Published in final edited form as:

Curr Behav Neurosci Rep. 2019 June ; 6(2): 37–50. doi:10.1007/s40473-019-00174-5.

Galantamine-Memantine Combination as an Antioxidant Treatment for Schizophrenia

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Abstract

Purpose of Review—The objective of this article is to highlight the potential role of the galantamine-memantine combination as a novel antioxidant treatment for schizophrenia.

Recent Findings—In addition to the well-known mechanisms of action of galantamine and memantine, these medications also have antioxidant activity. Furthermore, an interplay exists between oxidative stress, inflammation (redox-inflammatory hypothesis), and kynurenine pathway metabolites. Also, there is an interaction between brain-derived neurotrophic factor and oxidative stress in schizophrenia. Oxidative stress may be associated with positive, cognitive, and negative symptoms and impairments in white matter integrity in schizophrenia. The antipsychotic-galantamine-memantine combination may provide a novel strategy in schizophrenia to treat positive, cognitive, and negative symptoms.

Summary—A “single antioxidant” may be inadequate to counteract the complex cascade of oxidative stress. The galantamine-memantine combination as “double antioxidants” is promising. Hence, randomized controlled trials are warranted with the antipsychotic-galantamine-memantine combination with oxidative stress and antioxidant biomarkers in schizophrenia.

Keywords

Antioxidant; Clinical high risk; Galantamine; Memantine; Oxidative stress; Schizophrenia

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Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Introduction

Oxidative stress, also known as redox dysregulation, is an imbalance between the generation of reactive oxygen species or reactive nitrogen species and the antioxidant defense capacity of the body, also known as scavenger. A redox imbalance in schizophrenia was first postulated almost a century ago [1•, 2•]. However, the interest in free radical pathology and oxidative injury in schizophrenia and the potential use of antioxidant treatment peaked only in the last few decades [3–5]. The oxidative stress hypothesis of schizophrenia [6] and the redox-inflammatory hypothesis [7•] are gaining popularity in the field. There is substantial evidence of oxidative stress pathophysiology in schizophrenia [8–14, 15•, 16–20]. This evidence is further supported by meta-analyses that showed that patients with schizophrenia have a decreased antioxidant potential in serum, plasma, and red blood cells that is largely independent of antipsychotic drug use [21•, 22•].

We have previously reviewed how the antipsychotic-galantamine-memantine combination may concurrently target several systems such as nicotinic-cholinergic, glutamate/*N*-methyl-D-aspartate (NMDA), GABA, and kynurenic acid (KYNA) [23••, 24, 25••]. The objective of this article is to highlight the potential role of the galantamine-memantine combination as an antioxidant treatment for patients with schizophrenia.

Oxidative Stress and Antioxidant Biomarkers

Lipid hydroperoxides, nitric oxide metabolites, advanced oxidation protein products [26], malondialdehyde [27], and apolipoprotein D [28] are oxidative stress biomarkers. The critical antioxidant enzymes include superoxide dismutase (SOD; SOD 1, 2, and 3 proteins have been reported), catalase (CAT), and glutathione peroxidase (GPx) [5]. SOD1 and GPx were studied in people with schizophrenia several decades ago [29•]. SOD [30], GPx [30], CAT [30], glutathione (GSH) [31], total radical-trapping antioxidant potential [32], total antioxidant reactivity [32], thiobarbituric acid reactive substances (TBARS, [33]), lipid peroxide [30], homocysteine [34], nitric oxide (NO) [30], microsomal glutathione-S-transferase 1 [35], and paraoxonase 1 [26], are potential antioxidant biomarkers in schizophrenia. Decreased SOD, GPx, GSH, and CAT and increased TBARS, lipid peroxide, homocysteine, and NO have been consistently validated in schizophrenia [36••]. SOD, GPx, and GSH are commonly studied in schizophrenia [36••].

