including negative, cognitive, general psychopathology
Topiramate	potentiation of GABAergic transmission and (AMPA)/kainite glutamate receptor antagonism	5 clinical trials 4 open label 2 case series 6 case reports	218	5 studies showed improvement of total score or general psychopathology 5 studies showed no efficacy 1 study had worsening
NAC	Modulator of glutamatergic system thru redox/glutathione sensitive site of the NMDA receptor	5 clinical studies	159	All 5 studies reported improvement, but in a different and wide range of outcome domains including positive, negative, cognitive, general psychopathology

* Total number of completers in active (medication) arm. PANSS: positive and negative syndrome scale. GAF: global assessment of functioning.

active arm of the studies. No major side effects were reported.

Of the ten clinical trials which reported on clinical outcomes, five reported a positive outcome and five failed to show efficacy. Tsai et al (1998) [36] and Heresco-Levy et al (2005) [40] demonstrated improvement of positive, negative and cognitive symptoms using 30 mg/kg/d for 6 weeks. In an open label study, Kantrowitz et al (2010) [49] assessed the efficacy of three doses of 30, 60 and 120 mg/kg/d for 4 weeks. All doses resulted in improvement of positive, negative and general psychopathology domains on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Doses of 60 and 120 mg/kg/d were associated with additional improvement in cognitive symptoms. A study by Kantrowitz et al (2015) [46] showed use of D-serine 60 mg/kg was associated with improvement of negative symptoms in a sample of individuals at high risk for psychosis. A more recent study by Kantrowitz et al (2018) [48] demonstrated statistically significant improvement of total PANSS scores by about 8%; however, there were no significant differences in PANSS subscale scores.

Studies with a negative outcome used a dose range of 2gr/D-30 mg/kg/d for a duration of 6–16 weeks. Among all studies, Weiser et al (2012) [43] had the largest number of participants, with n = 87 completers for the active arm (D-serine 2 g/d for 16 weeks) and n = 85 completers for the placebo arm. Another relatively large negative trial by D'Souza et al (2013) [45] compared 46 participants on D-serine 30 mg/kg/d for 12 weeks with 45 placebo completers, with and without cognitive remediation training. The negative outcome observed in these two studies [43,45] was in part attributed to the use of a lower dose of D-serine compared to studies with a positive outcome. Nonetheless, these two studies have the largest number of participants among all studies and a longer trial duration than the majority of the included studies.

Two studies reported on the impact of D-serine on electrophysiological parameters. Kantrowitz et al (2016) [47] showed improvement of auditory plasticity, frequency response and mismatch negativity to trained and untrained tones, using once/week dosing of D-serine for 2–3 weeks, prior to an auditory task. Kantrowitz et al (2018) [48] demonstrated significant modulation of mismatch negativity as a biomarker with the use of adjunct D-serine.

In a case report study, Herseco-Levy et al (2015) [50] described use of D-serine 1.5-4gr/d in a patient with schizophrenia who had positive anti-NMDA antibodies. They noted a significant improvement of all PANSS subscale scores at the end of the 6-week trial.

While some of the studies in this review demonstrated promising

potential for D-serine, the current evidence does not support the use of adjunct D-serine, in particular considering the negative outcome of larger trials. Of note, two recent meta-analyses demonstrated the superiority of adjunct D-serine over placebo in improvement of outcome; however, not all of the studies reviewed in our review were included in those meta-analyses. The Cho et al (2016) [51] meta-analysis revealed a small effect size of 0.3 for negative and 0.2 for positive symptoms. The meta-analysis by Kantrowitz et al (2018) showed a medium overall effect size of 0.7 for improvement of negative symptoms [48].

3.1.3. Glycine

Glycine is an obligatory co-agonist at the glycine modulatory site of the NMDA receptor and is required for activation of the NMDA complex by glutamate. Glycine has also been shown to reverse phencyclidine-induced hyperactivity and stereotypy in rodents [52]. Ten clinical trials [22,53–61], three open label studies [62–64] and one case series [65], involving a total number of 171 completers of the active treatment arm, were identified. Overall, there were no major adverse effects; however, nausea was reported by some studies [55,59,60] at the effective dose of 60 g/d (or 0.8gr/kg/d), limiting its tolerability.

Early studies on use of glycine in patients with schizophrenia, including a case series and two open trials, reported overall improvement in 4 out of 11 participants [65], 2 out of 5 [62], and 2 out of a total of 6 cases [63]. Among these studies, two participants experienced worsening [62] and the remaining cases did not experience any changes in their symptomatology.