In a magnetic resonance spectroscopy (MRS) study with 20 participants with schizophrenia, a significant correlation was found between cerebral GSH levels in the posterior medial frontal cortex and the severity of negative symptoms [37]. The serum total antioxidant level was significantly lower in 23 participants with deficit schizophrenia (characterized by enduring, idiopathic negative symptoms) compared with 42 participants with non-deficit schizophrenia and 31 healthy controls [38]. Deficits in GSH impair myelin maturation, which may cause impairments in white matter integrity in people with schizophrenia [39]. Also, oxidative stress may be linked to psychosis [40].

Short-term treatment with antipsychotics reduces oxidative stress as shown by a decrease in neopterin levels and increase in antioxidant levels in schizophrenia [41]. However, typical

antipsychotics have been reported to increase oxidative stress during longer-term use [42, 43], though there are some reports of antioxidant activity [44]. This effect is also seen with atypical antipsychotics, albeit less than with older drugs [45]. In first-episode psychosis, treatment with antipsychotics for 7 months reduced indices of oxidative stress such as total level of peroxides, oxidative stress index, and the ratio of oxidized methionine to methionine [46]. The inconsistent effects of antipsychotics could be related to differences in chemical properties, leading to different products that have pro- or antioxidant effects, remission of clinical symptoms, improvement in sleep, or emergence of adverse effects [17, 44, 47].

Role of Galantamine and Memantine in Oxidative Stress

Galantamine is not only an acetylcholinesterase inhibitor but also a positive allosteric modulator of α -7 nicotinic (α 7nACh) receptors. In addition, galantamine may also have antioxidant properties as first described in an in vitro study showing that it acts as a scavenger of reactive oxygen species [48••]. Several other studies [49••, 50••, 51••, 52••] have replicated this finding.

Memantine is a non-competitive NMDA receptor antagonist, but interestingly, the antioxidant activity of memantine has also been reported in preclinical studies [53, 54, 55••, 56, 57••, 58]. GSH is synthesized by glutamate-cysteine ligase and glutathione synthase from cysteine, which is transported through the cystine/glutamate antiporter system xc (Sxc) [59–64]. This knowledge may be useful for the novel therapeutics development for diseases associated with depletion of GSH [65] like schizophrenia. A recent study showed that the effects of therapeutically relevant concentrations of memantine on thalamocortical glutamatergic transmission are mainly caused by the activation of Sxc rather than inhibition of NMDA receptors [66••]. This finding is suggestive that the combination between reduced NMDA receptors and activated Sxc may contribute to the neuroprotective effects of memantine [66••]. Another study found that memantine reduced the oxidative damage to proteins in the cortex and hippocampus that corresponded to better recognition memory in aged rats compared with aged rats that received saline and showed long-term recognition memory deficits [55••]. These findings suggest that age-induced memory deficits in rats are related to oxidative damage induced by the overactivation of the NMDA receptor and that memantine can partly prevent or delay this process.

Although preclinical evidence showed potential benefit of antioxidant treatment on cognition [67••, 68••], randomized controlled trials (RCTs) with antioxidants in Alzheimer's disease (AD) did not achieve the expected outcomes and benefits [69]. It was argued that a "single antioxidant" may be incapable of sufficiently counteracting the complex cascade of oxidative stress [70]. AD may be a good clinical model for schizophrenia because of the overlap of pathophysiological mechanisms and treatment in the two diseases. The galantamine-memantine combination as "double antioxidants" is promising [71••]. The "double antioxidants" approach was corroborated as the galantamine-memantine "combination" increased the SOD2 immunoreactivity and preserved spatial memory after ischemia-reperfusion injury transient global cerebral ischemia in gerbils [67••]. This protective effect was not seen with either galantamine or memantine alone [67••].