Six clinical trials and one follow up open label study (involving the same participants of the index study) demonstrated positive results. The number of completers of the active arm ranged between 7 and 19 participants. Glycine was used at the dose of 0.4–0.8 mg/kg/day for 6–8 weeks. These studies reported improvement in a range of symptom domains including only negative symptoms [53,55,64], negative, positive and cognitive symptoms [58,59], negative, depressive and cognitive symptoms [54] and, negative symptoms and general psychopathology [61]. Greenwood et al (2018) [61] showed improvement of mismatch negativity with acute administration of glycine but not with chronic use (daily for 6 weeks).

Four clinical trials found no effect of adjunctive glycine [22,56,57,60]. Three of the negative studies involved participants who were only on clozapine. The Cognitive and Negative Symptoms in Schizophrenia Trial (COSIST) [22] is the largest study conducted on the use of add-on Glycine (and D-Cycloserine) compared to placebo. This trial had 42 completers in the glycine arm (50gr/d for 16 weeks) and showed no superiority over placebo.

In summary, there are a number of positive small trials in the literature on the efficacy of adjunct glycine; however, the result was not replicated by the only available large multicentre study on the use of add-on glycine.

3.2. Glycine transporter (GlyT1) inhibitors:

Glycine transporter 1 (GlyT1) modulates the concentration of glycine in the synaptic cleft of the NMDA complex. Inhibitors of GlyT1 prevent removal of glycine from the synapses by blocking the GlyT1 transporter, enhancing NMDA function. GlyT1 inhibitors have been repeatedly shown to improve cognitive and “psychosis” equivalent symptom domains in animal models of schizophrenia. In rodents, treatment with GlyT1 inhibitors prevented dopaminergic dysregulation induced by PCP administration and reduced cognitive deficits [42]. The GlyT1 heterozygote knockout mice demonstrated a better working memory, spatial retention and an increase in NMDA function. Furthermore, these mice were less susceptible to PCP-induced hyperactivity, prepulse inhibition and sensory gating [42,66]. Together with the promising findings from animal studies, GlyT1 inhibitors have become the site of interest for development of novel agents for schizophrenia [66].

3.2.1. Sarcosine

Sarcosine (N-methylglycine) is a potent endogenous non-selective GlyT1 inhibitor. In our search of the literature, we identified seven clinical trials [41,43,67–71], one open label trial [72] and two case reports [73,74] on use of sarcosine in patients with schizophrenia including a total of 141 completers in the active arm. All trials used sarcosine at the dose of 2 g/d, except the Amiaz et al (2015) [72] open trial which used 4 g/d. Across trials, the number of completers in the active sarcosine arm ranged from 10 to 25 participants. Most of the studies had a duration of 6 weeks, with a range of 1 week to 6 months across trials.

Six trials reported improvement in a range of clinical outcomes including positive, negative, depressive and cognitive symptoms, general psychopathology and total PANSS scores [41,43,67,69–71]. Lane et al (2005) [41] and (2010) [43] reported improvement in outcome measures with adjunct sarcosine (2gr/day for 6 weeks) but not D-serine (see D-serine section for details). Lane et al (2008) [69] used sarcosine monotherapy at doses of 1gr/d or 2gr/d in drug free acutely psychotic participants. Five out of sixteen completers showed clinical improvement as defined by a 20% reduction in PANSS total score. There was no significant effect of sarcosine dose, although all responders were receiving the dose of 2gr/d. Approximately half of the drug-naïve participants (5/11) were considered responders but none of the non-naïve patients responded. Strzelecki et al (2015) [75] correlated clinical improvement associated with adjunct sarcosine 2 g/d for 6 months with neuroimaging findings. Their result indicated add-on sarcosine was associated with statistically significant improvement in PANSS negative and general psychopathology scores in comparison to placebo. Furthermore, using Proton nuclear magnetic resonance (H-NMR) spectroscopy, they demonstrated reversal of the pathological increase in glutamatergic transmission in the left frontal lobe [75] and hippocampus [70] as well as increased markers of neuron viability and neuroglial activity in the left dorsolateral prefrontal cortex (DLPFC) [76].

In a recent placebo controlled randomized trial, Lin et al (2017) [71] compared adjunct sarcosine (2gr/d) plus benzoate (1gr/d) vs sarcosine (2 g/d) for clinical symptoms as well as cognition and global functioning. Forty nine patients with chronic schizophrenia completed the 12 week duration of the trial (n = 16–17 in each arm). Cognition was measured in native language using a battery of tests analogous to Matrics Consensus Cognitive Battery (MCCB). Their results showed a combination of adjunct sarcosine plus benzoate (but not sarcosine alone) was associated with improvement in cognition and global assessment of functioning (GAF). The sarcosine group displayed only improvement in reasoning and problem-solving subscales of cognitive functioning. In contrast to previous trials, there was no effect on other symptom domains.