Interplay of Oxidative Stress, Inflammation, and the Kynurenine Pathway

Oxidative stress closely correlates with inflammation [72]. The neurodevelopmental animal models shed light on the “convergent” role of neurotransmitter systems, inflammation, and oxidative stress as biomarkers of schizophrenia [7]. The interplay between inflammation and oxidation has potential implications for novel therapeutic discovery and is gaining popularity in the field [7]. The immune-inflammatory response in schizophrenia may be associated with an imbalance in tryptophan metabolism, resulting in increased production of KYNA in the brain [73]. The kynurenine pathway (KP) is tightly controlled by the immune system [74], and the interactive effects of cytokines, oxidative stress, and the KP are well documented (see Fig. 3) [7•, 75]. KYNA acts as an antagonist of NMDA and $\alpha 7$ nACh receptors and has potential antioxidant properties [76••]. Several KP metabolites are involved in the complex pro- and antioxidative processes in the brain [32, 77–86]. Along these lines, deficit schizophrenia ($N = 40$) was associated with increased plasma KP metabolites such as quinolinic acid, xanthurenic acid, 3-hydroxykynurenine, and picolinic acid, which may further increase inflammatory and oxidative stress processes [75]. Finally, the inhibition of the KP prevented behavioral disturbances (reduced locomotor activity) and oxidative stress in the rat brain in a schizophrenia animal model induced by the NMDA receptor antagonist ketamine [87].

Acetylcholine binds to the $\alpha 7$ nACh receptor expressed on macrophages to suppress pro-inflammatory cytokine production [88–90]. The activation of the $\alpha 7$ nACh receptor on the cholinergic anti-inflammatory pathway prevents cytokine release [91]. The anti-inflammatory actions of galantamine [90, 92, 93] and memantine [94, 95] are well documented. Galantamine decreased the expression of microglia and astrocyte markers, pro-inflammatory cytokines (interleukin-1 β , interleukin-6, and tumor necrosis factor α [TNF- α]), and NF- κ B p65 in the hippocampus of lipopolysaccharide (LPS)–exposed mice, thereby improving cognition [92]. Galantamine modulated a myriad of inflammatory/oxidant/apoptotic signals involving HMGB1/RAGE/NF- κ B/TNF- α , ICAM-1/MPO, IL-10, Jak2/STAT3, and Akt/Bcl-2 pathways (janus kinase 2, signal transducer and activator of transcription 3, high mobility group box 1, protein kinase B, B cell lymphoma 2, nuclear factor kappa B, intercellular adhesion molecule 1, receptor for advanced glycation end products, suppressor of cytokine 3 signaling) in rats [90]. Memantine treatment protected against TNF- α induced decrease in hippocampal precursor proliferation in postnatal mice [94]. Finally, in an RCT with bipolar depression, memantine significantly reduced TNF- α levels compared with placebo [95].

Brain-derived neurotrophic factor (BDNF) plays a critical role in neuronal survival, morphogenesis, synaptic plasticity, and cognitive functioning. BDNF mediates its action through various intracellular signaling pathways triggered by activation of tyrosine kinase receptor B (TrkB). Brain and plasma BDNF have been shown to be lower in schizophrenia [19, 96, 97]. Galantamine [98] and memantine [99] have been shown to increase BDNF levels in rats. BDNF-induced activation of TrkB is essential for synaptic plasticity [100]. Decreased BDNF/TrkB signaling was found in the frontal cortex of the reeler mouse model of schizophrenia [101]. Galantamine increased TrkA and TrkB phosphorylation in the mouse hippocampus [102]. In the same study, galantamine increased the phosphorylation of

protein kinase B (also known as AKT) and cAMP response element-binding protein (CREB) in the mouse hippocampus [103]. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a prodrug to the neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺). MPTP-induced changes in hippocampal synaptic plasticity and memory were prevented by memantine through the BDNF-TrkB pathway [103]. Memantine reversed memory impairments and significantly increased BDNF and TrkB mRNA levels in both the prefrontal cortex and hippocampus of stress-exposed rats [104]. The interactive effects of KP, nuclear factor kappa B, and BDNF are well documented [105, 106]. Also, there is an interaction between BDNF and oxidative stress in schizophrenia [107]. Hence, the galantamine-memantine combination may concurrently improve BDNF, oxidative stress, antioxidant, and anti-inflammatory biomarkers.

It is well known that the inflammatory process can induce oxidative stress [108]. In one study, 23 participants with schizophrenia were found to have increased cerebrospinal fluid IL-6 compared with 37 healthy controls [109]. In those with schizophrenia, a positive correlation was found between IL-6 and the tryptophan:KYNA ratio, suggesting that IL-6 may activate the KP. These findings suggest that IL-6 induces the KP, leading to increased production of KYNA in participants with schizophrenia [109]. Increased KYNA may be associated with cognitive impairments in schizophrenia [110–112]. Therefore, because of the anti-inflammatory action of galantamine and memantine, the combination could lower the production of KYNA in schizophrenia [113]. The galantamine-memantine combination may stabilize pathophysiological mechanisms including but not limited to KP, inflammation, and oxidative stress concurrently with its anti-inflammatory and antioxidant properties.

Use of biomarkers in the discovery of novel drugs to treat schizophrenia has been suggested [114]. Along these lines, KYNA and mismatch negativity (MMN) have been proposed as potential biomarkers with the galantamine-memantine combination treatment in schizophrenia [115] and CHR [116••]. KYNA levels bidirectionally modulate levels of neurotransmitters such as glutamate, dopamine, acetylcholine, and GABA [85, 111, 117–124]. Keep in mind that the antipsychotic-galantamine-memantine combination can modulate multiple systems (dopamine, nicotinic-cholinergic, glutamatergic/ NMDA, GABA, KYNA, redox-inflammatory) concurrently because these systems are intertwined [25]. Imbalance in one system (neurotransmitter/receptor/pathway/enzymes) may affect the “central hub”/entire system [125]. Thus, a reversal of abnormal activity in one system, or any combinations thereof, might have beneficial effects on the entire system [126••].

The galantamine-memantine combination may improve positive, cognitive, and negative symptoms of schizophrenia through counteracting the effect of increased KYNA in schizophrenia [23••, 24, 25••, 71••, 112, 115, 116, 127, 128]. Also, considering the increase in oxidative stress with longterm antipsychotic treatment [43, 45], addition of the galantamine-memantine combination could potentially reverse the oxidative damage. The advantages of combining galantamine and memantine are summarized in Table 1 and Fig. 1 [171]. The key to success is targeting drugs at the main pathophysiological mechanisms [172] as shown in Fig. 1.

Role of Galantamine and Memantine in Oscillatory Activity

Altered oscillatory gamma activity is a core pathophysiological mechanism of positive, cognitive, and negative symptoms of schizophrenia [173–176]. High-frequency oscillations have been suggested as a translational biomarker in CHR [177] and schizophrenia [178–181]. The gamma-band auditory steady-state response may be utilized as a biomarker for early detection of psychosis [182]. GABA-ergic interneurons play a pivotal role in the primary generation of high-frequency oscillations and their local synchronization [183, 184], whereas glutamatergic inputs/ NMDA receptors control their strength, duration, and long-range synchronization [185–188]. In addition, the activation of $\alpha 7$ nACh receptors enhanced hippocampal oscillations [189] and induced plasticity in gamma oscillation [190], suggesting the potential of galantamine (via $\alpha 7$ nACh receptor activation) to enhance gamma oscillations. Furthermore, there is association of gamma oscillations and oxidative stress in animal models [191] and people with schizophrenia [192]. Galantamine [139] and memantine [140] have significantly enhanced gamma oscillations in the hippocampus of rodents. On the basis of these pathophysiological mechanisms, it is not surprising that galantamine [141] improved oscillatory response in healthy participants and memantine [142] improved oscillatory response in participants with schizophrenia compared with placebo.