A 6-week placebo controlled double blind trial by Lane et al (2006) [68] revealed no benefit of adjunctive sarcosine in patients on clozapine. This finding was in line with previous studies on use of adjunct glycine agonists in patients on clozapine. The authors hypothesized those on clozapine may have already reached the “ceiling” effect of NMDA complex enhancement and therefore addition of another NMDA modulator may not have further benefit.

Overall, sarcosine was reported to be well-tolerated. However, there are two case reports by Strzelecki et al (2014) [73] and (2015) [76] on association of adjunct sarcosine with activation symptoms and hypomania. Case 1 was on citalopram and quetiapine and case 2 was on olanzapine and venlafaxine. The authors concluded concomitant use of glutamatergic and serotoninergic agents may cause a synergistic activating effect.

In short, there are a number of positive small studies on use of add-on sarcosine; however, further large scale trials are required to replicate these findings. The history of other previous agents reviewed above suggests that success in small-scale studies does not predict positive effects in larger-scale studies.

3.2.2. Bitopertin

Bitopertin is a selective and potent inhibitor of GlyT1 which has been shown to modulate both glutamatergic and dopaminergic neurotransmission in preclinical studies of schizophrenia [77]. We identified seven primary publications [78–84] involving nine clinical trials and including a total of n = 1936 completers of the active bitopertin arm. All studies, except one [84], were multicentre international studies across multiple sites and countries in Asia, Europe, South and North America. There were no major reports of side effects across the studies.

Three studies have demonstrated positive results [81–83]. Umbricht et al (2014) [81] in a phase II study on adjunct bitopertin for persistent negative symptoms showed a significant beneficial effect at doses of 10 and 30 mg/d (but not 60 mg) in a per-protocol analysis. This trial involved 323 participants (273 completers) across 66 sites worldwide. Hirayasu et al (2016) [82] investigated the use of add-on bitopertin in patients with either prominent negative symptoms or suboptimal response. They demonstrated improvement in all outcome measures at the one-year study endpoint, and in all three arms of the study: bitopertin 5 mg, 10 mg and 20 mg. There was no clear-cut dose response.

Bugarski-Kirola et al (2016) [83] presented the results of three phase III 12-week adjunct bitopertin trials (MoonLyte, TwiLyte, NightLyte), involving a total of 6 active arms (bitopertin 5 mg (one arm), 10 mg (three arms), 20 mg (two arms), and three placebo arms). These were multicentre studies conducted in outpatient clinics in Asia, Europe, South and North America (TwiLyte was run at 109 sites, NightLyte at 84, and MoonLyte at 87). The study aimed to assess efficacy of adjunct bitopertine in schizophrenia patients with suboptimally controlled positive symptoms despite treatment with antipsychotics. Only the NightLyte study demonstrated a positive result in a 10 mg active arm, with improvement in total PANSS and PANSS Positive Symptom Factor Score (PFSF). Although the overall result seemed discouraging, the observed improvement in one arm of the study is considered significant, suggesting add-on bitopertin might offer modest benefit to partial responders. A major issue with these trials was the high magnitude of placebo response (SD1.0–1.5); such a magnitude of placebo response might obscure the difference between active medication versus placebo [85]. Furthermore, the observed strong inverted U-shaped dose response of bitopertin further narrows the potential therapeutic window [85].

Four additional negative trials of bitopertin have been reported. The FlashLyte and DayLyte trials used add-on bitopertin (5–20 mg) in patients with predominant negative symptoms. Both trials reported improvement in outcome measures by the end of the study (24 weeks) which fell short of statistical significance when compared to placebo. Bugarski-Kirola et al (2014) [79] used monotherapy of bitopertin 10 mg and 30 mg in comparison to olanzapine 15 mg and placebo in patients with acute exacerbation of schizophrenia. This trial (CandeLyte) was considered failed due to a lack of separation of the active arm (bitopertin or olanzapine) from placebo at the study end point (4 weeks). Kantrowitz et al (2017) [84] assessed the effect of 6 weeks of add-on bitopertin 10 mg on electrophysiological and clinical outcome measures, in a single centre study of patients with schizophrenia. No significant change was observed between active and control groups.