Role of Oxidative Stress and Inflammation in Clinical High Risk for Psychosis

In a positron emission tomography–MRS study, a significant association was found between the translocator protein and GSH levels in participants with CHR for psychosis ($N = 27$) compared with 21 healthy controls [193]. At 7-year followup, 15 of 36 individuals with CHR had transitioned to psychosis [194]. A low baseline erythrocyte GSH level was found to be a significant predictor of transition to psychosis [194]. In another study, IL-6 concentrations were found to be significantly higher in 17 people with CHR compared with 25 healthy controls. Participants with CHR who developed psychosis had increased IL-6 concentrations compared with those who did not transition to psychosis. The authors argued that IL-6 may be a marker of transition from CHR to psychosis [195]. In another study, individuals with CHR ($N = 12$) had significantly increased serum IL-6 and decreased serum IL-17 concentrations compared with 16 healthy controls [196]. Finally, in a 16-week RCT (subsample of $N = 27$), a significant reduction in IL-6 concentrations and concurrent negative symptom improvement in prodromal schizophrenia was seen with D-serine compared with placebo [197].

In the North American Prodrome Longitudinal Study that included participants aged 12–35 years, blood levels of oxidative stress biomarkers such as malondialdehyde-modified low-density lipoprotein and apolipoprotein D were found to be increased in 32 CHR participants who developed psychosis compared with 35 healthy controls and 40 CHR participants who did not develop psychosis during a 2-year follow-up [198]. The authors argued that these results support the hypothesis that inflammation, oxidative stress, and dysregulation of hypothalamic-pituitary axes may be prominent in CHR. This finding underscores the

paradigm that the redox, neuroimmune, and glutamatergic/NMDA receptor systems may form a “central hub” in schizophrenia [125]. Steullet and colleagues argued that medications such as *N*-acetylcysteine (NAC, GSH precursor) with antioxidant and anti-inflammatory properties, which can also regulate glutamatergic transmission, are promising tools for prevention of psychosis in CHR patients [125]. We argue that the galantamine-memantine combination may also be used for this purpose because the combination has similar properties as NAC. The combination is superior to NAC because of the action of galantamine on $\alpha 7$ nACh receptors. However, the varenicline-NAC combination [199] may be comparable with the galantamine-memantine combination.

In a study using MRS, grandiosity significantly correlated with glutamate concentration in the anterior cingulate cortex (ACC) in 12 individuals with CHR. Striatal GSH significantly correlated with grandiosity [200]. ACC GSH significantly correlated with grandiosity and disorganized speech [200]. These findings suggest that glutamatergic therapies may be useful in psychosis prevention [201]. NAC (2 g/day for 60 days), which modulates glutamate, improved MMN in seven participants with schizophrenia who completed a randomized, double-blind, cross-over study [202]. Along these lines, it was suggested that the galantamine-memantine combination may prevent psychosis in those with CHR by enhancing MMN [116••]. In another RCT with early psychosis ($N=32$), NAC 2700 mg/day for 6 months improved brain GSH levels compared with 31 participants on placebo [203]. The galantamine-memantine combination may have a similar effect by improving oxidative stress and antioxidant biomarkers.

The slow progression (2.4–14.9 years after presentation) [204•] from the prodromal phase to a first psychotic episode [205, 206] is an opportunity for novel prophylactic therapeutic intervention [207]. A common mechanism impacting parvalbumin-positive interneuron (PVI) is redox dysregulation, which represents a novel target for preventive neurodevelopmental intervention [207]. Once PVI functional impairment is detected (e.g., MMN, gamma oscillations biomarkers), preventive treatment with redox regulators/antioxidants may be considered [207]. In a double-blind, randomized, placebo-controlled study, single-dose memantine (20 mg) enhanced cortical oscillatory dynamics in 18 participants with schizophrenia compared with 14 healthy controls [142]. Therefore, the galantamine-memantine combination may prevent psychosis not only by enhancing MMN [116••] but also by improving oxidative stress and antioxidant biomarkers and enhancing gamma oscillations (Table 1). Medications that target redox, immune, and glutamatergic/NMDA receptor systems may be more beneficial for young people with CHR than for people with chronic schizophrenia because the defects in parvalbumin interneurons and oligodendrocytes/myelination may precede illness onset [125].

KYNA applied to rat prefrontal cortex reduced extracellular GABA levels; this effect was prevented by co-application of galantamine GABA [137]. An increase in GABA release was found in the hippocampus of the memantine-treated rat compared with the saline-treated rat [138]. GABA may be associated with MMN in people with schizophrenia [208]. Hence, GABA release and increased concentration of GABA (GABA is one of the hypotheses in quintuple hypotheses [25]) with the galantamine-memantine combination may lead to

enhancement of MMN. This is important not only for the treatment of schizophrenia but also for the prevention of psychosis.

In rats with a neonatal ventral hippocampal lesion (NVHL, developmental rodent model), juvenile and adolescent treatment with NAC prevented the reduction of prefrontal parvalbumin interneuron activity. In addition, NAC significantly improved MMN in NVHL rats compared with sham rats [209]. The authors argued that it is possible to prevent or reverse a deficit even if antioxidant treatment is initiated after the development of oxidative stress. This finding is clinically relevant because the redox modulation can be beneficial even if initiated after CHR is identified in adolescence. Hence, this therapeutic modality may be on the horizon as an early intervention in people with CHR [210•]. Because of the long duration of the prodromal phase [205], the antioxidant treatment may be able to prevent or delay schizophrenia onset (see Fig. 2) [211].

Randomized Controlled Trials with Antioxidant Treatment in Schizophrenia

Antioxidants such as vitamins C [212] and E [212], *Ginkgo biloba* [213, 214], dehydroepiandrosterone [215], and selegiline [216] had only modest effects in RCTs in schizophrenia [217]. Notably, in a Cochrane database systematic review of 22 RCTs with antioxidants in schizophrenia ($N = 2041$), only three studies (NAC [218] and allopurinol [219, 220]) reported any clinically meaningful response [217]. Overall, the evidence with antioxidants in schizophrenia is limited, taking into consideration all 22 RCTs reviewed [217]. RCTs with omega-3 fatty acid [212, 221], erythropoietin [222], and L-lysine [223] with antioxidant activity also had no clinically meaningful effect in schizophrenia. Finally, in RCTs, minocycline had some efficacy signal in schizophrenia [224–226].

The approach of using an antipsychotic plus one adjuvant/ augmentation medication to treat schizophrenia has not been a viable option for the field [227–229, 230•]. The pharmacological treatment of schizophrenia needs a paradigm shift [126•]. A “magic bullet” or single molecular target may not be the best way to move forward in the pharmacological treatment of schizophrenia [231]. Rather, drugs acting at several molecular targets may lead to more effective novel therapeutics in schizophrenia [231]. Along these lines, it was argued that multitarget-directed ligands may play a role in the treatment of schizophrenia [23]. Systematic reviews and meta-analyses have shown that NAC [228, 232–234] and minocycline [228, 235–237] are promising add-on treatments for schizophrenia. In addition, the combination of minocycline and NAC has synergistic effects [238–242]. Like galantamine and memantine, minocycline and NAC are also FDA-approved medications. If the antipsychotic-galantamine-memantine combination produces only partial response, NAC or minocycline may be added [243] to enhance the effect size for positive, cognitive, and negative symptoms to obtain FDA approval as antischizophrenia treatment (Table 2). The single modality of “one-molecule-one-target” strategy for treating AD has failed. Hence, future therapies that use the “combination-drugs-multi-targets” strategy (CDMT) addressing multiple aspects to block the progression of pathogenesis of AD have been suggested [244]. CDMT may be the way to move forward for schizophrenia as well.

Conclusion and Future Directions

A crucial next step is to examine antioxidant combinations in individuals with CHR and schizophrenia, as the redox system is quite complex [245••]. The RCTs to date in CHR and schizophrenia with a “single antioxidant” had some efficacy signal. The galantamine-memantine combination with “dual-hit antioxidants” is promising. Hence, RCTs are warranted.

Acknowledgments

We thank Drs. Joshua Kantrowitz, Laura Rowland, and Iris Sommer for their valuable comments. This material was presented at the 57th American College of Neuropsychopharmacology meeting, December 9–13, 2018, Hollywood, Florida, USA; at the Schizophrenia International Research Society conference, April 10–14, 2019, Orlando, Florida, USA, and at the 74th Annual Society of Biological Psychiatry Scientific Conference, May 16–18, 2019, Chicago, Illinois, USA. The authors thank Ms. Sasha Koola for preparing Fig. 1.