Nonetheless, the positive signal from a large-scale phase III multicentre trial is encouraging, and is prompting further investigation of bitopertin. One of the issues is that relatively limited dose response information was available prior to the launch of the phase III trials and it is not clear that dosing of this compound has been fully examined.

3.3. D-Amnio acid oxidase (DDAO) inhibitors

DDAO is a flavoenzyme responsible for degrading D-amino acids such as D-serine and D-alanin. An alternate strategy to enhance NMDA function is through inhibition of DDAO, resulting in increased levels of endogenous D-serine at the NMDA complex. Furthermore, post-mortem studies have demonstrated elevated expression and activity of DDAO in the cerebellum and cortex of patients with schizophrenia [86]. Therefore, it has been hypothesized that inhibitors of DDAO may have a role in new therapeutic developments for schizophrenia.

3.3.1. Sodium benzoate

Sodium Benzoate is a prototype competitive inhibitor of DDAO. In a preclinical study, single dose sodium benzoate produced antipsychotic effects in the phencyclidine-induced model of schizophrenia, characterized by behavioural abnormalities such as prepulse inhibition deficits and hyperlocomotion [87]. We identified three small scale randomized clinical trials (including 81 active participants) on use of adjunct sodium benzoate in patients with schizophrenia. All of these studies reported positive results, without any major side effects. Thus far, sodium benzoate lacks approval in North America, limiting its potential investigation and applicability to this continent.

In a randomized, double blind, placebo-controlled trial, Lane et al (2013) [88] compared the efficacy of add-on sodium benzoate (1gr/d for 6 weeks) versus placebo in 52 patients with chronic schizophrenia. They reported improvement in multiple domains including negative and cognitive symptoms, clinical improvement and a 21% reduction in PANSS total score. Lin et al (2017a) [89] showed adjunct sodium benzoate (at both doses of 1gr/d and 2gr/day) was superior to placebo in improvement of negative symptoms in sixty clozapine-refractory patients. They observed additional benefit on positive symptoms and quality of life only at the dose of 2gr/day. Lin et al (2017b) [72] revealed a precognitive effect with a combination of sodium benzoate plus sarcosine over sarcosine alone or placebo (see section on sarcosine for more details).

3.4. Metabotropic glutamate receptor (mGlu) agonists

There are two main categories of glutamate receptors: inotropic (iGlu) and metabotropic (mGlu) receptors. iGlu receptors have an ion channel structure that mediates fast excitatory neurotransmission and are classified into NMDA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and kainate receptors [90]. mGlu receptors are members of the G-protein coupled receptor (GPCR) family, characterized by possessing a large N-terminus extracellular domain and creating functional homodimers. mGlu receptors have eight isotopes ($mGlu_1$-$mGlu_8$) and are classified into three groups, based on their physiological and pharmacological characteristics [91,92]. In recent years, group II mGlu receptors (mGlu2 and mGlu3) have garnered a great deal of interest in the development of novel treatment agents for schizophrenia. As mentioned earlier, GWAS has demonstrated an association between the metabotropic glutamate receptor 3 and risk of schizophrenia. Post-mortem studies have also linked the alteration of mGlu2 and mGlu3 in the brain of patients with schizophrenia [91]. mGlu2/3 receptors modulate the presynaptic glutamine release. The mechanism of action of mGlu agonists is through normalization of excess glutamatergic tone which is caused by disinhibition of glutamate neurons due to NMDA hypofunction [5].

Preclinical studies provide promising potential for agonists of mGlu2/3 (such as LY354740) as non-dopaminergic antipsychotics, with evidence for improvement of working memory, stereotypy, and hyperlocomotion in animal models of schizophrenia induced by PCP [93]. Phase II clinical studies of mGlu2/3 have been inconclusive for the most part. Data from the clinical studies suggests potential receptor desensitization to mGlu agonists over time, leading to loss of efficacy [94].

Considering the preclinical evidence in support of mGlu2/3 agonists as novel antipsychotics, Eli Lilly progressed LY2140023 (oral prodrug of the active mGlu2/3 agonist LY404039) into clinical trials. In a 4-week randomized, three-arm, placebo controlled trial of 196 patients with schizophrenia, LY2140023 (40 mg bid) demonstrated efficacy superior to placebo and comparable to Olanzapine (15 mg/d), the active control arm, in improvement of both positive and negative symptom domains of the PANSS [95]. The second phase II dose finding study did

not separate either LY2140023 or Olanzapine from the placebo arm. LY2140023 was generally well tolerated, but the serious adverse event of convulsion was reported in four cases [96]. Subsequently, a 24 week phase II open label comparative study of LY2140023 versus atypical antipsychotics, as standard of care (SOC), was conducted. Only 27% of LY2140023 and 45% of SOC patients completed the 24-week study period. The result revealed reduction of PANSS scores over the 24-week period but from weeks 16 to 24 it was less effective than the SOC group (olanzapine, aripiprazole, or risperidone) [97]. The following double blind placebo-controlled comparator phase II trial of 1013 patients, LY2140023 (at both doses of 40 mg bid and 80 mg bid) failed to show improvements in PANSS total score compared to placebo, while risperidone (2 mg bid) significantly separated from placebo [98]. A separate phase 1b study on adjunct LY2140023 failed to demonstrate efficacy compared to placebo, in patients with prominent negative symptoms who were receiving SOC (aripiprazole, olanzapine, risperidone, or quetiapine) [98]. A Phase 3 clinical development program for LY2140023 (pomaglumetad methionil) in the treatment of schizophrenia, failed to show efficacy compared to aripiprazole at 24 weeks [99]. This study was stopped early after Eli Lilly announced termination of phase III trials after one of the trials failed to meet its primary endpoint [93].

Nonetheless, investigational mGlu2/3 agonists have been under further development but as mentioned earlier, discussion of the details of the investigational agents are out of the scope of this paper.

3.5. Other agents with glutamatergic activities

3.5.1. Memantine

Memantine is a non-competitive NMDA antagonist which can reduce the pathological activation of the NMDA complex without impacting its physiological activation [100]. Memantine has been shown to delay cognitive decline in dementia and is approved for treatment of Alzheimer's dementia [101]. Although phencyclidine and memantine are both considered NMDA receptor antagonists, memantine has a different effect and outcome profile than PCP or ketamine. Some studies suggest memantine is a partial antagonist, acting as a NMDA receptor agonist at a lower dose [102]. Other studies attributed memantine's potential benefit in schizophrenia through reversal of glutamatergic inhibition in the prefrontal cortex caused by NMDA-mediated GABA interneurons [101].

Our search revealed nine clinical trials [101,104–110], two open label studies [111,112], one retrospective case series [113], and five case reports [114–118] on the use of adjunct memantine in patients with schizophrenia, involving a total number of 277 completers of the active memantine arm. All of the trials used memantine 20 mg/d except one [110] which used flexible dosing of 5–20 mg/d. The majority of trials had a duration of 8–12 weeks. We further identified two studies looking at electrophysiological parameters in patients with schizophrenia following acute single dose administration of memantine [119,120].

Nine clinical trials (including a one-year open label extension trial) [103,105–112] and a case series [113] revealed a beneficial effect of adjunct memantine. All the studies with positive results reported improvement of negative symptoms. Across studies, a various range of other symptoms were also reported to improve including positive and cognitive symptoms, general psychopathology, quality of life and global functioning. De Lucena et al (2009) [103] demonstrated a beneficial effect of add-on memantine in 10 patients on clozapine. Verman et al (2016) [108] also showed improvement of negative symptoms and memory in 47 participants on clozapine in a 26 week cross-over trial. They included the responders to memantine in a one-year follow up open label study [111] which showed sustained effect of memory improvement but also further improvement of positive and overall symptomatology.

Two studies revealed no effects of adjunct memantine. The Lieberman et al (2009) [101] study included participants with residual positive symptoms on atypical antipsychotics. There was no difference between the active arm (the number of completers = 56) and placebo after an 8-week trial. They observed a higher rate of adverse effects (8.7% vs 6%) and a higher dropout rate due to side effects (11.6% vs 3%) in the memantine group compared to placebo. Side effects included headache, insomnia, constipation, fatigue, dizziness and auditory hallucinations (in 5.7% of the memantine group). The Lee et al (2012) [104] study also revealed no benefit of add-on memantine (n = 15) compared to the placebo group (n = 11). Other studies included in this review reported memantine as well-tolerated without a significant difference in the side effect profile between memantine and the placebo group.

Of the five case reports on adjunct memantine, two reported improvement of catatonia [114,115], three reported improvement of negative symptoms [116–118] and one also reported reversal of clozapine-related weight gain [117]. Electrophysiological studies following acute administration of memantine have shown mild enhancement of mismatch negativity following administration of memantine 20 mg (but not 10 mg) [119], and improvement of cortical oscillatory response dynamics [120].