Funding The funding support to Pillai from NIH/NIMH (MH 097060) is acknowledged.

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Fig. 1.

Advantages of targeting nicotinic and NMDA receptors concurrently. *BDNF* brain-derived neurotrophic factor, *MMN* mismatch negativity, *PPI* prepulse inhibition, *KYNA* kynurenic acid. The three domains of psychopathology and several target engagement biomarkers are likely to improve by targeting nicotinic and NMDA receptors concurrently

Table 1**Advantages of the galantamine and memantine combination**

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- Synergism of cholinergic and glutamatergic systems [71, 129, 130]
 - Synergism of $\alpha 7$ nACh and NMDA receptors [67, 71, 129, 131]
 - Targets quadruple receptors (NMDA, nicotinic, AMPA, and kainate) concurrently [23••, 71, 132–134].
 - Interactive effects of $\alpha 7$ nACh and NMDA receptors on MMN [135, 136]. May synergistically enhance MMN [25••, 71, 115, 116].
 - Galantamine [137] and memantine [138] enhanced/released GABA.
 - Galantamine [139] and memantine [140] have significantly enhanced gamma oscillations in rodent hippocampus. Galantamine [141] and memantine [142] improved oscillatory response in healthy participants and schizophrenia, respectively.
 - MK-801 treatment impaired prepulse inhibition (PPI) in rats; galantamine enhanced PPI [143]. In participants with schizophrenia, memantine significantly enhanced PPI compared to placebo [144].
 - Galantamine [48••, 49••, 50••, 51, 52] and memantine [54, 55••, 56–58] have antioxidant activity; combination may have synergistic antioxidant activity [71••].
 - Galantamine [90, 92, 93] and memantine [94, 95] have anti-inflammatory action.
 - Galantamine [145] and memantine [146] inhibited microglial activation.
 - Galantamine [98, 147] and memantine [99, 148] increased BDNF. An interaction between $\alpha 7$ nACh and NMDA receptors may synergistically enhance BDNF and induce synaptic plasticity and long-term potentiation [149, 150]. BDNF has the vast majority of evidence among all the biomarkers focused on cognition in schizophrenia [151]. The combination may synergistically enhance BDNF [71].
 - Higher brain lactate (magnetic resonance spectroscopy) was associated with lower MCCB scores in schizophrenia [152]. Galantamine and memantine significantly reduced lactate dehydrogenase (LDH) release in rat hippocampal slices subjected to oxygen and glucose deprivation [153]. The interference with cellular energy metabolism reduced kynurenic acid (KYNA) formation in the rat brain, which was reversed by lactate and pyruvate [154]. KYNA may decrease LDH release [155].
 - The elevated lactate concentration in schizophrenia may be due to increased anaerobic glycolysis possibly because of mitochondrial dysfunction [81, 156, 157] and oxidative stress [152]. Hence, the antioxidant activity of galantamine and memantine may reduce lactate concentration. Mitochondrial dysfunction in schizophrenia [158–160] may be improved by galantamine and memantine [161].
 - Galantamine and memantine cross the blood-brain barrier [162, 163] and may counteract the effects of KYNA in the brains of people with schizophrenia [23••, 24, 25••, 112, 115, 116, 127].
 - Galantamine [164] and memantine [165] prevented apoptotic cell death and cognitive impairments by inducing neuroprotection via regulation of Bcl-2.
 - Galantamine [145, 166] and memantine [167] modulate the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway.
 - Galantamine [92, 168] and memantine [99, 169] increased synaptophysin. Reduced synaptophysin, a marker of synaptic density, is seen in schizophrenia [170].
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Table 2

Potential antischizophrenia treatments

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- Antipsychotic-galantamine-memantine combination
 - Antipsychotic-galantamine-memantine-minocycline combination [243]
 - Antipsychotic-galantamine-memantine-NAC combination [243]
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