In summary, there are a number of small-scale positive trials on the use of adjunct memantine in patients with schizophrenia. Consistent with previous studies of other agents reviewed in this paper, larger studies revealed less efficacy. Of note, memantine was efficacious in small studies when added to both clozapine and non-clozapine antipsychotics. This is in contrast to the effect of previously discussed NMDA receptor enhancers, which produced no effect (or even worsening) in combination with clozapine. The Zheng et al (2017) [121] meta-analysis showed add-on memantine was associated with improvement of negative symptoms (effect size: 0.6); such impact on negative symptoms was not significant in studies with 8 weeks duration (as opposed to 12 weeks or longer). Memantine outperformed placebo in three studies which used MMSE as a test of neurocognition.

3.5.2. Antiepileptics: lamotrigine and topiramate

Antiepileptics have been used as augmenting agents in patients with schizophrenia. Among these agents, lamotrigine and topiramate are thought to have glutamatergic modulating effects.

3.5.2.1. Lamotrigine. Lamotrigine's mechanism of action is through inhibition of presynaptic glutamate release by blockade of sodium channels. Moreover, lamotrigine modulates the aberrant inhibitory neuronal feedback and increases the release of GABA [122]. Using the ketamine model of schizophrenia, it has been shown that pretreatment with lamotrigine results in attenuation of ketamine-induced positive, negative and cognitive symptoms in healthy volunteers [123]. Our search of the literature on adjunct lamotrigine in patients with schizophrenia identified nine clinical trials [122–129] with a total n = 292 completers of the lamotrigine arm, six case series (n = 52) [130–135], and six case reports (n = 12) [136–141].

Five out of the nine clinical trials showed improvement of outcome measures including positive symptoms and general psychopathology [123–125], negative symptoms and general psychopathology [126], and positive, negative and some domains of cognitive symptoms [127] when lamotrigine (200–400 mg/d for 8–24 weeks) was added to clozapine [124,125,127] or non-clozapine [123,126] antipsychotics. The remaining four trials (including one trial in patients on clozapine [129]) showed no superiority of lamotrigine over placebo. Of all the included studies, Goff et al (2007) [122] report on two negative trials that encompass the largest number of participants, involving a total of 155 completers of the active arm. In the two studies the cognitive composite score was improved by z = 0.58 and z = 0.47 in the lamotrigine group, with corresponding improvements in the placebo group of z = 0.21 and z = 0.20. The effect of treatment compared to placebo was statistically significant in one study and it was not in the other.

Three out of six case series studies of adjunct lamotrigine reported improvement of total scores on the PANSS or BPRS [131–133]. Dursun et al (2001) [130] reported positive results with lamotrigine only in patients on clozapine. Poyurovsky et al (2010) [134] demonstrated improvement of obsessive symptoms, in particular among those with schizoaffective disorder. Ohnuma et al (2013) [135] showed improvement in 3 out of 5 cases. Case reports (involving 1–3 cases) include improvement of treatment refractory symptoms [136], sobriety from alcohol dependence [139], and a synergic effect with clozapine in decreasing aggressiveness [140]. Three case reports (involving a total n = 5) reported worsening of symptoms with addition of lamotrigine [137,138,141].

Based on the reviewed literature, add-on lamotrigine may have some beneficial effects in a subset of patients with schizophrenia, in particular those on clozapine; however, at this time use of adjunct lamotrigine is not supported by the evidence.

3.5.2.2. Topiramate. Topiramate is an antiepileptic and antimigraine medication which has been explored as an adjunct agent in treatment of schizophrenia. Its mechanism of action includes the potentiation of the GABAergic transmission and a-amino-3-hydroxy-5- methyl-isoxazole-4-propionic acid (AMPA)/kainite glutamate receptor antagonism [121]. In the animal model of schizophrenia, topiramate has been shown to be effective in attenuating popping behaviour, the equivalent of psychotic behaviour induced by MK-801, a high-affinity analogue of PCP. Popping behaviour is irregular episodes of intense jumping and is considered as equivalent to psychotic behaviour in mice [142]. We included nine clinical trials (including four open label trials) [142–150], two case series [130,151] and six case reports [152–156] on use of adjunct topiramate in patients with schizophrenia. We excluded two trials [157,158], one case series [159] and one case report [160] which solely reported on impact of topiramate on weight and metabolic parameters. The total number of completers in the topiramate trials was n = 218, and topiramate was used at the dose range of 100–300 mg/d in the majority of the studies for a duration ranging from 8 weeks- 6 months.

Results of the eleven studies demonstrated add-on topiramate was associated with improvement (n = 5 studies) [143,144,147–149], no effects (n = 5 studies) [130,142,145,146,150] and worsening (n = 1 study) [151] on clinical rating scales. The studies with a positive outcome mainly showed improvement of total scores or general psychopathology. One of the studies with a positive outcome reported worsening of verbal fluency [143]. Another study also reported a trend toward worsening of some cognitive domains [142]. The case reports described improvement of negative symptoms [152,156], total scores on the PANSS [153], discontinuation of cocaine use [155] and abstinence from alcohol [154].

Based on the present review, the evidence for efficacy of adjunct topiramate is not appealing. The Zheng et al (2016) [161] meta-analysis (including 16 English and Chinese articles) revealed superiority of topiramate over placebo (SDM:- 0.58) regarding total symptomatology. However, topiramate was associated with more attention/concentration difficulties, psychomotor slowing and paresthesia. Given the pre-existing cognitive impairment in people with schizophrenia, medications that worsen cognition, even minimally, are contraindicated.

3.5.3. N-Acetylcysteine

N-Acetyl cysteine (NAC) is an antioxidant that increases intracellular oxidized glutathione and has some anti-inflammatory properties [162]. As a glutathione precursor, NAC is proposed to modulate the glutamatergic system through the redox/glutathione sensitive site of the NMDA receptor [102]. We found five clinical trials [162–166] of adjunct NAC in schizophrenia (n = 159 completers in the active arm), three electrophysiological studies [167–169] and one case report [170]. Studies used a dose range of 1200–3700 mg/day for a duration of 8–52 weeks. Overall, NAC was well-tolerated.

All of the five clinical trials reported some positive outcomes but in inconsistent domains across trials, including positive and general psychopathology [163], negative and total PANSS scores [164], positive, negative, general psychopathology and some cognitive domains [162], negative, total PANSS and disorganized thoughts [165], and lastly, processing speed and verbal fluency in patients with early psychosis [166]. Electrophysiological studies demonstrated improvement of MMN [167], EEG synchronization [168] and auditory event-related potential in early psychosis [169]. The case report described improvement of CGI and PANSS scores following addition of NAC in a treatment resistant case [170].

In short, a few small scale trials have shown positive results but in a variety of symptom domains with limited overlap across these studies. Further large scale trials are required before any conclusions can be drawn.

4. Discussion

This review provides a summary on glutamatergic agents in patients with schizophrenia. While there is a growing body of literature on the role of glutamate dysfunction in the pathophysiology of schizophrenia, the evidence regarding the use of glutamatergic agents remains inconclusive. Nevertheless, this review raises important points for further discussion and consideration:

4.1. Heterogeneity of the results

As described in the text, various glutamatergic agents have yielded highly heterogeneous results. Such heterogeneity was observed at two levels: 1) within the group of studies investigating a particular agent, and 2) across different subgroups of glutamatergic agents.

First, among those studies with variable results, a positive response was observed in a wide range of symptom domains, which did not necessarily overlap across the studies. Factors such as heterogeneity of study participants, methodology and outcome measures likely contributed to the observed inconsistencies. Various inclusion criteria were used across the studies, with participants anywhere on the psychosis continuum from ultrahigh risk populations to acutely psychotic, to treatment resistant with prominent negative or positive symptoms. Another factor to consider is the concurrent use of antipsychotics (and other medications) by participants and their interaction with glutamatergic drugs. As discussed earlier, when used as an adjunct to clozapine, NMDA receptor co-agonists were associated with worsening or lack of efficacy. One explanation is that patients on clozapine have already reached the maximum NMDA enhancement and may not experience additional benefit by adding another NMDA receptor modulator. Another possible hypothesis may involve competing interest at the glycine site of the NMDA complex between clozapine and NMDA co-agonists.

Second, there was a heterogeneous range of outcomes for the glutamatergic agents reviewed here. As such, for some agents the outcome of the studies was almost uniformly negative whereas for others the result was more variable. This may suggest the glutamatergic pathway (s) involved in schizophrenia are rather specific, and therefore, only agents acting through certain glutamatergic mechanisms may be efficacious.

4.2. Discouraging outcome

Despite some preliminary potential for certain glutamatergic agents, so far the overall outcome has not been impressive. As discussed by Beck et al (2016) [171] possible explanations include variable CNS levels of the glutamatergic agents, high rate of placebo response, and the fact that schizophrenia is a highly heterogeneous illness and no single medication is expected to treat all patients.

Another potential explanation for the inconsistent results of these

studies is that perhaps the studied outcome domains are too broad for these agents. As such, many studies focused on the impact on negative symptoms as the primary outcome measure; however, even negative symptoms may be heterogeneous and better approached as two or more dimensional targets [172–174]. Unpublished conference presentations have suggested that treatment of avolition-anhedonia with these agents leads to better benefits compared to global negative symptom scores.

4.3. Severity scores for inclusion into treatment studies of negative symptoms

While it has generally been presumed that substantial levels of negative symptoms should be the entry criteria for clinical trials, the actual definition of the severity and persistence of negative symptoms has not been agreed upon. In addition to the issue of subtypes of negative symptoms, both the overall severity and persistence of negative symptoms requiring treatment is not clear. As noted by Rabinowitz et al. (2005) [175], there are variable definitions of negative symptom complexes that are used to select patients within trials. Prominent negative symptoms are moderately severe negative symptoms against a backdrop of less severe but still notable positive symptoms. Predominant negative symptoms include moderately severe negative symptoms that are required to be more severe than positive symptoms. When the authors examined existing large databases (n = 7450) to see how many patients actually met criteria for these two definitions, they found that 62.3% met relaxed criteria for prominent symptoms, 8.1% met strict criteria based on specific symptoms and that 10.2% met criteria for predominant symptoms. These data suggest that there is wide variability in the types of patient populations across different definitions of negative symptoms.

They also addressed symptom severity and prevalence of residual symptoms. When examining the prevalence of residual negative symptoms after treatment, they found that 64% of the treated subsample (n = 3658) had at least one negative symptom that was moderate (PANNS score of 4) in severity. However, requiring more negative symptoms leads to considerable drops in prevalence, with 31% having one or two residual symptoms, and 16% having 4 or more. When more symptom severity of greater than moderate is required, there is even more variability. The prevalence of moderately severe (PANSS Score of 5) negative symptoms ranges from 16% to 30% for individual symptoms and the prevalence of severe or extremely severe (PANNS score of 6 or 7) ranges from 2% to 10%. Obviously requiring more than 1 moderately severe negative symptom would lead to even greater decreases in prevalence.

A consensus statement on selection of patients for negative symptom treatment studies (Marder et al., 2013) [176] made several recommendations. They included age, clinical stability, and presence of depression. Importantly, there was no consensus as to whether predominant or prominent symptoms should be the defining feature. This inability to achieve consensus was based on the fact that prominent negative symptoms seem very common and hence do not reflect a unique illness feature while predominant symptoms define a small, but likely very important group.

4.4. Negative and cognitive divergence of effects

Although memantine is used in dementia for its effects on cognition, this review revealed consistent improvement of negative symptoms, but not cognition, across all studies with a positive outcome (10 out of 12 studies). It seems quite likely that cognitive impairment in dementia arises from considerably different neurobiological factors in Alzheimer's disease and schizophrenia, so a direct extrapolation is not really valid. In contrast, the Goff et al. (2007) [122] studies found a more substantial effect for cognition than for negative symptoms. In general, the results on cognition have not been any better than those for negative symptoms.

4.5. Future directions

This review highlights the heterogeneity of the results of Glutamatergic studies which could be in part due to highly heterogeneous inclusion of participants and a broad approach to outcome measures. Such observed heterogeneity across the studies makes interpretation of the results notoriously difficult and may contribute to failure of replication of the findings. The authors of this review suggest future studies to attempt to increase homogeneity by narrowing the inclusions criteria and having a more focused outcome measure. As such, studies may consider focusing on a clearly defined subgroup of patients and separating participants with treatment responsive vs. treatment resistant vs ultra- treatment resistant as well as separating those at different stages of the illness (first episode, vs early stages, vs chronic stages). Furthermore, outcome measures could focus on specific domains of negative or cognitive symptoms.

Our current conceptualization of schizophrenia includes categorizing patients based on their response to antipsychotic medications as treatment responsive, treatment resistant and ultra-resistant. The latter category refers to patients with minimal or suboptimal response to clozapine. The current schizophrenia guidelines have no further recommendations for the ultra-resistant category considering the lack of evidence for all of the agents studied to date [177]. When clozapine fails, there are a number of pharmacological options including augmentation with antiepileptics, a second antipsychotic, glutamate modulating agents, ECT, etc [178]. In choosing between these options, most clinicians adopt a personalized approach, taking into consideration the patient's prominent symptoms, potential contributing neuropathophysiological pathways, and may even consider pharmacogenomics-informed treatment. Arguably, taking a similar individualized approach for inclusion into research studies, may lead to finding a target subset of patients for treatment with various glutamatergic agents.

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